

**BENZERİ OLMAYAN
ANALJEZİK**

METAMİZOL (NOVALGİN)

*Hakkında bilinmeyenler,
yanlış bilinenler ve doğrular*

**METAMİZOL
(Novalgin)**

dipyrone

**aminopyrine
sulfonate**

analginum

methapyrone

noramidopyrine

sulpyrine

**A UNIQUE
ANALGESIC**

METAMIZOLE (NOVALGIN)

*The unknown, the
misconceptions, and the facts*

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Preface

Metamizole has been one of the molecules that influenced me most during a professional life of more than fifty years. I have carried out various studies on this drug and given dozens of lectures in Turkey and abroad. The common picture I observed at these lectures was that the audience approached the subject with suspicion and eventually turned the discussion to the drug's capacity to cause agranulocytosis. In the lectures I gave in the USA in particular, I saw that most of the audience did not even know the name metamizole (dipyrone). Those who did know it remembered only its agranulocytosis-inducing effect, copied from one textbook to the next.

The situation in the literature is no different. Although metamizole has been in use for more than a century, comprehensive works covering the drug in all its aspects are few. The broadest work in this field is the 355-page symposium volume edited by Brune and published in 1986, marking the centenary of the pyrazolone derivatives [1]. In the same year Brogden reviewed the pyrazolone derivatives extensively in the journal *Drugs* [2]. However, these works belong to the same period as the first results of the IAAAS. They could not include the population-based agranulocytosis studies, the pharmacogenetic research or the assessments of the European Medicines Agency carried out over the following forty years. Later reviews have generally focused on a single topic. The two-part review by Nikolova et al. examined the drug's pharmaceutical, experimental and clinical profile [3], and the review by Jasiecka et al. its pharmacological properties [4]. The systematic reviews by Kötter et al. and Andrade et al. addressed its safety [5, 6], and Lutz's review its effects on the liver [7]. Brinkman et al. [8] and Cascorbi and Baron [9] summarise current clinical use and drug interactions. There are also short benefit-risk assessments prepared with manufacturer support [10]. The most detailed documents on agranulocytosis are the European Medicines Agency's 2018 and 2024 assessment reports [11, 12]; however, these reports focus only on safety and do not address efficacy or pharmacology.

Writing this monograph took a long time. I hope that among its readers there will be physicians who re-evaluate metamizole, free themselves of prejudice and use it in the right patient in the right way, and academics who will continue to study this drug.

Prof. Dr. F. Cankat Tulunay

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Summary

Metamizole (dipyrone, noramidopyrine methanesulfonate, analgin) is a non-acidic pyrazolone analgesic and antipyretic in use since 1922. Although it is not marketed in the United States, Canada, the United Kingdom, Australia or the Scandinavian countries, it is used by hundreds of millions of people in the rest of the world. Unfortunately, in Turkey, on the basis of hearsay, metamizole is described even among physicians and pharmacists as a drug that is not used anywhere in the world. It is authorised in 18 member states of the European Union and sold without prescription in Bulgaria, Hungary and Poland. Even in Germany, where prescriptions are strictly controlled, the number of defined daily doses rose from 15 million in 1991 to 280 million in 2022. Metamizole is prescribed at least once to 8.1% of people covered by statutory health insurance, i.e. to about 5.5 million people a year. Among those over 80 years of age this proportion reaches 37.9%.

In Latin America metamizole, under the name "dipirona", is one of the most frequently used painkillers and is sold without prescription in most countries. In Mexico it is so widespread under the name "Neo-Melubrina" that the US medical literature refers to it as "Mexican aspirin"; its carriage by immigrants into the USA, where the drug is banned, has become a public health issue in its own right. In Russia and the former Soviet countries it is a staple household medicine under the name "Analgin". India suspended the drug in 2013 but re-authorised it in 2014, restricting its use to severe pain, tumour-related pain and fever unresponsive to other drugs. China exports around 10,000 tonnes of metamizole a year, and in China metamizole is a prescription drug. In Turkey, too, it is one of the first drugs used for pain and fever, particularly in hospital emergency departments (Novalgin ampoules) and at home. Behind such divergent regulatory decisions for the same molecule lies a single adverse effect: agranulocytosis.

This monograph is a chronological and methodological re-evaluation of a century of evidence on the risk of agranulocytosis, evidence that has been propagated in many articles and books largely by copy-and-paste. Published risk estimates differ by a factor of about 800: 1 in 1,439 prescriptions in Sweden in 2002 versus 0.85 cases per million person-weeks in Spain in 2024. Most of this difference arises not from the biology of the drug but from the measurement itself:

- (1) attribution to metamizole of data on its ancestor aminopyrine (aminophenazone, Pyramidon) in the early literature;
- (2) division of cases collected from different sources by a local denominator (the "pooling error");
- (3) comparison of non-convertible denominators such as users, prescriptions, user-weeks and population-years;
- (4) selection and stimulated-reporting biases in numerators based on spontaneous reports;
- (5) regional and possibly genetic heterogeneity.

Modern, well-designed studies confirm a genuine increase in relative risk of agranulocytosis with metamizole (adjusted relative risk 25.8 in Barcelona). The absolute

risk, however, is low: population-based studies find fewer than 1 case per million people per year (Berlin 0.96; Barcelona 0.56). In the LATIN study in Latin America, where the drug is most widely used, the incidence of agranulocytosis from all causes was 0.38 per million per year, and no significant association with metamizole use was found. Mortality has fallen markedly as awareness has grown (in Switzerland from 13.5% in 2014–2018 to 1.8% in 2024). In its 2024 urgent review the European Medicines Agency found the benefit-risk balance positive but introduced a boxed warning.

This monograph also documents metamizole's unique place among the non-opioid analgesics:

- (1) In our assessment it is the most potent of the non-opioid analgesics. Even its lowest effective dose is as effective as the standard dose of ibuprofen; it is equivalent to morphine in cancer pain and superior to tramadol in renal and biliary colic.
- (2) Whereas the analgesic effect of NSAIDs reaches a ceiling at low doses, the effect of metamizole continues to increase with dose up to 2.5–3 g. The currently recommended dose limits are not based on a systematic dose-response study.
- (3) Its antipyretic effect is stronger than that of paracetamol and equivalent to that of nimesulide.
- (4) Its smooth muscle relaxant effect is unique.
- (5) It is effective epidurally and, in a patient with Buerger's disease, unlike local anaesthetics, it increased circulation in the diseased region without stealing blood from the diseased extremity. This last finding was observed for the first time in the world by our team.

In conclusion, the thesis that early risk estimates were largely exaggerated and methodologically flawed is supported by documentary evidence; this does not mean, however, that the risk can be ignored. The right policy is not a ban. The right policy is short-term use in line with the indication, and educating patients about the warning symptoms.

1. Introduction: Why Metamizole Again?

Metamizole stands at the centre of one of clinical pharmacology's oldest "banned or not" debates. In one country it is a mainstay of emergency departments and postoperative analgesia, while in another it has been off the market for almost fifty years. This contradiction can be explained by different national regulators giving different weight to the same evidence; but the real question is how reliable that evidence itself is.

In Germany in 2021, 14.1% of insured persons were prescribed metamizole at least once, a proportion that reached 37.9% among those over 80 [9]. More than 8 billion grams of metamizole are estimated to be sold in the EU in total [11]. For a drug used on this scale, measuring the risk correctly is critical both to avoid unnecessary bans and to prevent unnecessary deaths.

The thesis of this monograph is as follows: metamizole-induced agranulocytosis is real, but the risk estimates produced between the 1930s and the 1970s, which formed the

basis of regulatory decisions, contain serious methodological errors when viewed by today's standards of pharmacoepidemiology. This monograph re-evaluates them, showing the errors one by one from the primary documents and bringing them up to date.

As summarised in the Preface, information on metamizole is scattered. The aim of this monograph is to bring this information together under one roof. To our knowledge, no other study has re-analysed the agranulocytosis literature chronologically and methodologically from 1934 to the present. In no such study have the transfer of aminopyrine data to metamizole, the division of cases compiled from different sources by a local denominator, and denominator problems been examined one by one. The monograph also covers pharmacology, clinical efficacy, safety, regulatory history and economic context together. It also includes the work of our team in Ankara on vascular smooth muscle and epidural metamizole, most of which does not appear in other reviews. This monograph is not a systematic review; the literature search was not based on a pre-registered protocol. Its scope should therefore be judged within the limit of "to our knowledge".

2. Chemical and Historical Background

2.1 The pyrazolone family

Metamizole is a member of the pyrazolone family, which began with Ludwig Knorr's synthesis of antipyrine (phenazone) at the end of the 19th century. Aminophenazone (aminopyrine, trade name Pyramidon) was later added to the family. Metamizole was developed by Hoechst as the water-soluble methanesulfonate derivative of aminopyrine and launched in 1922 under the name Novalgin [9]. In the USA in the 1930s it was also sold under the name "Novaldin".

This chemical kinship is the key to the agranulocytosis story. The agranulocytosis epidemic seen in the USA and Europe in the 1930s was associated mainly with **aminopyrine**. When metamizole came on the market it was presented as a "safer" alternative to aminopyrine. Aminopyrine itself had a severe and frequent bone marrow toxicity and was therefore banned in most countries. Yet in the case series of that period the two drugs were frequently mentioned together, and in later reviews the high rates reported for aminopyrine were carried over to metamizole; in other words, metamizole paid for aminopyrine's sins.

A documented observation

Brogden [2] states this plainly in his review of the pyrazolones in *Drugs*: blood dyscrasias have received wide coverage in the medical literature, but they are **mostly associated with aminopyrine**, and the true incidence with dipyrone is **markedly lower than the frequently quoted incidence reported for amidopyrine more than 30 years ago**.

2.2 Nomenclature

The same molecule is known by different names in different regions: metamizole sodium (INN), dipyrone (USA, Latin America), novaminsulfon (Germany), analgin (Bulgaria, Russia and the former Eastern Bloc countries), Novalgin/Novaljin (Turkey). Failure to use all of these names in literature searches leads, in particular, to Eastern European data being overlooked.

3. Clinical Pharmacology

3.1 Pharmacokinetics

Metamizole is a prodrug. After oral intake it undergoes non-enzymatic hydrolysis in the gastric fluid to form its active metabolite **4-methylaminoantipyrine (4-MAA)**; the parent compound is not detected in plasma or urine after oral use. When given intravenously, the parent compound can be measured in the blood for about 15 minutes and is then again rapidly converted to 4-MAA [13]. In the liver, 4-MAA is converted by demethylation to the second active metabolite **4-aminoantipyrine (4-AA)** and by oxidation to the inactive end product 4-formylaminoantipyrine (4-FAA). 4-AA is acetylated by N-acetyltransferase 2 (NAT2) to 4-acetylaminoantipyrine (4-AAA). Thus, whatever the route of administration, the molecule that carries the clinical effect is the same: 4-MAA, followed by 4-AA.

To date 22 metabolites of metamizole have been identified; of these only two, 4-MAA and 4-AA, are pharmacologically active. The scheme below summarises the main metabolic pathways: hydrolysis yields 4-MAA, demethylation 4-AA, oxidation 4-FAA and acetylation 4-AAA.

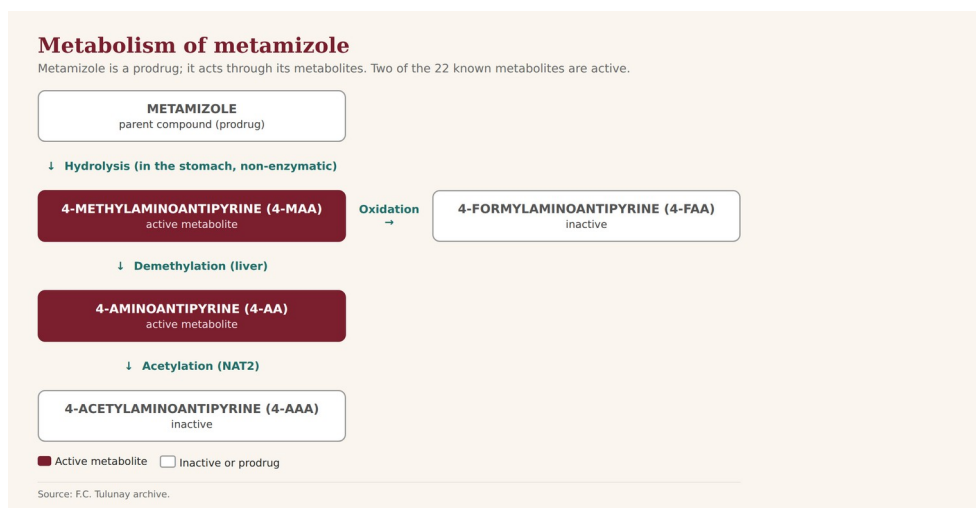


Figure 1. Metabolism of metamizole. The parent compound is hydrolysed to 4-methylaminoantipyrine (4-MAA); 4-MAA is converted by demethylation to 4-aminoantipyrine (4-AA) and by oxidation to 4-formylaminoantipyrine (4-FAA); 4-AA is acetylated to form 4-acetylaminoantipyrine. Of the 22 known metabolites, the two marked with an asterisk (4-MAA and 4-AA) are active. Source: F.C. Tulunay archive.

Parameter	Value	Clinical meaning
4-MAA bioavailability	Oral tablet 85%; IM 87%; rectal 54%	No difference in systemic exposure between the oral and IM routes

Parameter	Value	Clinical meaning
Time to peak concentration (t _{max}), oral	1.2–2.0 hours	Rapid absorption
4-MAA elimination half-life	2.6–3.5 hours	Dosing interval of 6–8 hours
4-AA half-life	3.8 h in fast acetylators; 5.5 h in slow acetylators	NAT2 polymorphism alters metabolite exposure
Plasma protein binding	Below 60% for the four main metabolites (4-MAA 58%)	Displacement interactions negligible
Urinary excretion	Four metabolites about 60% of the dose	
Old age	4-MAA clearance reduced by 33%	Dose reduction should be considered
Repeated dosing	4-MAA clearance reduced by 22%	Non-linear kinetics; accumulation
Liver cirrhosis	Clearance of all metabolites reduced	Dosing interval should be extended
Kidney disease	4-MAA clearance unchanged; 4-AAA and 4-FAA accumulate	

Table 1. Pharmacokinetics of metamizole metabolites [14] (product information for protein binding).

Metamizole is a clinically important **enzyme inducer**: it is a moderate inducer of CYP2B6 and CYP2C19, a weak inducer of CYP2C9 and a weak inhibitor of CYP1A2. Use of 500 mg three times daily can reduce the bioavailability of ciclosporin through CYP3A4 induction [9]. This interaction profile calls for caution, especially in long-term use and in transplant patients (Section 3.1.1). This knowledge has changed markedly over the last twenty years: a review from 2000 stated that drug interactions were very few and that blood levels needed monitoring only when it was used together with ciclosporin [15].

3.1.1 Pharmacokinetic drug interactions

Mechanism. The main metabolite of metamizole, 4-MAA, moderately induces CYP2B6, CYP2C19 and CYP3A4 and weakly induces CYP2C9 via the nuclear receptor CAR (constitutive androstane receptor); it weakly inhibits CYP1A2. CAR dependence has been demonstrated, but whether the receptor is activated directly or indirectly is not certain. Bachmann et al. [16] gave 12 healthy male volunteers metamizole 3 g a day (1 g × 3) for one week and measured the activity of six CYP enzymes with probe drugs (Table 2). CYP2D6 activity was unchanged.

Probe drug (enzyme)	Change in exposure (AUC)	Interpretation
Efavirenz (CYP2B6)	79% decrease	Moderate induction
Midazolam (CYP3A4)	68% decrease	Moderate induction
Omeprazole (CYP2C19)	66% decrease	Moderate induction
Flurbiprofen (CYP2C9)	22% decrease	Weak induction
Caffeine (CYP1A2)	79% increase (1.79-fold)	Weak inhibition
Metoprolol (CYP2D6)	No change	Not affected

Table 2. Effect of one week of metamizole use (1 g × 3/day) on CYP enzymes [16]. The percentages are changes in the exposure of the probe drugs, not rates of increase in the amount of enzyme.

Interactions documented in clinical practice. Tacrolimus: Serious falls in tacrolimus concentrations have been reported in transplant patients during concomitant use with metamizole; the evidence is at the level of case series [17]. This combination should be avoided or close therapeutic drug monitoring should be carried out. Ciclosporin: In a small placebo-controlled study, metamizole 1.5 g a day for four days caused a slight fall

in ciclosporin concentration, with no consistent change in AUC or trough levels; this finding should not be given the same weight as the tacrolimus findings. Bupropion: Metamizole reduced the AUC of the parent drug by about 31% while increasing the AUC of the active metabolite hydroxybupropion by 43% [18]; the net clinical effect cannot be inferred from the parent drug level alone.

Psychiatric drugs: In retrospective studies based on therapeutic drug monitoring databases, the median plasma concentration of sertraline was 67% lower [19] and the dose-adjusted concentration of quetiapine 69% lower [20] during concomitant use with metamizole; in the same database ibuprofen did not significantly change sertraline levels. Methadone: Cases have been reported in which withdrawal symptoms developed after metamizole was added; there is no reliable figure for the change in AUC. Apixaban and rivaroxaban: There is a mechanistic concern that exposure may be reduced through CYP3A4 induction; there are no confirmed human data specific to metamizole.

Clinical conclusion. In short-term use (a few days) the clinical significance of these interactions is limited; induction develops over days. However, with use beyond one week, in patients taking drugs with a narrow therapeutic range that are metabolised by CYP3A4, CYP2B6 or CYP2C19 (tacrolimus, ciclosporin, some antidepressants and antipsychotics, efavirenz), drug levels should be monitored or another analgesic chosen.

3.2 Route of administration: oral or parenteral?

This is the most important clinical conclusion to be drawn from the pharmacokinetics of metamizole, and it deserves particular emphasis with regard to practice in Turkey. Because metamizole is a prodrug, the effect is carried by the same metabolite (4-MAA) whatever the route of administration. Oral bioavailability (85%) and intramuscular bioavailability (87%) are practically identical. Oral absorption is rapid. Therefore, in a patient able to take it by mouth, the parenteral route **does not provide higher exposure**. Nor does the intramuscular route offer any advantage in speed: after a single IM injection the time to peak 4-MAA concentration is 1.7 hours (Dutch Medicines Evaluation Board, public assessment report) [21], i.e. no different from the 1.2–2.0 hours of the oral route. Only the intravenous route brings the effect forward markedly; but this gain is limited to a few tens of minutes and comes with the risks of hypotension and anaphylaxis described below.

Clinical data confirm this pharmacokinetic expectation. In a randomised study in Lima, 75 febrile children aged between 6 months and 6 years were given a single dose of oral ibuprofen (10 mg/kg), oral metamizole (15 mg/kg) or intramuscular metamizole (15 mg/kg). In all three groups fever fell by about 0.5 °C at 45 minutes and by about 1.0 °C at 120 minutes; **no difference between the groups was found at any of the 30, 45, 60, 90 or 120-minute time points** [22]. In a double-blind, double-dummy study of 293 patients with acute renal colic, too, it was the dose and not the route that was decisive: when metamizole 2 g was given IM or IV, analgesia was more marked and longer-lasting than with diclofenac, whereas metamizole 1 g, by whichever route, did not differ from diclofenac 75 mg [23].

While the added benefit of the parenteral route is limited, its added risk is documented. The product information of a metamizole product authorised in Europe (Nolotil, Spain)

[24] states clearly that parenteral administration is indicated **only in acute severe pain where the enteral route is not appropriate**; that parenteral administration **increases the risk of anaphylactic or anaphylactoid reactions**; that **the most frequent cause** of a critical fall in blood pressure and shock **is injecting faster than necessary**; and that intravenous injection must be given very slowly with equipment for treating shock at hand. Metamizole-induced reactions, comprising non-allergic (pseudoallergic) reactions, true anaphylaxis and delayed-type allergy, have been described as a "paradigm" of drug hypersensitivity [25]. The Berne Comprehensive Hospital Drug Monitoring programme has also documented metamizole-induced falls in systolic blood pressure [26].

The contradiction between the oral and parenteral single doses. In the product information the maximum single dose is 1 g by the oral route and 2.5 g by the parenteral route. This difference cannot be explained pharmacologically. Whatever the route, the effect of metamizole is carried by the same metabolite (4-MAA), and oral bioavailability (85%) is practically identical to intramuscular bioavailability (87%); systemic exposure at the same dose is therefore also the same (Sections 3.1 and 3.2). Nor can the difference be justified on safety grounds. Agranulocytosis is not dose-dependent. The risk of hypotension, shock and anaphylaxis, on the other hand, is higher with the parenteral route; if the dose of one route were to be kept lower, it should have been the intravenous route, not the oral one. Clinical data also support high oral doses: a single oral dose of 2 g was found to be more effective than 1 g [27], and in cancer pain oral metamizole 2 g every 8 hours (6 g a day) was used for a week and found to be equivalent to morphine [28]. The most likely explanation for the difference is historical, not scientific: the tablet was produced as 500 mg and the ampoule as 2.5 g in 5 ml for emergencies such as colic; the parenteral route is used under medical supervision and the oral route at home. This contradiction is a clear indication that the dose limits of metamizole are based not on a systematic dose-response study but on the way the products came onto the market. That a century-old drug is dosed by empirical methods is food for thought.

Clinical principle

If the patient can take it by mouth, metamizole should be given orally. The intramuscular route offers no gain in speed over the oral route; the intravenous route brings the effect forward by only a few tens of minutes. By contrast, the parenteral route increases the risk of pseudoanaphylactic or anaphylactic shock and hypotension.

The parenteral route should be restricted to patients who are vomiting, unable to swallow, unconscious or unable to take food by mouth. Intravenous administration should be slow (preferably by infusion), the patient should be monitored and equipment for treating shock should be at hand.

The habitual IM/IV "Novalgin" administration in emergency departments and primary care in Turkey should be reviewed in this light.

Onset of action by route of administration. According to the product information harmonised by the European Medicines Agency in 2019, a marked analgesic effect is expected **30-60 minutes** after oral administration and **about 30 minutes** after parenteral administration (EMA, Article 31, Annex III). The EMA document does not quantify the onset times of the intravenous and intramuscular routes separately. Taking clinical observations and pharmacokinetic data together, the approximate values are as follows:

Route of administration	First analgesic effect	Marked clinical effect	Peak effect	Basis
Intravenous (IV)	May begin within 5-10 minutes	15-30 minutes	About 20-45 minutes	EMA: about 30 min for the parenteral route; onset with 2.5 g IV metamizole in biliary colic 10.9 ± 5.8 min [29]; our clinical observation: spasmolytic effect 5-10, analgesic effect 20-30 min
Intramuscular (IM)	15-30 minutes	About 30 minutes	Usually 1-2 hours	EMA: about 30 min for the parenteral route; 4-MAA t _{max} after IM 1.7 hours
Oral	About 30 minutes	30-60 minutes	About 1-2 hours	EMA: 30-60 min; 4-MAA t _{max} 1.2-2.0 hours [14]

Table 3. Approximate onset of action of metamizole by route of administration. EMA values are from the harmonised product information and t_{max} values from pharmacokinetic studies; IV onset was measured in a randomised study in biliary colic (mean 10.9 minutes); IM values and peak times are based on clinical observation.

With intravenous administration analgesia begins early: in biliary colic the onset of effect with 2.5 g intravenous metamizole was measured at a mean of 10.9 ± 5.8 minutes, significantly shorter than with tramadol (15.8 minutes) [29]. Clinical observations also show that analgesia begins within the first 5-10 minutes, but that the strongest analgesic effect usually appears at 20-45 minutes. The statements "IV onset of effect 5-10 minutes" and "marked clinical effect 20-30 minutes" therefore do not contradict each other. Oral metamizole is rapidly converted to 4-MAA in the gastrointestinal tract; 4-MAA reaches peak concentration in 1.2-2.0 hours [14]. The analgesic effect can begin before the peak plasma level, within about 30 minutes; the dosing interval of 6-8 hours (EMA) indicates that the effect lasts several hours.

Summary statement for clinical use

The analgesic effect of metamizole **begins in about 5-15 minutes with IV administration, 15-30 minutes with IM administration and 30-60 minutes with oral administration**; the full or strongest effect appears later.

The intramuscular route offers no meaningful gain in speed over the oral route; if the patient can take it by mouth, the oral route should be preferred.

Rapid administration of IV metamizole increases the risk of serious hypotension; **the injection should be given very slowly, and the bolus should not be speeded up to obtain a rapid effect.**

A detail: the difference between IM and IV. The absence of a difference in systemic exposure between the oral and parenteral routes does not mean that the two parenteral routes are clinically equivalent. The Cochrane review of renal colic reports that intravenous metamizole is more effective than intramuscular metamizole [30].

Therefore, if the parenteral route is genuinely needed (a vomiting patient, a patient unable to swallow, severe colic), the route of choice is the intravenous route given at the correct rate; intramuscular injection has no additional advantage.

Continuous intravenous infusion. In our experience, long-term use of metamizole by intravenous infusion was a frequent practice in Turkey in the past; however, this practice has not been documented in publications. In a randomised study in Germany (203 patients) in which a mixture of metamizole and tramadol was given after abdominal surgery either by continuous intravenous infusion or by patient-controlled analgesia (PCA) pump, pain scores did not differ between the two methods; PCA resulted in lower tramadol consumption and more responders [31]. Pharmacologically, infusion reduces the risk of a fall in blood pressure caused by rapid injection (Section 3.2.1) and keeps the level of the active metabolite 4-MAA more stable. The total daily dose should not exceed 5 g, and in long-term use the patient should be informed about the symptoms of agranulocytosis.

3.2.1 Rapid intravenous injection: hypotension, syncope and death

When metamizole-related deaths are discussed, there is a cause that deserves as much attention as agranulocytosis but is talked about far less: **rapid intravenous injection of the drug**. When metamizole is given rapidly, severe hypotension, syncope and shock can develop. The EMA's harmonised product information states that intravenous injection should be given "very slowly" to minimise the risk of a hypotensive reaction (EMA, Article 31, Annex III). National product information is even more explicit: the most frequent cause of a critical fall in blood pressure and shock is injecting faster than necessary; intravenous injection must be given very slowly, haemodynamic parameters must be monitored and equipment for treating shock must be at hand [24]. The Berne Comprehensive Hospital Drug Monitoring programme has also documented metamizole-induced falls in systolic blood pressure [26].

This reaction depends largely not on the dose but on the **rate of administration**, and is therefore preventable. The usual dose of 2.5 g for colic pain (5 ml from a 500 mg/ml ampoule) should be given **over at least 5 minutes**, i.e. at about 1 ml per minute [32] (intravenous injection "should not be faster than 1 ml [500 mg metamizole] per minute"; "rapid intravenous injection increases the risk of a hypotensive reaction"). Administration as a short diluted infusion reduces this risk further. Metamizole injections given as a "rapid bolus" in emergency departments are a preventable source of the deaths attributed to metamizole, and putting these deaths in the same basket as agranulocytosis gives a false picture of the drug's risk profile.

3.2.2 Pseudoanaphylactic and anaphylactic reactions

The second cause of shock seen with metamizole is hypersensitivity reactions. These can present as IgE-mediated true anaphylaxis or as non-immune pseudoanaphylactic (anaphylactoid) reactions [25]. The risk is higher with parenteral administration than with oral use [24]; this is another reason supporting the "oral first" principle of Section 3.2.

However, pseudoanaphylactic shock **is not specific to metamizole; it can be seen with almost all analgesics**. Acetylsalicylic acid and the other NSAIDs are well-known causes of cross-intolerance reactions due to cyclooxygenase-1 inhibition; parenteral opioids can also cause anaphylactoid pictures through histamine release. Comparative data support this: the incidence of anaphylaxis with metamizole has been calculated at 8.1 per 10,000 exposed persons (95% CI 3.5–19), the same level as the 7.2 per 10,000 reported for diclofenac [9]. In a meta-analysis of 79 studies assessing short-term use, too, the frequency of adverse events with metamizole did not differ from that with placebo, paracetamol or NSAIDs [5].

Preventing metamizole-related deaths

Rapid IV injection must not be given. Metamizole 2.5 g should be given over at least 5 minutes (about 1 ml per minute) or diluted as an infusion; the patient should be lying down and blood pressure should be monitored.

If the patient can take it by mouth, the oral route should be chosen; the parenteral route increases the risk of both hypotension and anaphylaxis.

A history of previous pyrazolone reaction or analgesic intolerance (asthma, urticaria) should be sought.

Wherever parenteral administration is carried out, adrenaline, fluids and airway equipment for treating shock should be at hand.

Against agranulocytosis, the patient should be educated about fever, sore throat and mouth ulcers; it should not be used together with methotrexate (Section 14).

3.3 Mechanism of action

Metamizole is a pyrazolone derivative with potent analgesic and antipyretic, marked spasmolytic, but relatively weak anti-inflammatory effects. It is not a classical drug acting through a single receptor or enzyme. Current data show that its effect arises from several complementary mechanisms; yet a single, definitive molecular mechanism explaining all its clinical effects has not yet been established. A comprehensive pharmacology review from 2025 also states that the exact mechanism is not fully known [8].

- Conversion to the active metabolites (4-MAA, 4-AA)
- Redox-dependent modulation of the cyclooxygenase–prostaglandin system
- The endocannabinoid system and descending pain inhibitory pathways from the PAG–RVM
- Inhibition of TRPA1 channels
- The nitric oxide–cGMP–ATP-sensitive potassium channel pathway
- Suppression of intracellular calcium mobilisation and smooth muscle relaxation
- Suppression of the prostaglandin-dependent and -independent components of fever

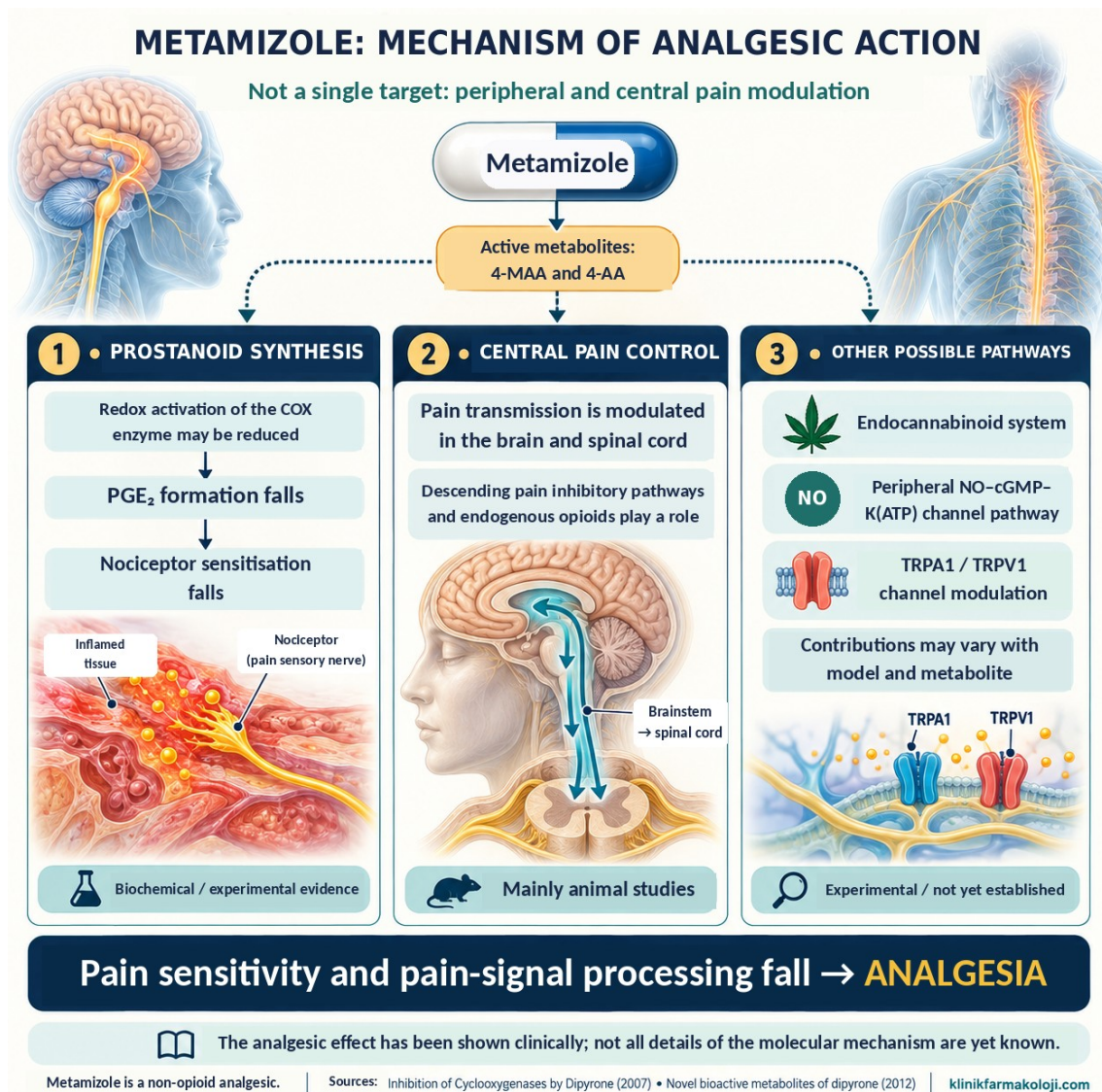
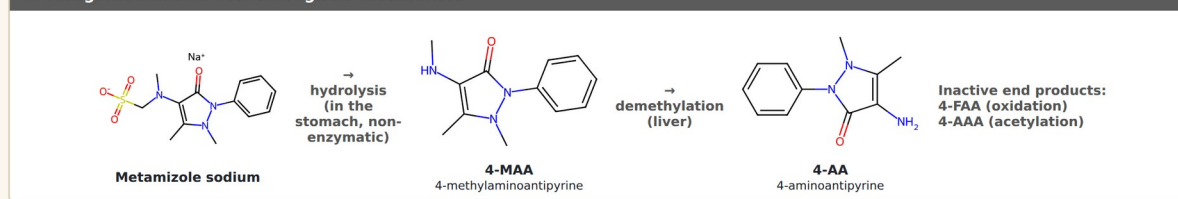


Figure 2. Overview of the mechanism of the analgesic action of metamizole: prostanoid synthesis, central pain control and other possible pathways. The analgesic effect has been demonstrated clinically; not all details of the molecular mechanism have yet been elucidated.

Proposed mechanisms of the analgesic action of metamizole

Analgesia does not depend on a single mechanism; the relative contribution of the pathways in humans is not known with certainty.

Prodrug: metamizole acts through its metabolites



1. Suppression of prostaglandin synthesis

Arachidonic acid → **COX-1 / COX-2** → PGE₂ ↓
The effect is mainly central; it is weak in inflamed tissue, so the anti-inflammatory effect is weak.

COX-3: a splice variant described in canine brain; it has not been shown to be a functional enzyme in humans.

in vitro COX-3 hypothesis disputed

2. Descending pain inhibitory system

PAG → RVM → dorsal horn of the spinal cord
Metamizole activates the descending inhibitory pathway in the PAG; the effect is mediated in the RVM by **endogenous opioids**.

Naloxone partly reverses the effect. Metamizole does not bind directly to the opioid receptor.

animal experiment

3. Endocannabinoid system

4-MAA and 4-AA + arachidonic acid → **arachidonoyl amides** → CB1 / CB2
The effect in the PAG is reduced by the CB1 antagonist AM251.

How much of these metabolites is formed in humans at therapeutic doses is not known.

animal experiment

4. Peripheral NO-cGMP-K⁺ pathway

NO → cGMP → protein kinase G → **K(ATP) channels open** → hyperpolarisation of the nociceptor
Directly antagonises established nociceptor sensitisation.

In some pain models blockade of this pathway did not change the effect.

animal experiment

Level of evidence: shown in humans animal experiment in vitro / ex vivo disputed or conflicting

Source: Sections 3.3.2–3.3.6 of the monograph (Chandrasekharan 2002; Kis 2005; Vasquez and Vanegas 2000; Rogosch 2012; Escobar 2012; Duarte 1992; Beirith 1998).

Figure 3. Proposed mechanisms in the analgesic action of metamizole and their levels of evidence: prodrug and active metabolites, four main pathways. Details are given in Sections 3.3.1–3.3.6.

3.3.1 The active metabolites

Metamizole itself is unstable in biological fluids; a major part of the pharmacological effect arises through 4-MAA and, at lower concentrations, through 4-AA. 4-FAA and 4-acetylaminoantipyrine (4-AAA) are clinically inactive or only weakly active metabolites. Human studies have shown that 4-MAA is metabolised in the liver by cytochrome P450 enzymes to 4-AA and 4-FAA, the most important enzyme at this step being **CYP1A2** [33]. Therefore, in studying the effect of metamizole, it is the effects of 4-MAA and 4-AA, rather than of the parent molecule, that need to be assessed.

3.3.2 Cyclooxygenase and prostaglandin synthesis

COX inhibition different from that of classical NSAIDs. Classical NSAIDs such as indometacin, naproxen and ibuprofen inhibit COX-1 and/or COX-2 by binding to the arachidonic acid-binding catalytic channel of cyclooxygenase. 4-MAA and 4-AA can also reduce COX-1 and COX-2 activity and PGE₂ production, but they do not do so by occupying the arachidonic acid-binding site of the enzyme. Pierre et al. [34] showed that these metabolites suppress activity by scavenging the radicals that initiate the catalytic cycle of COX or by reducing the oxidised states of the enzyme; that is, the metabolites interfere with the oxidation-reduction cycle in the peroxidase part of the enzyme (Figures 4 and 5).

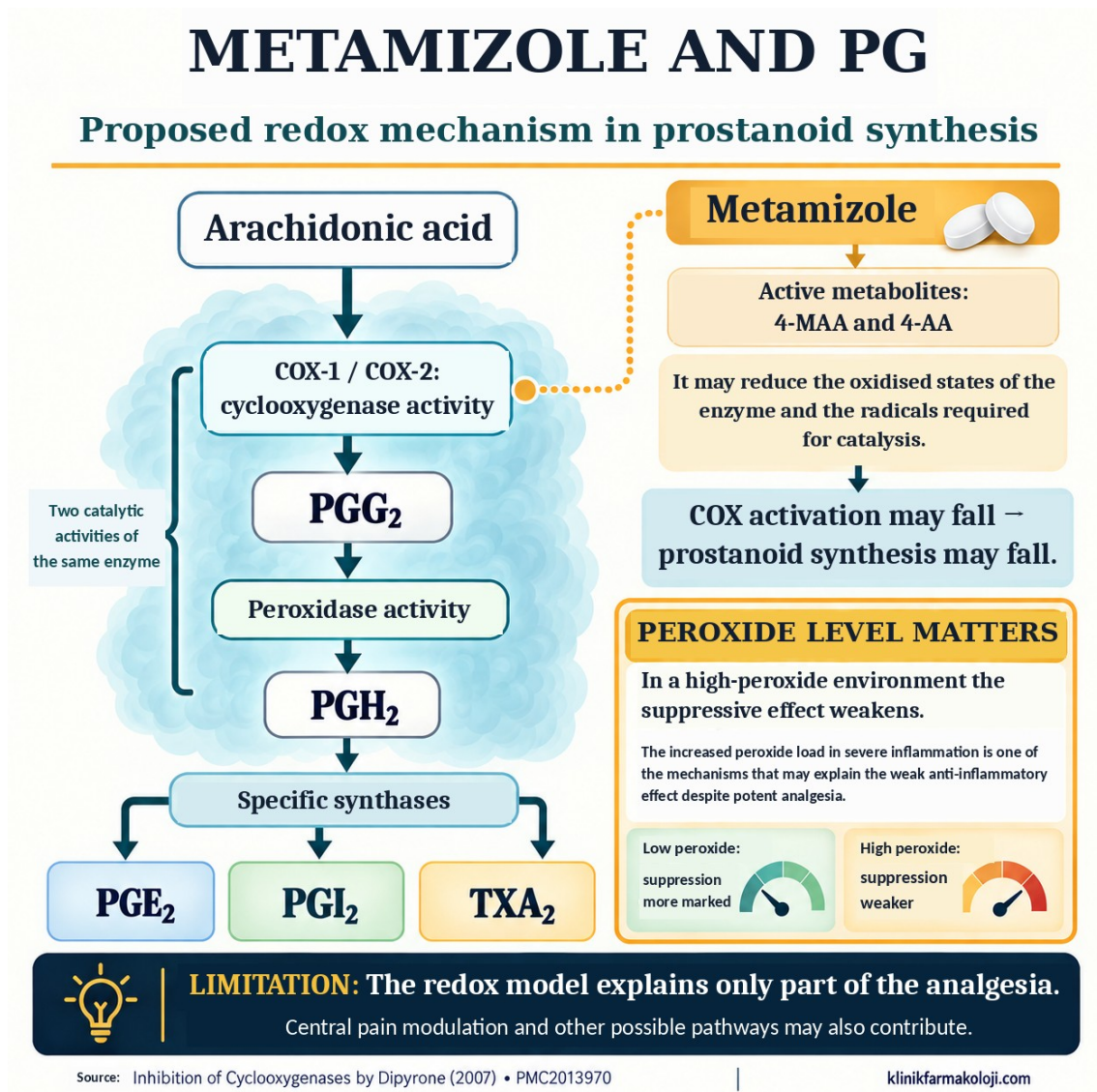


Figure 4. Metamizole and prostaglandin synthesis: the proposed redox mechanism in prostanoid synthesis and the importance of the peroxide level [34].

Redox effect of metamizole metabolites on cyclooxygenase

Unlike NSAIDs, 4-MAA and 4-AA do not sit in the arachidonic acid-binding channel of the enzyme; they reduce the radical that initiates catalysis and the oxidised states of the enzyme.

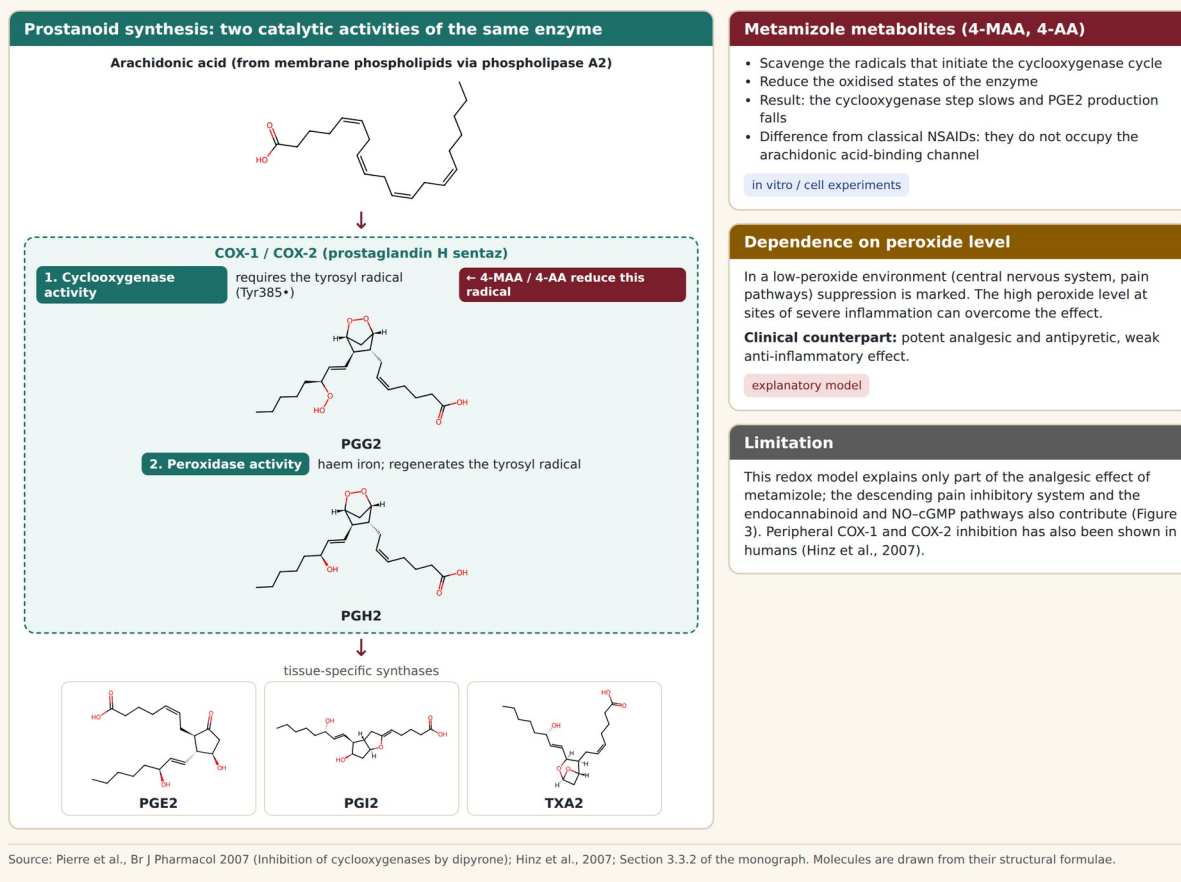


Figure 5. Redox effect of metamizole metabolites on cyclooxygenase: 4-MAA and 4-AA reduce the tyrosyl radical that initiates catalysis and the oxidised states of the enzyme; the effect weakens in a high-peroxide environment. Details are given in Section 3.3.2.

Dependence of the effect on the local peroxide level. While the COX-suppressing effect may be marked at the low peroxide concentrations of the central nervous system and some peripheral tissues, the high peroxide concentration at sites of severe inflammation can overcome this effect. This property is one of the most plausible models explaining why metamizole is a potent analgesic and antipyretic but a weak anti-inflammatory. Nevertheless, metamizole is not merely a "central COX inhibitor": in humans, significant inhibition of peripheral COX-1 and COX-2 activity has been shown in relation to 4-MAA and 4-AA concentrations [35].

Redirection of prostaglandin synthesis. In some cell-free experiments 4-MAA has been reported to redirect the intermediate PGG2 towards PGF2 α -like products rather than stopping prostaglandin synthesis altogether; however, this finding has not been replicated in all cell systems [34]. It is an interesting mechanism whose clinical significance has not yet been established.

3.3.3 Is "COX-3 inhibition" a correct explanation?

In older reviews the analgesic and antipyretic effect of metamizole was often explained by "COX-3 inhibition". Chandrasekharan et al. [36] cloned from canine cerebral cortex a splice variant of the COX-1 gene that retains intron 1 and named it COX-3. This enzyme

was selectively inhibited by acetaminophen (paracetamol), phenacetin, antipyrine and **dipyrone**, and was found to be strongly expressed in brain and heart; the authors suggested that COX-3 inhibition might be the primary central mechanism by which these drugs reduce pain and possibly fever.

This statement should be used with caution today. COX-3 was first described in canine brain; it has not been confirmed that it is an equally functional COX enzyme in humans, and the pharmacological significance of the human protein product is uncertain. It has been shown that in humans retention of intron 1 shifts the reading frame and no functional enzyme is formed [37]; in the paracetamol literature, too, the COX-3 hypothesis has largely been abandoned for the same reason [38]. Therefore **the statement "metamizole acts by inhibiting COX-3" is not established human pharmacology**. The lasting contribution of the hypothesis is that it led metamizole and paracetamol to be considered together as "centrally acting" analgesics; this central action is now explained by redox-dependent modulation of COX-1/COX-2, endocannabinoid mechanisms and ion channels.

3.3.4 Central analgesia and the descending pain inhibitory system

The analgesic effect of metamizole cannot be attributed solely to reduced prostaglandin at the site of inflammation; the drug also activates the brain's pain control networks. Pathways descending from the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) to the dorsal horn of the spinal cord suppress the transmission of nociceptive signals at the spinal level. It was shown early on that a central component, manifested by activation of inhibitory systems in the PAG, plays a role in the analgesic effect of metamizole [39]. In animal experiments, metamizole given into the PAG reduced inflammation-induced spinal neuronal hyperactivity, activated the descending antinociceptive system via the RVM, and lost its analgesic effect when the PAG-RVM connection was blocked [40].

The contribution of endogenous opioids. Vasquez and Vanegas [41] showed that metamizole microinjected into the PAG (100 µg/0.5 µl) suppressed the response of spinal wide-dynamic-range neurons to a noxious stimulus and that naloxone applied to the RVM (0.5 µg/0.5 µl) reversed this inhibition; that is, the effect of metamizole in the PAG is mediated by endogenous opioids in the RVM. The studies of Tortorici and Vanegas also showed that endogenous opioids are partly responsible for the analgesic effect of metamizole: the antinociception produced by metamizole given into the PAG (100 µg) through medullary "off" and "on" cells was partly reversed by intravenous or intra-PAG naloxone [42]; the antinociceptive effect of systemic or intra-PAG metamizole began within 5 minutes and peaked at 30–60 minutes [43]. Metamizole has also been reported to bind to peripheral opioid receptors and to stimulate beta-endorphin release [44]. A similar picture exists in peripheral tissue: it has been shown that metamizole given locally into the rat paw is completely hydrolysed to 4-MAA, and that the antihyperalgesic effect of 4-MAA is completely reversed by the CB2 antagonist AM630, naloxone and the selective kappa opioid antagonist nor-BNI, but is unchanged by mu and delta antagonists [45]. The antinociceptive effect on spinal neurons of intravenous metamizole (200 mg/kg), a clinically relevant mode of administration, was also abolished by naloxone applied to the PAG, the nucleus raphe magnus or directly to the spinal cord [46].

Repeated administration of metamizole into the PAG has also been shown to produce opioid tolerance [47]. Endocannabinoid (CB1) and opioidergic mechanisms are not mutually exclusive; they are thought to work together along the PAG-RVM axis. This opioidergic component is the pharmacological basis for metamizole having been found equivalent to morphine in some clinical studies (Section 3.4). The contribution of endogenous opioids has also been shown in the periphery: in mice, naloxone completely abolished the local antinociceptive effect of metamizole injected intradermally into the tail, but did not change the effect of diclofenac, ketorolac or salicylates [48] (Section 15.4).

METAMIZOLE: ANALGESIC EFFECT

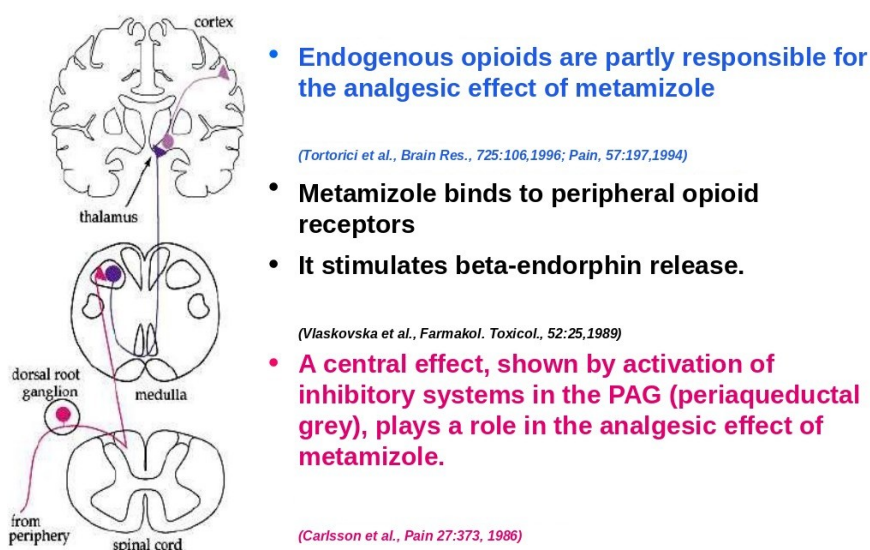


Figure 6. Central mechanisms in the analgesic action of metamizole: endogenous opioids are partly responsible for the effect [42, 43]; metamizole binds to peripheral opioid receptors and stimulates beta-endorphin release [44]; a central effect demonstrated by activation of inhibitory systems in the PAG plays a role [39]. Left, pain transmission and descending inhibition pathways: cortex, thalamus, PAG, medulla and spinal cord. Source: F.C. Tulunay archive.

3.3.5 The endocannabinoid system

Arachidonoyl amide metabolites. Conjugation of 4-MAA and 4-AA with arachidonic acid can form new lipid metabolites such as arachidonoyl-4-MAA and arachidonoyl-4-AA; these substances have shown the capacity to bind to CB1 and CB2 receptors [49]. This pathway, reminiscent of the AM404 metabolite of paracetamol, is of interest; however, the extent to which these metabolites are formed in humans at therapeutic doses and their contribution to clinical analgesia are uncertain.

CB1 receptors and central analgesia. In rats with inflammation, the antinociceptive effect of metamizole at the level of the PAG was reduced by the CB1 antagonist AM251; CB1 blockade in the PAG or the RVM was sufficient to reduce the effect [50]. The possible sequence is as follows: metamizole or its metabolites increase endocannabinoid transmission in the PAG; CB1 receptors are activated; GABA release is reduced; inhibition of PAG output neurons is lifted (disinhibition); the descending pain inhibitory pathway to the spinal cord via the RVM is activated and spinal nociceptive transmission

is reduced. This mechanism is based mainly on animal experiments; it has not been directly confirmed in humans.

Peripheral CB1 and metabolite-specific effects. In a rat model of peripheral pain the antihyperalgesic effect of 4-AA was abolished by a CB1 antagonist and the CB2 antagonist was ineffective; by contrast, the peripheral effect of 4-MAA was found to be associated mainly with cGMP and ATP-sensitive potassium channels [51]. Different metabolites may use different signalling pathways. CB1-dependent desensitisation of TRPV1 in sensitised primary sensory neurons also contributes to the analgesic effect [52].

3.3.6 The nitric oxide-cGMP-K(ATP) channel pathway

Part of the peripheral analgesic effect of metamizole is explained by the following signalling chain: metamizole/4-MAA → NO → soluble guanylate cyclase → increased cGMP → protein kinase G → opening of ATP-sensitive potassium channels. Opening of these channels increases K⁺ efflux from the neuron, hyperpolarises the cell membrane, reduces the opening of voltage-sensitive Ca²⁺ channels, and lowers nociceptor excitability and neurotransmitter release.

In pharmacological experiments the effect of metamizole was reduced or abolished by nitric oxide synthase inhibitors, soluble guanylate cyclase inhibitors, protein kinase G inhibitors and the K(ATP) channel blocker glibenclamide; this pathway has been shown particularly in models of peripheral hyperalgesia induced by PGE2 [53, 54]. Its clinically important consequence is this: NSAIDs prevent developing hyperalgesia, whereas metamizole **directly antagonises established nociceptor sensitisation**; that is, it is also effective in pain that has already started. In some pain models, however, nitric oxide or K(ATP) blockade did not change the effect of metamizole [55]; the contribution of this pathway appears to depend on the tissue, the pain model, the site of administration and the active metabolite.

A recent review [13] presents the L-arginine-NO-cGMP-K⁺ channel pathway as the peripheral and spinal analgesic mechanism of metamizole, but attributes the spasmolytic effect not to this pathway but, on the basis of the guinea-pig trachea study of Gülmez et al. [56], to suppression of inositol phosphate-mediated intracellular Ca²⁺ release. The contribution of this pathway in smooth muscle has not been directly shown; in rabbit aorta, methylene blue (a soluble guanylate cyclase inhibitor) did not change the relaxant effect of metamizole [57].

3.3.7 Inhibition of TRPA1 ion channels

TRPA1 is an ion channel found particularly on small-diameter nociceptive sensory neurons and activated by oxidative stress products, formalin, acrolein and some irritants. Its activation leads to Ca²⁺ and Na⁺ influx, neuronal depolarisation, release of substance P and CGRP, pain and neurogenic inflammation.

Nassini et al. [58] showed that metamizole and some pyrazolone derivatives inhibit TRPA1-induced calcium influx and electrical currents. Metamizole reduced mechanical allodynia in the formalin, carrageenan, partial sciatic nerve ligation and bortezomib neuropathy models. Notably, in the carrageenan model analgesia was achieved while

tissue PGE2 levels were unchanged; this indicates that TRPA1 inhibition may be a prostaglandin-independent analgesic mechanism. The same study reported that 4-MAA and 4-AA did not inhibit TRPA1 directly, and that the effect might be related to metamizole itself or to shorter-lived intermediates. Another study reporting that the metabolites activate TRPA1 and TRPV1 in a redox-dependent manner [59] shows that the relationship is complex. Although the TRPA1 findings rest on strong experimental evidence, their quantitative contribution to clinical analgesia is not yet known.

3.3.8 Spasmolytic effect

One of the important properties distinguishing metamizole from classical NSAIDs is that it reduces smooth muscle contraction; this effect has been studied in biliary, ureteric, gastrointestinal and airway smooth muscle. Smooth muscle contraction generally proceeds through the following chain: Gq-coupled receptor → phospholipase C → inositol trisphosphate (IP3) → Ca^{2+} release from the sarcoplasmic reticulum → activation of calmodulin-myosin light chain kinase → contraction.

In the study by Gülmez, Gürdal and Tulunay [56], metamizole relaxed tracheal smooth muscle contractions induced by histamine and ATP, reduced inositol phosphate accumulation and suppressed the ATP-induced rise in intracellular Ca^{2+} , but did not markedly reduce the contraction induced by KCl, which depolarises the cell membrane directly. That indometacin did not prevent the relaxation showed that the effect is independent of COX inhibition. These findings suggest that metamizole reduces receptor-mediated inositol phosphate formation and Ca^{2+} release from intracellular stores.

Accordingly, the strongest explanation of the spasmolytic effect is: reduced IP3 → reduced intracellular Ca^{2+} → reduced myosin light chain kinase activation → smooth muscle relaxation. Opening of K(ATP) channels and, in some tissues, β_2 -adrenoceptor-mediated relaxation have also been proposed; however, these mechanisms have not been shown as consistently as the reduction in intracellular Ca^{2+} . This is the pharmacological basis of its clinical superiority in renal and biliary colic. In biliary colic this basis is supported in humans by sphincter of Oddi manometry; in renal colic part of the effect may also be explained by suppression of the prostaglandin-mediated component that raises intraureteric pressure during obstruction (Section 15.6).

Blockade of intracellular Ca^{2+} release due to reduced inositol phosphate synthesis is also accepted in pharmacology reviews as the explanation of the spasmolytic effect of metamizole [4]. Some reviews attribute this to the metabolites suppressing phospholipase C directly or indirectly via G protein-coupled receptors [60]; the same review states that these mechanisms require further research. What has been shown experimentally is a reduction in receptor-mediated inositol phosphate accumulation, not direct inhibition of phospholipase C [56]. The β_2 -adrenoceptor mechanism proposed for the biliary tract rests on rat studies: β_2 blockade abolished the delaying effect of metamizole on gastric emptying [61]. Whether this mechanism applies in the human biliary tract has not yet been shown [62]. The finding measured in humans is that 2.5 g IV metamizole lowers the basal pressure of the sphincter of Oddi [63]; in guinea-pig small intestine metamizole did not impair peristalsis [64].

According to Fendrich's review [15], the spasmolytic effect of metamizole on the sphincter of Oddi and on urinary tract and gallbladder smooth muscle is comparable to that of butylscopolamine, but without the anticholinergic side effects of butylscopolamine.

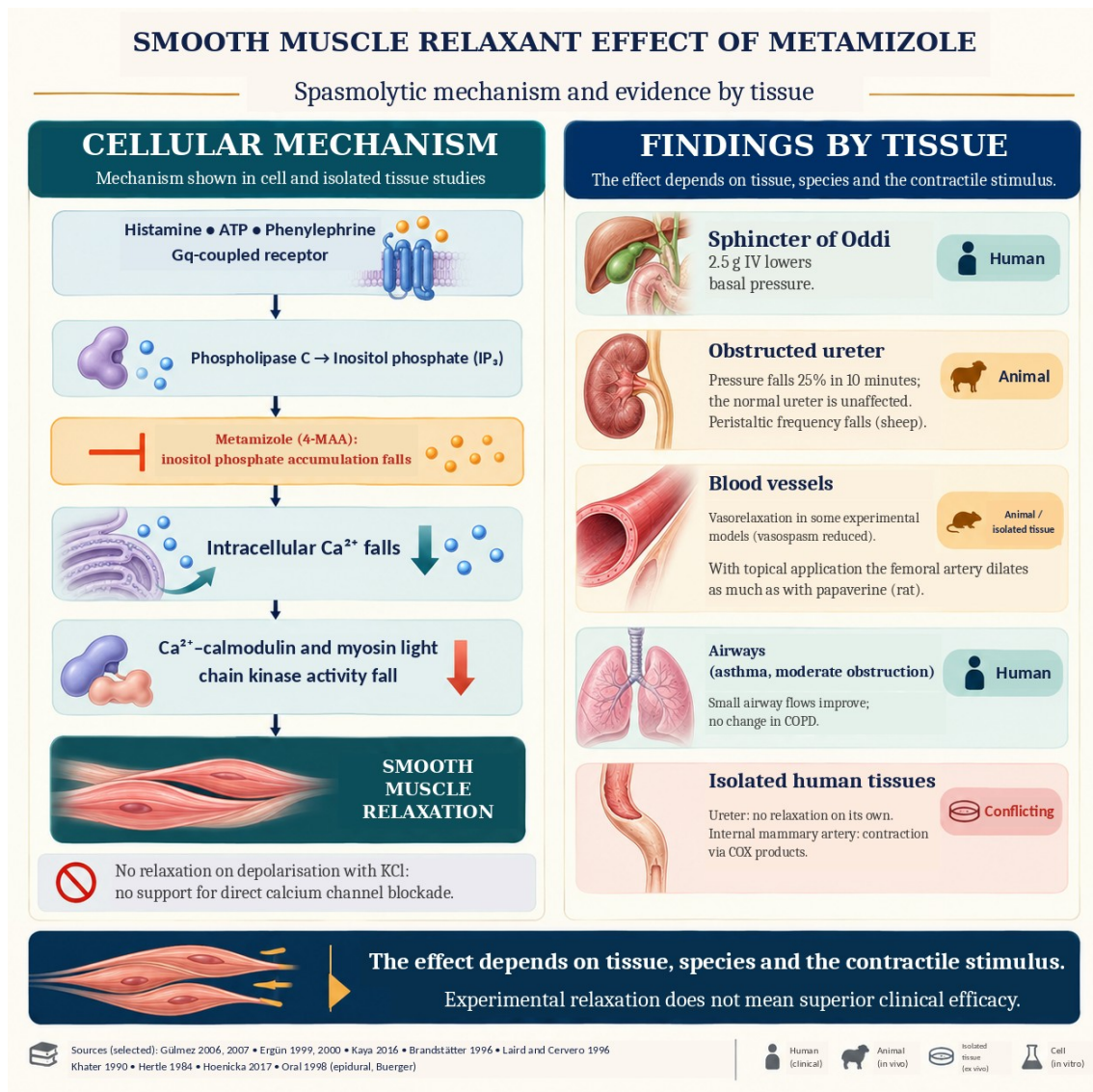


Figure 7. Smooth muscle relaxant effect of metamizole: cellular mechanism and findings by tissue. The effect depends on the tissue, the species and the stimulus that initiates contraction. Details are given in Sections 3.3.8, 3.5 and 15.6.

3.3.9 Antipyretic effect

In fever, cytokines activate COX-2 and microsomal prostaglandin E synthase-1; the PGE₂ formed raises the body temperature set point via EP₃ receptors in the hypothalamus. Metamizole lowers fever, but the mechanism is more complex than the explanation "it stops hypothalamic PGE₂ synthesis". In the rat study of Malvar et al. [65], metamizole abolished fever induced by lipopolysaccharide and endothelin-1 and reduced the rise of PGE₂ in cerebrospinal fluid, but did not abolish the increase of PGE₂ in hypothalamic tissue; the antipyretic effect cannot be reduced to direct inhibition of hypothalamic PGE₂.

There are also differences between the metabolites: 4-MAA can suppress both PGE₂-dependent and PGE₂-independent fever and can produce hypothermia, whereas 4-AA suppresses mainly PGE₂-dependent fever [66]. This suggests that 4-MAA also has central targets in thermoregulation that are independent of prostaglandin synthesis. Reduction of peripheral or cerebrospinal PGE₂ signalling, the endocannabinoid system, endogenous antipyretic pathways and modulation of endothelin and cytokine signalling are possible additional mechanisms; their order of clinical importance is uncertain.

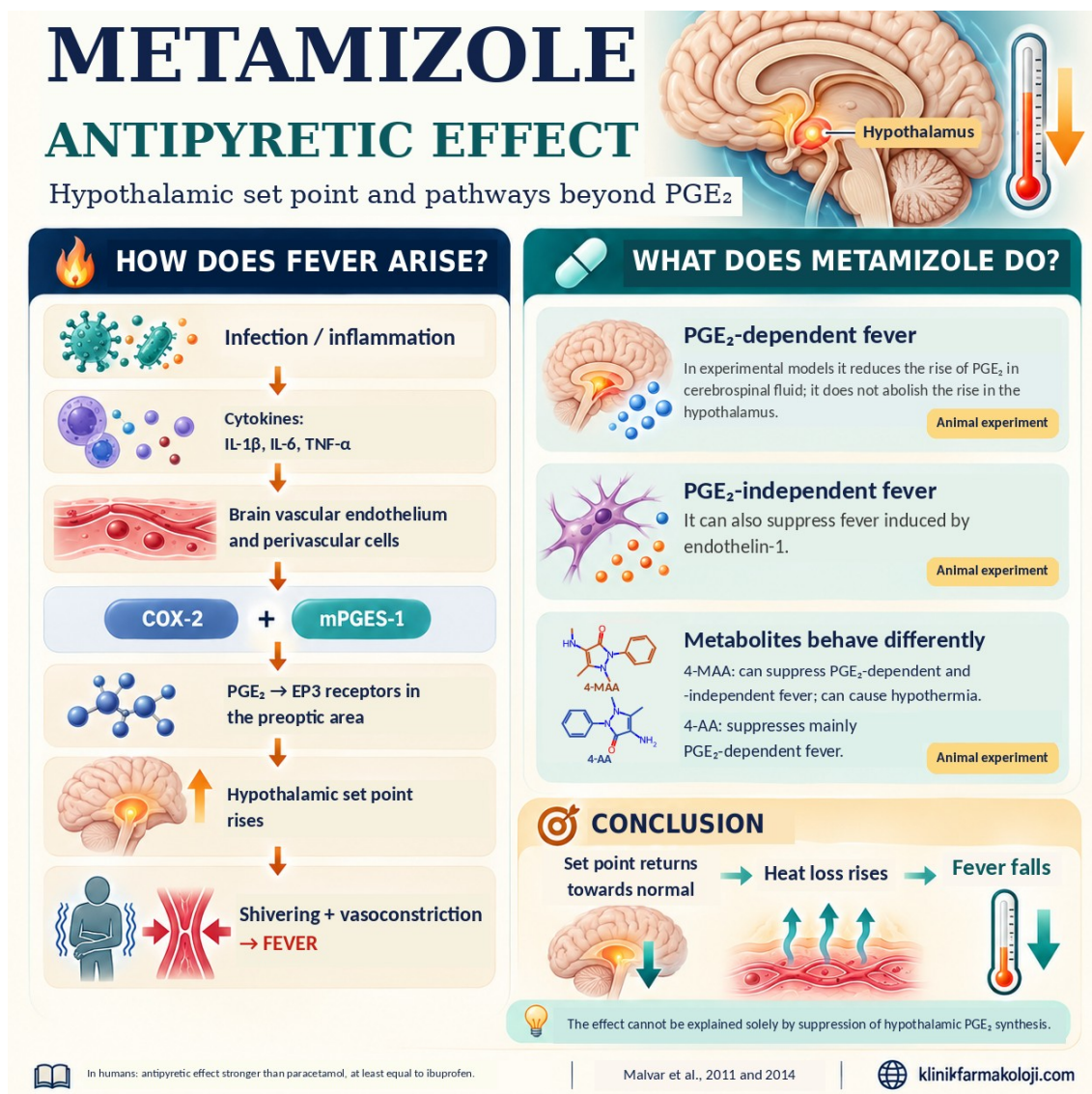


Figure 8. Antipyretic effect of metamizole: the hypothalamic set point, PGE₂-dependent and -independent pathways [65, 66]. Details are given in Section 3.3.9.

3.3.10 Why is the anti-inflammatory effect weak?

- Weakening of COX inhibition at high peroxide concentrations
- Inability to maintain sufficient active metabolite concentration at the site of inflammation
- No prolonged, strong binding to the classical active site of COX
- A large part of the analgesia derives from COX-independent central and neuronal mechanisms

- More limited effect than classical NSAIDs on neutrophil migration, cytokine production and vascular inflammation

It is therefore pharmacologically more accurate to describe metamizole not as "a potent NSAID" but as **a multimodal analgesic, antipyretic and spasmolytic drug**.

Mechanism	Main consequence	Quality of evidence
Conversion to 4-MAA and 4-AA	Emergence of the pharmacological effect	Human pharmacokinetics; strong
Redox modulation of COX-1/COX-2	Reduced prostaglandin synthesis	Cellular, animal and human data; strong-moderate
COX-3 inhibition	Presumed central analgesia	Not confirmed in humans; weak
PAG-RVM descending inhibition	Central analgesia	Animal experiments; moderate
Endocannabinoid-CB1 system	Central and peripheral analgesia	Mainly animal data; moderate
NO-cGMP-K(ATP) pathway	Nociceptor hyperpolarisation	Animal, peripheral pain models; moderate
TRPA1 inhibition	Prostaglandin-independent analgesia	Cellular and animal data; moderate
Reduced IP3 and intracellular Ca ²⁺	Smooth muscle relaxation	In vitro experiments; moderate-strong
PGE2-dependent and -independent fever pathways	Antipyretic effect	Animal data; moderate

Table 4. Mechanisms of action of metamizole: an overall assessment of the evidence.

Current model

Metamizole is **a multimodal analgesic** that is rapidly converted to active pyrazolone metabolites; modulates the COX-prostaglandin system in a redox-dependent manner; activates the endocannabinoid system and the descending pain inhibitory systems arising from the PAG-RVM; inhibits the TRPA1 channel; and uses the NO-cGMP-K(ATP) signalling pathway in the periphery. Its spasmolytic effect rests mainly on suppression of inositol phosphate formation and intracellular Ca²⁺ release.

3.4 Clinical efficacy

Postoperative pain. A Cochrane systematic review [67] showed that a single oral dose of metamizole 500 mg gave at least 50% pain relief over 4–6 hours in more than 70% of participants, compared with 30% with placebo (**NNT 2.4; 95% CI 1.8–3.1**; moderate-quality evidence). Rescue medication was needed by 7% with metamizole and 34% with placebo. This NNT for 500 mg, the lowest effective dose of metamizole, is numerically better than that of 200 mg, the standard dose of ibuprofen (NNT 2.7), and at the same level as twice that dose, 400 mg (NNT 2.5) [68] (details: Section 17.1). A 2025 meta-analysis of 30 randomised trials reported that metamizole is as effective as other non-opioid analgesics in postoperative analgesia, and in intensive care patients reduced opioid consumption by 9.9 mg oral morphine equivalent more than paracetamol [69]. The area under the pain curve in the first 24 hours after hip replacement is 17.9 with metamizole and 30.6 with paracetamol (cited in [9]).

Direct comparisons. The results of studies comparing metamizole with other analgesics in postoperative pain vary with dose and setting. In impacted lower third molar surgery, oral metamizole 2 g gave stronger analgesia than ibuprofen 600 mg in the first hour, whereas the superiority of metamizole 1 g could not be shown [27]. In plastic surgery metamizole was superior to diclofenac in the first 18 hours, with no difference thereafter [70]. After breast cancer surgery intravenous paracetamol and intravenous metamizole were found to be clinically equivalent [71]. After day-case surgery the combination of metamizole and paracetamol at home was non-inferior to the combination of ibuprofen and paracetamol [72]; after shoulder arthroscopy, however, adding metamizole to ibuprofen and paracetamol did not further reduce pain on movement on day one (110 patients; mean difference -0.08 NRS points) [73]. These results show that metamizole is an effective analgesic but is not superior to other analgesics in every setting; in the studies showing superiority, doses of 2 g and above were generally used (Section 3.4.1).

In an earlier study of ours that was not published, we found that metamizole significantly reduced the use of narcotic analgesics in patients undergoing thoracotomy.

Prevention of procedural pain. Tulunay et al. [74] studied the pain caused by removal of nasal packing after septal surgery. Thirty-eight patients were divided into untreated control (12), placebo with normal saline (10) and intramuscular metamizole 1 g given 45 minutes before removal of the packing (16). In the metamizole group, pain intensity immediately on removal of the packing and at 5 and 10 minutes was significantly lower than in both the control and placebo groups. This finding shows that metamizole can be used preventively for short, predictable procedural pain.

Equivalence to morphine: cancer pain. Rodríguez et al. [28] compared oral metamizole 1 g or 2 g every 8 hours with oral morphine 10 mg every 4 hours for 7 days in a double-blind, randomised, parallel-group study of 121 cancer patients. **The analgesic effect of metamizole 2 g every 8 hours was found to be similar to that of morphine;** both treatments were significantly more effective than metamizole 1 g every 8 hours. At both doses metamizole tended to be better tolerated than morphine (difference not significant). A systematic review carried out for the German Guideline Programme in Oncology [75] showed that metamizole 3×2 g a day is **as effective as oral morphine 60 mg a day** and that even low doses (1.5–2 g/day) are superior to placebo; it recommended metamizole in cancer pain alone or together with opioids, and stated that it may be preferred to NSAIDs in long-term use because of a possibly better side-effect profile. In postoperative pain, too, 2.5 g intravenous metamizole has been reported to be equivalent to 50 mg pethidine [2].

In a crossover study of the effect of metamizole added to morphine in cancer pain (34 patients), in the first period the pain score at 48 hours was lower in those receiving metamizole with morphine than in those receiving placebo with morphine (VAS 5.50 versus 7.06) [76]. The systematic review of metamizole in cancer pain emphasises that metamizole can be used alone or together with opioids, but that the evidence is limited [75].

Low back pain. In 260 patients with acute lumbago or sciatic pain, intramuscular metamizole 2.5 g, diclofenac 75 mg and placebo were compared over one or two days in

an observer-blind multicentre study. The reduction in pain was greater in the metamizole group; the proportion rating the treatment as "very good" or "excellent" was 59% with metamizole, 30% with diclofenac and 18% with placebo [77]. This study is one of the rare direct comparisons of a high single dose of metamizole (2.5 g) with a standard dose of diclofenac.

Comparison with opioids. At equivalent doses the analgesic effect of metamizole has been reported to be comparable to that of opioid analgesics such as tramadol, pentazocine and pethidine [15].

What does "equivalent to morphine" mean?

In the study by Rodríguez et al. [28], oral metamizole 2 g every 8 hours (6 g a day) and oral morphine 10 mg every 4 hours (60 mg a day) gave the same analgesic effect over one week. This finding shows that metamizole, at this dose and in this patient group, is as effective as morphine. It does not mean that metamizole can replace morphine in every situation. The basic difference between the two drugs lies in the dose-response relationship. The effect of metamizole increases up to much higher doses than that of NSAIDs, but at some point it levels off. With opioids, by contrast, the effect keeps increasing as the dose is raised. For this reason metamizole cannot fully replace an opioid in very severe pain, but when added to it, it reduces the opioid requirement.

Clinical significance. In a suitable patient metamizole can delay the switch to an opioid or lower the opioid dose. Opioid side effects such as constipation, sedation, nausea and dependence are thus avoided. In a meta-analysis assessing short-term use, fewer adverse events were reported in patients receiving metamizole than in those receiving opioids: adverse events occurred in 90 of 279 patients treated with metamizole and in 115 of 290 patients treated with opioids, a relative risk of 0.79 [5].

Fever. In children the antipyretic effect of oral and IM metamizole did not differ from that of ibuprofen [22]. In a multinational randomised study of 628 children, the rate of return to normal temperature was 82% with metamizole, 78% with ibuprofen and 68% with acetaminophen ($p=0.004$); at 4–6 hours the mean temperature remained significantly lower in the metamizole group than in the other groups [78]. In a meta-analysis of three randomised trials no difference was found between oral metamizole and ibuprofen [79].

Headache. Headache, the most common use of metamizole, is discussed separately in Section 3.6.

Safety in short-term use. In a meta-analysis of 79 randomised trials covering about 4,000 patients (use for less than two weeks), no difference in the frequency of adverse events was found between metamizole and placebo, paracetamol or NSAIDs, and fewer adverse events were reported than with opioids; no study reported agranulocytosis or death [5]. However, these studies were not large enough or long enough to exclude an event occurring once in several thousand uses.

3.4.1 Dose, ceiling effect and comparison at the highest doses

The point often overlooked in analgesic comparisons is the doses at which the drugs are compared. In a considerable proportion of comparative studies metamizole was used at the lower end of its dose range, such as 500 mg or 1 g, while the comparator NSAID was used at its standard dose. Yet the dose-response curves of the two groups of drugs are different.

The ceiling effect of NSAIDs. The analgesic effect of NSAIDs reaches a ceiling at relatively low doses, while their side effects continue to increase with dose. In 240 emergency department patients with moderate to severe acute pain, intravenous ketorolac 10, 15 and 30 mg gave the same pain reduction at 30 minutes [80]. Similarly, in 225 patients oral ibuprofen 400, 600 and 800 mg showed the same effect at 60 minutes [81]. A daily ibuprofen dose of 2,400 mg, on the other hand, is associated with an increased risk of cardiovascular events, and avoiding these doses is recommended in patients with heart disease (Brufen product information). Thus, with NSAIDs, raising the dose increases the risk without markedly increasing analgesia.

Dose-response with metamizole. With metamizole, by contrast, the analgesic effect continues to increase with dose up to 2.5–3 g. In renal colic metamizole 2 g gave stronger and longer-lasting analgesia than 1 g, and 2 g intravenous metamizole was superior to 75 mg intramuscular diclofenac [23]. In dental surgery 2 g oral metamizole is stronger than ibuprofen 600 mg in the first hour, whereas 1 g is not [27]. In cancer pain metamizole 2 g every 8 hours is equivalent to morphine, while 1 g is weaker [28]. In low back pain 2.5 g intramuscular metamizole was found superior to diclofenac 75 mg [77], and in renal colic 2.5 g intravenous metamizole superior to tramadol 100 mg [82]. On the other hand, there is also a study in which no difference was found between 1 g and 2 g by the intramuscular route [83].

Drug	Maximum single dose	Maximum daily dose	Duration limit and notes
Metamizole	Oral 1 g; parenteral 2.5 g	Oral 4 g; parenteral 5 g	Analgesic effect increases with dose up to 2–2.5 g
Diclofenac	75 mg IM or IV (in renal colic a second 75 mg after 30 minutes)	150 mg	Ampoule for at most 2 days
Naproxen	500 mg (initial)	1,250 mg after the first day	In musculoskeletal pain and dysmenorrhoea
Ibuprofen	Oral 400–800 mg	2,400 mg	No additional analgesia shown above 400 mg; cardiovascular risk at 2,400 mg/day
Ketorolac	IV/IM 30 mg (initial 10 mg)	90 mg (60 mg in the elderly)	At most 2 days; no additional analgesia shown above 10 mg
Dexketoprofen	IV/IM 50 mg	150 mg	At most 2 days
Paracetamol	1 g	4 g	Daily dose must not be exceeded because of the risk of liver damage

Table 5. Maximum adult doses in the product information of analgesics used in acute pain (metamizole: EMA and Novalgin SmPC; diclofenac: Diclac ampoule product information; naproxen, ibuprofen and ketorolac: UK product information; dexketoprofen: Keral ampoule product information) [11, 84, 85]. Notes on the ceiling effect: Motov et al. [80, 81].

Assessment. These data suggest that when comparisons are made on the basis of the highest single doses, the picture changes in favour of metamizole: whereas NSAIDs

provide no additional analgesia at their ceiling doses, metamizole at 2.5–3 g has been found superior to standard NSAID doses and to tramadol. In our view, when the highest single doses are compared, metamizole 2.5 g is more effective than all the NSAIDs. This view is pharmacologically consistent and in line with the available direct comparisons; but since there is no study comparing all analgesics at their highest doses, it is not yet a proven conclusion but a hypothesis to be tested. This would require randomised trials comparing the drugs at equally highest doses. Moreover, the safety of high-dose metamizole, in particular the rate of intravenous administration (Section 3.2.1) and the risk of agranulocytosis in long-term use (Section 4.4), is an inseparable part of this comparison.

3.5 Colic pain: where metamizole is strongest

What distinguishes metamizole from other analgesics in colic pain is that **it combines analgesic and spasmolytic effects in a single molecule**. The pain caused by a stone in the ureter or biliary tract arises both from smooth muscle spasm and from wall distension and inflammation. NSAIDs act only on the prostaglandin component and butylscopolamine only on the spasm; opioids suppress pain centrally but can increase smooth muscle tone. Metamizole, by contrast, relaxes smooth muscle by reducing receptor-mediated inositol phosphate formation and intracellular Ca^{2+} release [56] and at the same time provides central and peripheral analgesia (Section 3.3). In our clinical observation, with intravenous administration the spasmolytic effect begins in 5–10 minutes and the analgesic effect in 20–30 minutes (see Table 3), and in colic-type pain metamizole provides analgesia equivalent to morphine. The usual dose in colic pain is **2.5 g**; this is the highest single dose permitted for parenteral administration in the EMA's harmonised product information (5 ml of the 500 mg/ml solution; the daily dose may go up to 5 g), and it was also used in most of the clinical studies below.

Maximum dose. These limits were harmonised by the EMA review in 2018. Before the review the maximum daily dose in the product information of EU countries ranged from 1.5 g to 6 g (6 g in Spain). After harmonisation, in patients aged 15 years and over the single dose is 500–1,000 mg, up to four times a day (6–8 hours apart), with a maximum daily dose of 4 g; with parenteral administration the daily dose may go up to 5 g, and if necessary a single dose of 2.5 g may be given [11].

Practice in Turkey is also consistent with these limits. According to the product information of Baralgin-M [86], formerly widely used in colic, the oral single dose in adults is 1–2 tablets (500–1,000 mg), which may be repeated up to four times a day; the intravenous or intramuscular single dose is 2–5 ml and the daily dose at most 10 ml (a 5 ml ampoule contains 2.5 g; two ampoules a day, 5 g in total). The summary of product characteristics of the Novalgin ampoule currently on the market [84] gives the same limits. An important point to be aware of is that none of these limits is based on a systematic dose-response study: to our knowledge, no study has ever been carried out to determine the highest effective and tolerated dose of metamizole. The EMA's reduction in 2018 of the maximum daily oral dose from 6 g in some countries to 4 g was likewise based not on a new dose-response or safety study but on harmonising differences between countries [11]. Today's dose limits are not scientifically determined but largely arbitrary; the dose range of metamizole needs to be re-evaluated (Section 3.4.1).

3.5.1 Renal colic

The Cochrane review. Edwards et al. [30] assessed the efficacy of single-dose metamizole in moderate to severe renal colic. Eleven double-blind randomised trials covering 1,053 patients (550 on metamizole) were included. Although most of the data rested on single, small studies, the results showed that metamizole has efficacy similar to that of other analgesics. Intravenous metamizole was found more effective than intramuscular metamizole, while intramuscular metamizole was less effective than diclofenac 75 mg. The most frequent side effects of intravenous metamizole were dry mouth and drowsiness; one study reported pain at the injection site. **No study reported agranulocytosis.** The review itself emphasises that metamizole is the first-line non-opioid analgesic for renal colic in many countries, whereas in countries such as the USA and the UK it has been banned because of blood dyscrasias.

Metamizole, tramadol and butylscopolamine. Stankov, Schmieder, Zerle, Schinzel and Brune [82] randomised 104 patients with "severe" or "unbearable" colic pain due to a confirmed stone in the upper urinary tract at 8 centres in Germany to intravenous **metamizole 2.5 g** (36 patients), tramadol 100 mg (35 patients) or butylscopolamine 20 mg (33 patients). Metamizole was found more effective than the other two treatments: rescue medication was needed by only 5 patients on metamizole, 13 on tramadol and 11 on butylscopolamine. Adverse events occurred in one patient each in the metamizole and tramadol groups and in 4 patients in the butylscopolamine group.

Dose and route of administration. Muriel-Villoria et al. [23] compared metamizole 1 and 2 g by the IM and IV routes with diclofenac 75 mg in a double-blind, double-dummy design in 293 patients. Metamizole 2 g, whether given IM or IV, gave more marked and longer-lasting analgesia; metamizole 1 g did not differ from diclofenac. All treatments were well tolerated. This study shows the importance of dose selection in colic: metamizole 1 g is often insufficient for colic.

Direct comparisons with diclofenac. In the double-blind study of Miralles et al. [87], diclofenac 75 mg IM reduced pain more than metamizole 2 g IM in the first 30 minutes. Arnau et al. [83] (Collaborative Study Group of the Spanish Society of Clinical Pharmacology) compared IM metamizole 1 g and 2 g with IM diclofenac 75 mg and IM pethidine 100 mg in 451 patients in 13 hospitals. Rescue medication was required by 24.1%, 22.8%, 16.4% and 19.5% respectively, and no significant difference was found between the groups either in these rates or in pain scores; the authors noted that statistical power was below 80% for some comparisons. The Cochrane review of NSAIDs and non-opioid analgesics [88] assessed these studies together. For at least a halving of pain there was no significant difference between diclofenac 75 mg IM and metamizole 1 g IM (2 studies, 335 patients; RR 1.03; 95% CI 0.72–1.47; I² 78%) or metamizole 2 g IM (3 studies, 366 patients; RR 1.06; 95% CI 0.81–1.37; I² 67%). No difference was found between metamizole and dexketoprofen (25 and 50 mg) either (2 studies, 610 patients; RR 1.03; 95% CI 0.85–1.26; I² 78%). By contrast, in a single study 2 g IV metamizole was superior to diclofenac 75 mg IM (103 patients; RR 0.64; 95% CI 0.49–0.84) [23]. This RR indicates that the probability of achieving at least 50% pain relief in the diclofenac group was 0.64 times that in the metamizole group; it does not mean that pain was reduced 36% more. High heterogeneity indicates that the results of the studies differ

considerably from each other; because of the wide confidence intervals, the finding of "no significant difference" is not firm evidence of equivalence either. Results for early pain scores are conflicting: in the study of Muriel et al. [89] metamizole was more effective than diclofenac in the first 60 minutes, whereas in the study of Miralles et al. [87] it was less effective in the first 30 minutes.

The dose problem. The common lesson of these comparisons is that the efficacy of metamizole in colic depends on dose and route of administration. In the studies where it was found equal to or less effective than diclofenac, metamizole was given at 1–2 g IM, whereas in the comparison where it was superior to diclofenac, 2 g IV was used. In the Cochrane review, too, IV metamizole is more effective than IM metamizole [30]. According to the studies carried out, the effective dose in renal colic is at least 2 g. Because of concern about agranulocytosis, metamizole is often given in practice at low doses and by the IM route, which leads to its efficacy in colic being underestimated. The dose used for colic in Turkey is 2.5 g: the Novalgin ampoule authorised in Turkey contains 2.5 g metamizole sodium in 5 ml; according to its SmPC the adult IV or IM single dose is 2–5 ml (1–2.5 g) and the maximum daily dose 10 ml (5 g) [84]. On the other hand, in the study of Arnau et al. [83] no difference was found between 1 g and 2 g by the IM route; the dose effect is seen most clearly with the IV route.

A study from Turkey. Derici and Ergün [90] compared IM metamizole 1 g (48 patients) with IM diclofenac 75 mg (40 patients) in 88 adults with acute renal colic in the emergency departments of two hospitals in Ankara. Over two hours of follow-up, pain scores did not differ at any time point; rescue medication was required by 5 patients (10%) in the metamizole group and 3 (8%) in the diclofenac group. The effect of metamizole began slightly later than that of diclofenac. Drug choice was not randomised but left to the physician's preference; patients receiving rescue medication were excluded from the analysis. The authors state that in Turkey diclofenac is the first choice for renal colic in the emergency department and that metamizole is also widely used.

Guideline. The European Association of Urology (EAU) guideline on urolithiasis recommends a non-steroidal anti-inflammatory drug as the first drug in renal colic, taking cardiovascular risk and side effects into account (strong recommendation); opioids are the second option (weak recommendation). In the guideline text metamizole is mentioned within this group: "NSAIDs, including metamizole, and paracetamol are effective"; the superiority of NSAIDs over opioids in renal colic is given with level of evidence 1b [91]. There is no separate recommendation for metamizole.

Assessment. The available comparative studies do not show that metamizole at doses below 2–3 g is consistently more effective than NSAIDs, particularly diclofenac, in renal colic; the weight of the evidence points to equivalence. A clear superiority of metamizole has been shown against tramadol and butylscopolamine [82] and, at 2 g IV, against IM diclofenac [23]. In the latter comparison the two drugs were given by different routes, so the effect of the drug cannot be separated from that of the route; but it does show that IV metamizole in an adequate dose is at least as potent as IM diclofenac in colic. A network meta-analysis of renal colic [92] gave the highest ranks to IM diclofenac, IV ibuprofen and IV ketorolac and did not report a separate result for metamizole. The place of metamizole in renal colic should therefore be defined not as a drug more effective than

NSAIDs, but as a drug at least as effective as them when given in an adequate dose and preferably IV. This property makes metamizole a strong option in patients in whom NSAIDs are contraindicated or require caution (history of gastrointestinal bleeding, cardiovascular risk).

Comparison with opioids. Opioids are effective analgesics in renal colic; however, side effects such as nausea and vomiting can worsen the patient's condition, and they have no relaxant effect on ureteric smooth muscle. That metamizole at an intravenous dose of 2.5 g was found more effective than tramadol [82], and that 2.5 g intravenous metamizole is equivalent to 50 mg pethidine in postoperative pain [2], show that metamizole is a serious alternative to opioids in renal colic.

Experimental evidence in the obstructed ureter. Laird and Cervero [93] showed in anaesthetised rats that IV metamizole (5–50 mg/kg) dose-dependently suppressed pain responses caused by distension of the ureter ($ID_{50} 8 \pm 1$ mg/kg). When the ureter was completely obstructed, metamizole dose-dependently lowered intraureteric pressure; with 25 mg/kg the pressure fell by 25% at 10 minutes. Under conditions of normal pressure, however, doses up to 50 mg/kg did not change the amplitude or frequency of pyeloureteral contractions or intraureteric pressure. The authors concluded that metamizole has a direct antinociceptive effect on ureteric pain and shows a spasmolytic effect after obstruction. Khater, Angelo-Khattar and Thulesius [94] compared metamizole (60–120 mg/kg IV) with indometacin in acute ureteric obstruction resembling renal colic in 12 anaesthetised sheep. Both drugs dose-dependently reduced the frequency of peristaltic waves but did not lower mean ureteric pressure; the authors thought the effect might be due to blockade of impulse conduction at the ureteropelvic junction. Only indometacin reduced urine flow. Taken together, these two studies suggest that metamizole leaves the normal ureter untouched but acts on the obstructed, spastic ureter.

The place of adding a spasmolytic. In renal colic the contribution of a pure antimuscarinic spasmolytic, butylscopolamine, to analgesia is limited. A review of the treatment of acute renal colic states that NSAIDs and metamizole are effective against the pain, whereas routinely added butylscopolamine was not found superior to placebo; according to the same review excessive fluid loading is of no benefit and alpha blockers increase the likelihood of passage of a stone in the distal ureter [95]. This finding is consistent with butylscopolamine being less effective than metamizole in the study of Stankov et al. [82], and suggests that the efficacy of metamizole in renal colic cannot be explained by a spasmolytic effect alone, but that potent analgesia and the effect of lowering intraureteric pressure act together.

3.5.2 Biliary colic

Metamizole has a special place in biliary colic, a subject almost never discussed in the literature of the countries where metamizole is banned. Biliary colic arises from spasm and distension of the smooth muscle of the gallbladder and bile ducts as a result of obstruction of the cystic duct or common bile duct by a stone. The ideal drug for this pain should relieve the pain, relax biliary smooth muscle and not contract the sphincter of Oddi.

Morphine and the sphincter of Oddi. Opioids, morphine in particular, can raise biliary pressure by increasing the tone and contractions of the sphincter of Oddi. Morphine may therefore increase rather than reduce pain in biliary colic and may worsen the clinical picture of biliary obstruction. A case in a patient who had undergone cholecystectomy, in whom morphine-triggered spasm of the sphincter of Oddi was abolished by naloxone, is an example of the clinical counterpart of this mechanism [96]. A review of the effects of opioids on the sphincter of Oddi and their implications in the treatment of pancreatitis concluded that all narcotic analgesics can affect sphincter pressure [97]. Although the evidence on clinical outcomes is limited, it is pharmacologically consistent that a drug without spasmolytic effect, and one that may increase sphincter tone, should not be the first choice in biliary colic.

The superiority of metamizole. Metamizole, by contrast, relaxes smooth muscle, including biliary smooth muscle, does not contract the sphincter of Oddi and provides potent analgesia. For this reason, in the countries where metamizole is authorised, biliary colic is one of its most appropriate indications. Schmieder, Stankov, Zerle, Schinzel and Brune [29], to test the analgesic and spasmolytic effects of metamizole together, compared it with an opioid analgesic (tramadol) and a pure spasmolytic (butylscopolamine). In a multicentre, observer-blind, parallel-group study conducted at 5 centres in Germany, 74 patients with "severe" or "unbearable" colic pain due to a stone in the biliary tract were randomised to intravenous **metamizole 2.5 g** (25 patients), tramadol 100 mg (25 patients) or butylscopolamine 20 mg (24 patients). The groups were similar in age, sex, height, weight and initial pain intensity. On the primary end point metamizole was found **significantly more effective** than both tramadol and butylscopolamine: the area under the curve on the visual analogue scale from baseline to onset of effect ($p < 0.05$) and the sum of pain intensity differences over the 2-hour observation period ($p < 0.005$). **The mean time to onset of effect was shortest with metamizole ($p < 0.005$): metamizole 10.9 ± 5.8 minutes, tramadol 15.8 ± 11.7 minutes, butylscopolamine 25.6 ± 24.3 minutes.** Metamizole was also more effective on the 5-point pain scale; at the end of the study it was rated by patients in their overall assessment as the most effective drug ($p < 0.005$). A second rescue injection was needed by 3 patients in the metamizole group, 1 in the tramadol group and 8 in the butylscopolamine group ($p < 0.05$). Guidelines also recommend NSAIDs in biliary colic; however, NSAIDs have no spasmolytic effect and carry gastrointestinal and renal risks. Metamizole is the only non-opioid option that provides analgesic and spasmolytic effects together.

Metamizole in colic pain: a practical summary

Dose: The usual dose in colic pain is 2.5 g; 1 g is often insufficient.

Route: Oral if the patient can take it by mouth; IV in a vomiting patient or one in severe pain (more effective than IM).

Rate: IV injection over at least 5 minutes or diluted as an infusion; a rapid bolus can cause hypotension, syncope and shock.

Biliary colic: Morphine can increase pain by contracting the sphincter of Oddi; metamizole is both analgesic and spasmolytic and does not contract the sphincter.

In biliary colic 2.5 g IV metamizole is significantly more effective than tramadol and butylscopolamine, and its effect begins at a mean of 11 minutes.

Renal colic: 2.5 g IV metamizole resulted in less need for rescue medication than tramadol and butylscopolamine.

3.6 Headache: the most common use of metamizole

Headache is the indication for which metamizole is most often used, both worldwide and in Turkey. In Brazil acute headaches account for a large proportion of attendances at primary care facilities and emergency departments, and metamizole is the drug most often used in these settings [98]. In our experience, in Turkey, too, headache tops the list of conditions for which metamizole is used, both at home and in emergency departments. Yet the place given to metamizole in headache guidelines is limited. The reason is not lack of efficacy but that the controlled studies are few and small, and most were carried out in countries where metamizole is widely used. The evidence is strongest for acute migraine attacks and episodic tension-type headache; in other headaches its use rests on the general analgesic effect of metamizole (Table 6).

Type of headache	Place of metamizole	Evidence
Migraine attack (with and without aura)	1 g oral and 1 g intravenous metamizole are effective; an alternative analgesic and emergency treatment option in guidelines	Placebo-controlled randomised trials [99-101]; guidelines [102, 103]
Episodic tension-type headache	500-1,000 mg oral and 1 g intravenous metamizole are effective	Placebo-controlled randomised trials [98, 99, 104]
Chronic migraine, chronic tension-type headache	Can be used for individual attacks; not a preventive treatment; the risk of medication overuse must be monitored	No direct studies
Status migrainosus	Can be used as rescue analgesia	No direct studies
Cluster headache	No place; attack treatment is oxygen and subcutaneous sumatriptan	Guideline [105]
Paroxysmal hemicrania, hemicrania continua	Does not replace indometacin	No specific studies
Other primary headaches (SUNCT/SUNA, stabbing, hypnic, cough and exercise headaches)	Not a standard treatment	No controlled studies
Secondary headaches (infection, trauma, dental and jaw-related)	May be an adjunctive analgesic; does not treat the underlying cause	No headache-specific studies

Table 6. The place of metamizole by type of headache. "No studies" means not lack of efficacy but the absence of direct data to support a recommendation.

3.6.1 Acute migraine attack

A multicentre migraine study from Turkey. Tulunay et al. [101] assessed the efficacy and safety of oral metamizole in migraine attacks in a double-blind, randomised, placebo-controlled, crossover, multicentre study (Ankara, Samsun, Trabzon, Kırıkkale and Istanbul). Patients aged 20-65 years with migraine with or without aura according to the criteria of the International Headache Society were included; hypersensitivity to metamizole, haematological or metabolic disease and pregnancy were excluded. Each patient treated three attacks (two with metamizole, one with placebo); for moderate or

severe headache 2×500 mg metamizole or placebo was taken, pain was assessed at 1, 2 and 4 hours, and rescue medication was allowed if the pain persisted after 2 hours. A total of 168 attacks of the 56 evaluable patients (47 women, 9 men; 18 with aura, 38 without aura) were analysed (112 metamizole, 56 placebo). Pain relief and complete pain freedom were achieved significantly more often with metamizole than with placebo at all of 1, 2 and 4 hours ($p<0.001$). At 2 hours complete pain freedom was achieved in 37.5% of metamizole attacks (42/112) and 10.7% of placebo attacks (6/56). Rescue medication (Cafergot®, containing 1 mg ergotamine, at the earliest at 2 hours) was needed in 12.5% of metamizole attacks (14/112) and 42.9% of placebo attacks (24/56) ($p<0.001$). Recurrence within 24 hours after complete pain freedom was 16.7% with metamizole (7/42) and 33.3% with placebo (2/6); the difference was not significant, but as the authors noted, the number of attacks with complete relief on placebo was too small for statistical comparison. Patient and physician assessments significantly favoured metamizole; side effects were few and minor in both groups, and no serious adverse events were reported.

Parameter	Metamizole 1 g	Placebo
Patients enrolled / completed	73 / 56 (23% drop-out; 13 did not return, 4 protocol violations)	
Sex, age	59 women (81%), 14 men; 32.7 ± 8.7 years	
Attacks evaluated	112	56
Baseline pain score (0-3)	2.45 ± 0.5 (both groups)	
Complete pain freedom, 1 / 2 / 4 hours	21.4% / 37.5% / 40.2% (24 / 42 / 45 attacks)	1.8% / 10.7% / 12.5% (1 / 6 / 7 attacks)
Pain relief, 1 / 2 / 4 hours	42% / 52.7% / 57.1% (47 / 59 / 64 attacks)	19.6% / 23.2% / 28.6% (11 / 13 / 16 attacks)
Need for rescue medication	14 attacks (12.5%)	24 attacks (42.9%); $p<0.001$
Recurrence within 24 hours (in attacks with complete relief)	7/42 (16.7%)	2/6 (33.3%); not significant
Treatment assessment score (0-3), patient / physician (a)	about 1.4 / 1.5	about 0.5 / 0.5
Serious adverse events	None	None

Table 7. Efficacy of oral metamizole in migraine attacks [101]. Percentages are per number of attacks (metamizole 112, placebo 56 attacks); rates and p values are from Tables I-II and the text of the article; $p<0.001$ at all of 1, 2 and 4 hours. (a) Approximate values read from the graph in Figure 4 of the article.

The conclusion of the study is that **oral metamizole 1 g is an effective and well-tolerated drug for the treatment of migraine attacks**. This finding also supports the principle of Section 3.2: even in acute, severe pain such as migraine, the effect of oral metamizole emerges clearly against placebo within the first hour. The Cochrane review of primary headaches [106] was not used as a source because it was later withdrawn (2014).

Intravenous metamizole. Bigal, Bordini and Speciali [99] compared intravenous metamizole with placebo in the acute treatment of migraine with and without aura and of episodic tension-type headache. At 30 and 60 minutes after administration the metamizole groups showed significant improvement in pain compared with placebo and significant improvement in all other symptoms at 60 minutes; side effects were mild and infrequent. The authors considered metamizole an effective, safe and low-cost option.

The same group later also found metamizole effective in a second randomised, double-blind study comparing intravenous metamizole with placebo in migraine with and without aura [100]. In a network meta-analysis comparing metamizole with triptans no difference was found between the two groups [107]; however, this is an indirect comparison and does not replace an equivalence test.

The intravenous route offers an advantage particularly in a patient who cannot take medication by mouth because of nausea and vomiting, and in the emergency department. But intravenous administration is not evidence of clinical superiority over the oral route (Section 3.2); the risk of hypotension with rapid injection must also not be forgotten (Section 3.2.1).

Its place in guidelines. The 2022 guideline of the German Society of Neurology and the German Migraine and Headache Society lists oral metamizole 1,000 mg for acute migraine attacks in severe pain where other analgesic measures are not suitable, and intravenous metamizole 1,000 mg, together with metoclopramide or alone, as an emergency treatment option; according to the guideline the evidence is broader for acetylsalicylic acid and ibuprofen [102]. The recommendations of the Brazilian Headache Society recommend oral metamizole 500 mg every 2–4 hours in mild attacks (at most 2 g a day) and intravenous metamizole 1,000 mg in severe attacks; in children and adolescents the dose is 6–10 mg/kg [103]. The caution of the guidelines stems not from any lack of efficacy of metamizole but from the absence of large comparative studies. That such studies have not been done for an old drug without manufacturer support is an example of the structural problem discussed in Section 12.3.

Special migraine presentations. In migraine with aura metamizole reduces the headache and the accompanying symptoms; however, there is no evidence that it specifically stops the aura. There are no studies specific to metamizole in menstrual migraine and vestibular migraine; planned, repeated use during menstruation is not a proven short-term prophylaxis. In a prolonged, severe attack (status migrainosus) metamizole can be used as rescue analgesia; but in this situation fluid loss, vomiting, prior medication use and secondary causes must also be assessed.

3.6.2 Episodic tension-type headache

In the randomised, double-blind, multicentre study of 417 patients by Martínez-Martín et al., oral metamizole 500 mg and 1,000 mg, acetylsalicylic acid 1,000 mg and placebo were compared; both doses of metamizole were superior to placebo on the pain end points [104]. Because patients who had previously benefited from non-opioid analgesics were enrolled, the response may appear more favourable than in the general patient population; moreover, the fact that each active arm was superior to placebo does not show that metamizole is superior to acetylsalicylic acid.

For intravenous use, Bigal et al. compared intravenous metamizole 1 g with normal saline in 60 patients [98]. From 30 minutes onwards metamizole reduced pain significantly more than placebo. The therapeutic gain was 30% at 30 minutes and 40% at 60 minutes; the number needed to treat (NNT) was 3.3 and 2.2 respectively. Headache recurrence was 25% with metamizole and 50% with placebo; rescue medication was needed by 20% with metamizole and 47.6% with placebo. The same group's first study

also showed that intravenous metamizole is effective in episodic tension-type headache [99]. These results support its use in the emergency department; but they do not call for routine recourse to injection in uncomplicated tension-type headache where oral treatment is possible.

3.6.3 Chronic headache and medication-overuse headache

Results obtained from treating a few attacks of episodic headache do not show the benefit-harm balance of almost daily use for months. In chronic migraine and chronic tension-type headache metamizole can be used for individual attacks, but it is not a preventive drug; it does not reduce attack frequency or prevent chronification. Although metamizole is not an opioid, it is not exempt from medication-overuse headache. According to the International Classification of Headache Disorders (ICHD-3), non-opioid analgesic-overuse headache is defined as headache on 15 or more days a month in a person with a pre-existing primary headache, with analgesic use on 15 or more days a month for more than three months; days of use of different non-opioid analgesics are counted together [108]. For combination analgesics containing adjuvants such as caffeine the threshold is 10 days a month. These values are diagnostic criteria, not safe-use limits; in chronic headache the number of days of use should be monitored and preventive treatment started when necessary.

3.6.4 Other primary and secondary headaches

Metamizole has no established place in cluster headache; the 2023 guideline of the European Academy of Neurology recommends high-flow 100% oxygen and subcutaneous sumatriptan for the acute attack [105]. Relief of pain after taking metamizole during an attack does not prove the effect of the drug, since the attack can also end spontaneously. In paroxysmal hemicrania and hemicrania continua a complete response to indometacin is part of the diagnosis, and metamizole does not replace it. There are no controlled studies specific to metamizole in SUNCT/SUNA or in primary stabbing, hypnic, cough, exercise and sexual-activity-related headaches.

In secondary headaches, for example in febrile infections, after trauma or in dental and jaw-related pain, metamizole can provide relief through its analgesic and antipyretic effects; but it does not treat the underlying cause. In conditions such as subarachnoid haemorrhage, meningitis, venous sinus thrombosis, giant cell arteritis, acute glaucoma or hypertensive emergency, relief of pain with metamizole does not exclude these diagnoses. Response to analgesia is not proof that a headache is benign.

Assessment. Metamizole is a cheap and widely available analgesic whose efficacy in acute migraine attacks and episodic tension-type headache has been shown in placebo-controlled studies. The multicentre study from Turkey showed that oral metamizole 1 g provides marked superiority over placebo in migraine attacks even at the first hour [101]. The right place for metamizole is attack treatment in a diagnosed, suitable patient, by the oral route where possible, with the frequency of use monitored. The absence of serious side effects in headache studies does not exclude agranulocytosis; therefore informing the patient about warning symptoms such as fever, sore throat and mouth ulcers applies here too (Section 14).

4. Agranulocytosis: Definition, Mechanism, Course

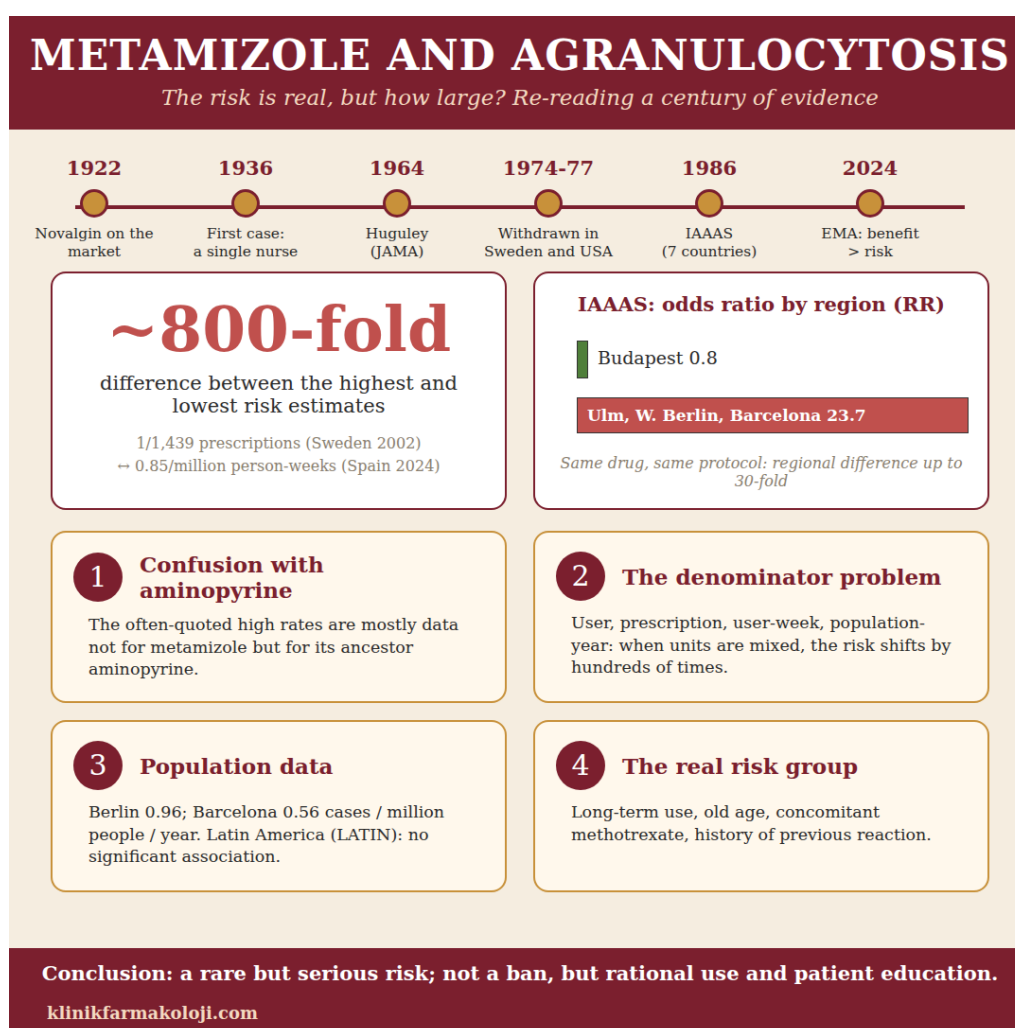


Figure 9. Visual summary: Metamizole and agranulocytosis: re-reading a century of evidence. The roughly 800-fold difference between risk estimates, the regional differences in the IAAAS and the four sources of high rates. Details are given in this section and in Sections 5–8.

4.1 The problem of definition

Agranulocytosis is a fall in the absolute neutrophil count below $0.5 \times 10^9/L$ ($500/\mu L$). Neutropenia (below $1.5 \times 10^9/L$), agranulocytosis and aplastic anaemia are different clinical entities. In a considerable proportion of the early studies these entities were not distinguished from one another, which inflated numerator (case count) estimates [109] (cited from Eleutério et al., 2024). The estimate of 1 in 1,602 prescriptions based on German insurance data also includes neutropenia; the authors themselves emphasised that the result may have been affected by confounding because of the association between metamizole use and chemotherapy, and that conclusions regarding treatment should be drawn with caution [110]. This is an example that directly supports the "numerator problem" argument of the thesis: neutropenia developing in patients receiving chemotherapy is being attributed to metamizole.

4.2 Mechanism

Two pathways have been described: (1) **The immune-mediated pathway**: antibodies dependent on the drug or its metabolites destroy mature neutrophils; the development of

the condition within hours or days on re-exposure in previously sensitised persons supports this pathway. (2) **The toxic pathway:** a direct toxic effect of the main metabolite 4-MAA, together with haemin, on granulocyte precursors [111]. Recent findings suggest that the mechanism of metamizole agranulocytosis may differ from that of agranulocytosis due to other drugs.

4.3 Genetic susceptibility

The question of genetic susceptibility is critically important for the main thesis of this monograph: if metamizole agranulocytosis arises in persons with particular genetic characteristics, a risk estimate obtained in one country cannot be transferred to another. In that case regulatory decisions would have to rest on each country's own data.

Why did a genetic explanation come to mind? In the IAAAS, conducted with the same protocol, the odds ratio for metamizole was 0.8 in Budapest and 23.7 in Ulm, West Berlin and Barcelona. High-risk reports from Sweden and Finland, severe cases reported among British and Irish tourists in Spain, and, by contrast, low case numbers despite widespread (often non-prescription) use in Latin America, Bulgaria and Hungary, suggested that the risk may differ from population to population [112].

4.3.1 Published pharmacogenetic studies

A systematic review from 2025 was able to identify only four publications on the pharmacogenetics of metamizole agranulocytosis [109]. This alone shows the evidence gap in the field.

Study	Population and sample	Genes studied	Finding	Limitation
Vlahov et al. [113] (Pharmacogenetics)	Bulgaria (Sofia); 9 cases, 180 healthy controls	HLA (serological and DQA1)	Increased risk with HLA-A24, B7, DQw1 and DQA1*05:01; HLA-A2 protective; role of more than one gene	Very small sample; concomitant drugs not detailed
Cismaru et al. [114]	Switzerland 45/191; Germany 12/92; Spain 29/145 (cases/controls)	HLA, high-throughput sequencing	No consistent HLA association; HLA-C*04:01 significant only in the Swiss cohort, not replicated in the others	Healthy persons and metamizole-tolerant persons combined in the control group; agranulocytosis and neutropenia together
Cismaru et al. [115] (genome-wide association)	The same three European cohorts	Genome-wide	Two candidate loci on chromosome 9: rs55898176 (OR 4.01; $p=1.01 \times 10^{-7}$) and rs4427239 in the SVEP1 gene (OR 5.47; $p=5.75 \times 10^{-7}$)	Below the genome-wide significance threshold (5×10^{-8}); no independent replication
Radulovic et al. [116]	Germany; 3 patients	NAT2, CYP2C9, CYP2C19	CYP2C9*3/*3 (poor metaboliser), CYP2C19*1/*2 (intermediate metaboliser), NAT2 slow acetylator; hypothesis of toxic metabolite accumulation	Case series; no statistics

Table 8. Publications on the pharmacogenetics of metamizole agranulocytosis (compiled from the systematic review of Fidelis et al. [109]; Cismaru et al. [114, 115] cite the Vlahov study as 5 cases, which should be checked against the original article).

4.3.2 Biological plausibility: metabolism and the toxic pathway

The most plausible route for genetic susceptibility is metabolism. The half-life of 4-AA is 5.5 hours in slow acetylators and 3.8 hours in fast acetylators [14]. The frequency of the NAT2 slow acetylator phenotype varies greatly between populations. Given that part of

the agranulocytosis is thought to be related to a direct toxic effect of 4-MAA on granulocyte precursors in the presence of haemin [111], it is biologically plausible that genotypes increasing metabolite exposure (slow NAT2, loss of function of CYP2C9 and CYP2C19) increase the risk. However, this hypothesis currently rests on a case series of only three patients.

For the immune-mediated pathway, on the other hand, HLA associations are to be expected; as in the examples of abacavir (HLA-B*57:01) or carbamazepine (HLA-B*15:02), HLA associations are often specific to ethnic origin. The failure to replicate the HLA associations of the Bulgarian study in the Western European cohorts therefore does not necessarily constitute a contradiction; different risk alleles may be involved in different populations.

4.3.3 Regulatory consequences

- The systematic review concluded that **there is not sufficient evidence to justify banning metamizole in some countries on the basis of genetic variants alone**. The frequencies of the identified alleles in populations do not show a pattern that would explain the different regulatory decisions around the world [109].
- According to the same review, in countries where metamizole is sold without prescription (Brazil, Mexico) the incidence of agranulocytosis is comparable to that in countries where it requires a prescription.
- The EMA's 2024 assessment noted that no significant association and no clear HLA risk allele had been found in genome-wide scans, and that it could "**neither confirm nor refute**" the assumption of ethnic differences.
- Many populations, African-descended populations above all, have not been represented in these studies at all; findings from European cohorts should not be generalised to other populations [109]. **There are no pharmacogenetic data at all on metamizole agranulocytosis in the Turkish population.**

This picture is directly relevant to the thesis: that the risk may differ between populations is supported both by epidemiological (IAAAS) and by limited genetic data. It is therefore scientifically indefensible to regard Swedish or Finnish data as directly valid for Turkey, Bulgaria or Latin America; each country should generate its own population-based and pharmacogenetic data.

4.4 Time of onset and risk factors

- In the EudraVigilance analysis the median time to onset is 7–14 days; 30–50% of cases occur within the first week; in previously exposed patients the median is 7.5 days [12].
- In the EMA's own EudraVigilance analysis the median time to onset is 10 days (range 0 days to 8 years), and 40.2% of cases occurred in the first week. Of the 571 cases for which time to onset could be calculated, 180 arose shortly after the drug was stopped (median 3 days); in the Berlin study, too, 35% of cases developed within 5 days after stopping the drug. The PRAC found insufficient data to compare the risk of short-term and long-term use, did not consider statements that the risk increases after one week or with long-term use to be supported by

evidence, and recommended their removal from the product information [12] (assessment report, pp. 8–9, 12, 16).

- In Germany, 30.5% of 161 spontaneous reports developed in the first 7 days and two-thirds within the first 6 weeks; in about 25% of cases there was off-label use [117].
- In Sweden 92% of cases occurred in the first 2 months of treatment; 36% of patients had an additional risk factor [118].
- Markers of poor prognosis: age over 65, a fall in neutrophil count below 100/ μ L, severe infection and **concomitant use with methotrexate** [111].
- In the 1985–2017 EudraVigilance analysis of Hoffmann et al. [119] (1,478 cases), the median time to onset was 13 days and the median dose 1,500 mg a day. The risk does not appear to be dose-dependent; there is as yet no genetic test or biomarker predicting individual risk [9].

4.5 Mortality: a declining curve

Source	Period / data	Fatality rate
Stammschulte et al. [117]	Germany, 161 spontaneous reports, 1990–2012	23.6% (38 cases)
Hoffmann et al. [119]	EudraVigilance, 1,478 cases, 1985–2017	16.2%; 20.9% before 1998, 15% after 2007
EMA [12]	EudraVigilance, 1,200 cases, 2014–May 2024	10% (120 cases)
Wildner et al. [120]	Swiss reports	2014–18: 13.5%; 2019–23: 5.8%; 2024: 1.8%

Table 9. Reported fatality rates in metamizole agranulocytosis. In Switzerland methotrexate was being used concomitantly in 39.5% of fatal cases.

This table alone carries an important message: the lethality of metamizole agranulocytosis is not a fixed biological property; it can be markedly reduced by early diagnosis, timely withdrawal of the drug, patient education and avoidance of the methotrexate interaction.

A distinction must be made in reading these rates. The 10% in EudraVigilance is the proportion of deaths among reported cases, not the true case fatality in the population, because fatal cases are more likely to be reported. Zinzi et al. [121] found deaths in 203 (9.6%) of 2,244 reports in the same database, but emphasised that because information on comorbidities and drugs was missing, these deaths could not be attributed to metamizole alone. The range of 2.5–10% cited by the PRAC is a literature value for drug-induced agranulocytosis in general, which has fallen from 60% to this level in recent decades [122; 12, pp. 8, 13].

5. A Chronology of the Evidence: 1934-2026

The table below brings together the main publications that have shaped the relationship between metamizole and agranulocytosis, their designs and their most important methodological limitations.

Year	Source	Country	Design	Main finding	Methodological note
1934-35	Madison and Squier; Bröchner-Mortensen [123]	USA, Denmark	Case series	Association of aminopyrine with agranulocytosis	Aminopyrine, not metamizole
1936	Benjamin and Biederman [124]	USA	Single case; provocation test	Leukopenia with a single dose of "Novaldin" in an aminopyrine-sensitive patient	Previously sensitised person; gives no incidence information
1937	Klumpp [125]	USA	Case reports	Agranulocytosis with Novaldin	
1952	Discombe [126]	England	Case series	Amidopyrine "a preventable cause of death"	Aminopyrine data; source of the high rates later carried over to metamizole
1964	Huguley [127]	USA	Cases from the AMA Registry on Blood Dyscrasias	Dipyrone "a hazardous antipyretic and analgesic"	No denominator (import quantity only); leukopenia and agranulocytosis not separated; risk transferred from aminopyrine
1965	Pretty et al. [128]	Canada	30 cases, 1946-64	Aminopyrine alone in 8 of 14 cases of known aetiology; 12 deaths	Predominantly aminopyrine
1970-72	Palva and Mustala [129]; Kantero; Palva	Finland	Case series and correspondence	Predominantly aminophenazone agranulocytosis	Kantero's 1972 objection and Palva's reply; full texts could not be accessed
1973	Böttiger and Westerholm [130]	Sweden	Spontaneous reporting	1/3,000 patients; the basis for the 1974 withdrawal decision [118]	Definition of numerator and denominator unclear; withdrawn from the market in Sweden in 1974
1977	FDA decision [131]	USA	Regulatory	NDA approvals of all dipyrone-containing products withdrawn on 27 June 1977	Reason: "agranulocytosis, which may be fatal"; size of the risk not stated
1979	Varonos et al. [132]	Greece	Survey for the year 1975	1/133,000-466,000 treatments	40-150 times lower than the Swedish estimate
1981	BGA [133]	West Germany	Spontaneous reporting	1/20,000 user-years	Restriction of indications and prescription requirement in 1986-87
1986	IAAAS [134]	Israel and 6 European countries	Population-based case-control	1.1/million user-weeks; RR: Budapest 0.8, Ulm-W.Berlin-Barcelona 23.7	The largest study; criticisms of sponsorship and analysis [135]
1995-99	Re-authorisation in Sweden and second withdrawal	Sweden	Regulatory	Withdrawn again after the Hedenmalm data	
2002	Hedenmalm and Spigset [118]	Sweden	Spontaneous reports ÷ prescriptions	≥1/1,439 prescriptions (95% CI 1/850-1/4,684)	8 cases ÷ 10,892 prescriptions (the calculation gives 1/1,362); off-label use for ≥13 days in 7 of the 8 cases

Year	Source	Country	Design	Main finding	Methodological note
2005	Ibáñez et al. [136]	Spain	Population-based case-control; 78.73 million person-years	177 cases; adjusted RR 25.8 (8.4–79.1); 0.56/million/year	Risk disappears 10 days after exposure
2008	Hamerschlak et al. (LATIN) [137]	Brazil, Argentina, Mexico	Case-control	All-cause agranulocytosis 0.38/million/year; no significant association with metamizole	Low incidence despite widespread use
2015	Huber et al. [138]	Germany (Berlin)	Prospective case-control surveillance	26 (30%) of 88 cases metamizole; 0.96/million/year	
2015	Stammschulte et al. [117]	Germany	161 spontaneous reports	Deaths 23.6%; 25% off-label	
2015	Blaser et al. [139]	Switzerland / WHO	Spontaneous reporting	0.46–1.63/million person-days	
2015	Akyay and Deveci [140]	Turkey	13 children, retrospective	4 agranulocytosis; all recovered	Association with dose and duration
2020	Klose et al. [110]	Germany	Insurance data	1/1,602 prescriptions	Includes neutropenia
2024	Maciá-Martínez et al. [141]	Spain	Cohort 2005–2022; 444,972 new users	8.52/10 ⁷ person-weeks; HR (vs NSAIDs) 4.40 (0.90–21.57)	26 cases in total; CI includes 1
2024	EMA Article 107i [12]	EU	Regulatory assessment	1,200 cases, 120 deaths (2014–2024); benefit > risk	11 PRAC members expressed a divergent opinion
2026	Wildner et al. [120]	Switzerland	Analysis of use and reports	Use +79%; reports from 13 to 57; deaths fell to 1.8%	

Table 10. Metamizole and agranulocytosis: the main publications. RR: relative risk/odds ratio; HR: hazard ratio; CI: confidence interval.

5.1 1936: A single nurse and a provocation test

The 1936 JAMA article by Benjamin and Biederman [124], often cited as the first publication on metamizole-induced agranulocytosis, is not an incidence study. In the article, a patient who had previously had attacks of agranulocytosis with **aminopyrine** was given a test dose of the newly marketed "Novaldin", and leukopenia developed. This observation shows cross-sensitivity; that is, it demonstrates that a person sensitised to aminopyrine may also react to its chemical relative metamizole. But it gives no information at all about how often metamizole causes agranulocytosis in the unsensitised general population.

5.2 1964: Huguley and the "hazardous antipyretic"

Huguley's article published in JAMA in 1964 [127], entitled "Agranulocytosis induced by dipyrone, a hazardous antipyretic and analgesic", is based on cases reported to the adverse reaction registry of the American Medical Association (AMA). Only 10 cases of leukopenia associated with dipyrone were reported to the registry from the USA between 1955 and 1959, and 18 cases were reported after 1960; 7 of these were children and 36% of the patients died. Huguley also took the increase in use into account: since no data on domestic production and sales were available, he turned to the import figures of the US Tariff Commission. Dipyrone imports were zero in 1958, and 220 pounds in 1959, 7,164 in 1960, 39,790 in 1961 and 18,879 in 1962. Huguley found this increase "surprising", because the pharmacological effects and indications of dipyrone are the same as those of aminopyrine. However, the quantity imported does not show how many

people used the drug, at what dose and for how long; no firm incidence can be calculated from these data.

Leukopenia is not the same as agranulocytosis. The title and first sentence of Huguley's article speak of agranulocytosis; but the 1955–1959 series in the registry consists of "leukopenia" cases. Leukopenia is a fall in the total white cell count below normal (usually below $4,000/\text{mm}^3$). It can be caused by drugs, viral infections and many other causes; it is often mild and reversible. Agranulocytosis, on the other hand, is a fall in the neutrophil count below $500/\text{mm}^3$; it is a separate, potentially fatal condition presenting with sudden fever, sore throat and severe infection (Section 4.1). The article does not state by which diagnostic criterion the 18 reports after 1960 were registered. Thus two conditions of different severity were merged into the same figure and presented under the heading "dipyrone agranulocytosis". The 36% fatality rate among the reported patients is likewise the rate of this mixed series; it cannot be regarded as a separate measure for either leukopenia or agranulocytosis. Because severe and fatal cases are more likely to be reported, this rate does not show the risk of death among those using the drug either.

The article is based on other people's data. Huguley's paper is not a clinical study; it describes not his own patients but reports sent to the AMA registry by other physicians. The real basis of its risk assessment is another drug: most of the article is devoted to the history of aminopyrine since 1897 and to studies carried out with aminopyrine in the 1930s. For example, Madison and Squier reproduced the syndrome by giving test doses to patients who had previously had agranulocytosis with aminopyrine. The causality and the magnitude of risk established for aminopyrine were transferred to dipyrone on the grounds of the chemical kinship of the two drugs. This is a variant of the problem discussed in Section 7: data from different sources and from a different drug were brought together to define the risk of a single drug.

Transfer of the risk from aminopyrine. Huguley described the relationship between aminopyrine and agranulocytosis as "clear causation" and referred to human studies suggesting a similar role for dipyrone [142]. According to the discussion section of the IAAAS report, Discombe and Huguley estimated the risk of agranulocytosis in long-term aminopyrine users at about 0.86% and 0.79%, and Huguley suggested that this risk might also apply to dipyrone; the IAAAS investigators considered these estimates biased [134]. Hedenmalm and Spigset of the Swedish Medical Products Agency also stated that the risk of dipyrone was initially assumed to be the same as that of aminopyrine, and that this estimate, proposed as about 1 in 120 patients, rested on possibly biased information from published and unpublished patient series [118]. The high risk attributed to Huguley in the literature was therefore carried over not from dipyrone data but from aminopyrine series. That both drugs can cause agranulocytosis does not mean that they do so with the same frequency.

An approximate calculation with Huguley's own data. The import figures given by Huguley allow a rough comparison. The total of 65,833 pounds of dipyrone imported between 1960 and 1962 is about 29.9 tonnes, i.e. about 30 million grams. If an average course is taken as 10 g (3 g a day for three days), this quantity corresponds to about 3

million courses. With the 18 cases reported after 1960, this means roughly 1 case per 165,000 courses; even assuming that reports reflect only one-tenth of the true cases, the risk would be about 1 in 16,500 courses. This value is 100 to 1,000 times lower than the 0.79% (about 1 in 127 users) attributed to Huguley. The uncertainties of the calculation are large: the dose per course is not known, the period in which the cases were reported does not exactly match the import period, and dipyrone was also used in veterinary medicine in the USA in those years; if part of the imports went to animals, the number of courses would be smaller and the risk higher. Nevertheless, the calculation shows that the usage data Huguley himself provided are not consistent with the magnitude of risk he proposed.

Institutional influence. The influence of the article grew with institutional support. The AMA Council on Drugs issued a statement to draw attention to dipyrone, and Huguley's article reinforced this warning [142]. In October 1964 the FDA set up a special advisory committee on aminopyrine and dipyrone and announced that 40 blood dyscrasias associated with dipyrone had been reported to the AMA since 1959, 13 of them fatal [143]. These figures cannot be combined directly with Huguley's series; "blood dyscrasia", "leukopenia" and "agranulocytosis" have different scopes. In the same year an editorial in the Canadian Medical Association Journal [144] discussed aminopyrine and dipyrone together; but it contains no new patient data. The title of the article became an effective warning that reinforced the perception of danger surrounding the drug.

Registry systems can give a serious safety signal; but since they do not know how many people used the drug, they cannot measure the frequency of the risk. Huguley's historical importance lies in making serious and fatal cases visible. Its methodological weaknesses are that it did not distinguish leukopenia from agranulocytosis, that there was no reliable exposure denominator, and that a quantitative risk was transferred from aminopyrine to dipyrone.

5.3 1973-1977: The Swedish and US decisions

Sweden withdrew metamizole from the market in 1974 and the USA in 1977. In the USA the approvals of dipyrone products (Dimethone tablets and injection, Protemp oral liquid, etc.) were withdrawn on 27 June 1977 on the grounds of their association with "agranulocytosis, which may be fatal" [131] (Federal Register, 17 June 1977, 42 FR 30893). The text of the decision gives no magnitude of risk. The Swedish estimate of "1/3,000 users" has been frequently repeated in later literature [133, 145]. According to Hedenmalm and Spigset, Sweden's 1974 decision rests on Böttiger and Westerholm's estimate of 1 case in 3,000 patients [118, 130]; most of the cases reported between 1966 and 1974 were patients using combination products containing a spasmolytic for biliary colic. The number of cases from which this value was calculated and how the number of users was determined are of key importance for judging the methodological soundness of the decision. As we emphasised in our earlier article published on klinikfarmakoloji.com, "Metamizol (Novalgin): Sahipsiz İlaç" ("Metamizole (Novalgin): The Orphan Drug") [146], the Swedish decision rests on a limited number of cases and an uncertain exposure denominator.

5.4 1979: A counter-finding from Greece

Varonos et al. [132] calculated the incidence of dipyrrone agranulocytosis in Greece for the year 1975 as 1 in 133,000 to 466,000 treatments (cited in [112]). This value is 40 to 150 times lower than the rate put forward in Sweden in the same period. The difference reflects either a real biological difference between the two populations or a serious difference between the two methods of calculation; most probably both.

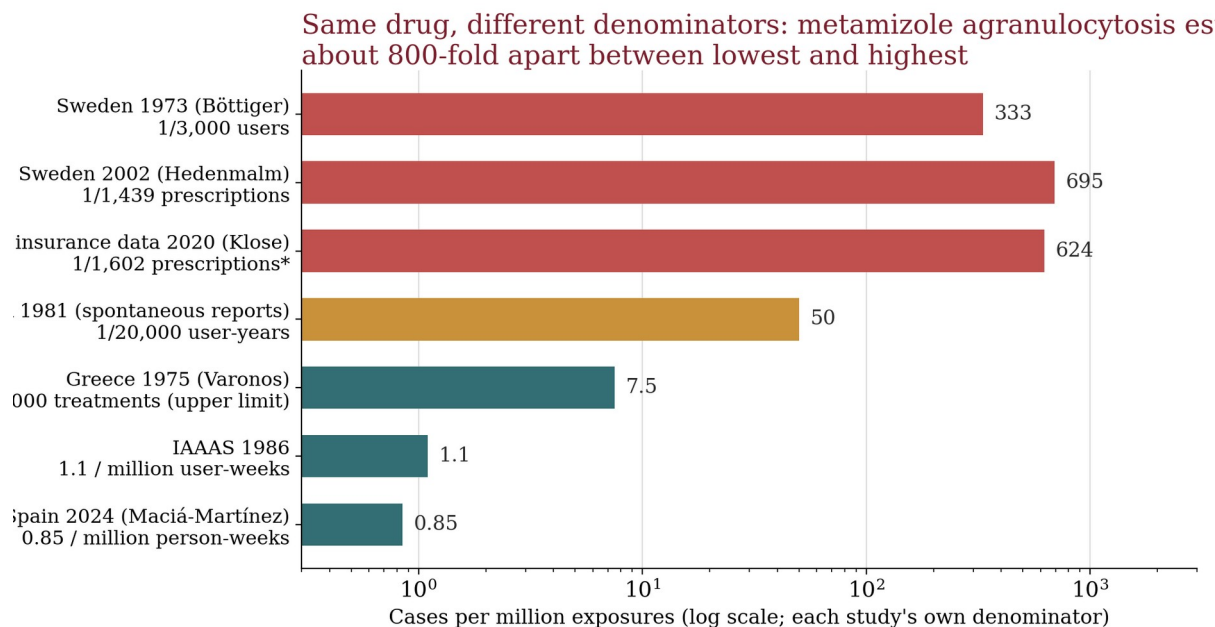


Figure 10. Published risk estimates, each with its own study's denominator, as cases per million exposures on a logarithmic scale. The difference between the red bars (user/prescription denominator) and the blue bars (person-time denominator) derives more from the unit of measurement than from biology.

6. IAAAS: The Largest Study and Its Controversies

The International Agranulocytosis and Aplastic Anemia Study (IAAAS), coordinated by the Slone Epidemiology Unit of Boston University, was conducted between July 1979 and December 1986 at centres in Israel, West Germany, Italy, Spain, Hungary, **Bulgaria** and Sweden, on a population base of about 22 million; in Sweden surveillance continued from 1987 to 1992. The study enrolled 325 cases of agranulocytosis, 185 cases of aplastic anaemia and about 2,500 controls [147]. The main result was that agranulocytosis is predominantly a drug-induced disease, with about two-thirds of cases attributable to drugs.

The first report for metamizole [134] reported an excess risk of **less than 1.1 per million users** in the one-week period after exposure. The same report showed a striking regional variability in the odds ratio: **0.8 in Budapest; 23.7 in Ulm, West Berlin and Barcelona** (cited in [11]). The absence of an association in Hungary, where metamizole was widely used, shows that even in data collected with the same protocol there were differences of up to 30-fold between regions.

6.1 The "6.2 per million per year" figure: anatomy of a citation drift

The value of "6.2 cases per million per year" attributed to the IAAAS is used in the literature in two different senses. Some sources [12, 111] give it as the risk due to metamizole, in the form "1 case per 1.1 million user-weeks or 6.2 cases per million per year", while a Colombian review [148] cites the same number as the annual incidence of agranulocytosis **from all causes** in the IAAAS. The circulation of the same figure with different meanings is a concrete example of how fragile the chains of sources in this field are.

6.2 Criticisms and counter-criticisms

The IAAAS has been criticised from two directions. Kramer, Lane and Hutchinson [135], while describing the IAAAS as "the most advanced example" of case-control pharmacoepidemiology, questioned the transferability of the reported risk estimates to clinical practice and suggested that there might be methodological problems in the selection of cases and controls, the assessment of exposure and the analytical approach. The IAAAS participants replied in the same issue [149]. Schönhöfer [133], on the other hand, pointing out that the study was supported by Hoechst, argued that the result was a "calculation trick": he contended that multiplying the IAAAS risk of 1/1.1 million per user-week by 52 yields the BGA's 1981 value of 1/20,000 user-years, and that the impression of "low risk" therefore arose merely from a change of units.

Assessing Schönhöfer's argument

This argument has a correct side: different denominators must be converted to the same unit before they are compared.

However, multiplying by 52 rests on the assumption that **every user takes the drug continuously throughout the year**. Metamizole is mostly used in courses of a few days. For a one-week course the correct unit of comparison is the risk "per course", which is around 1 per million. Continuous annual use applies only to chronic users.

The second problem: the IAAAS is not a spontaneous reporting system but a case-control study conducted on a defined population base of about 22 million and coordinated by the Slone (Drug Epidemiology) Unit in Boston [147, 150]. The BGA's value of 1/20,000, by contrast, rests on spontaneous reports and an estimated number of users; the numerators of the two values come from different sources.

The sponsorship allegation is a conflict-of-interest question that must be taken seriously; however, the accessible sources (the design paper, the Slone Center page) contain no information on funding. In any case, the source of funding alone does not invalidate a finding; the method behind the finding must be assessed. The same criterion must also be applied to findings unfavourable to the drug.

7. The Pooling Error: Adding Cases from Other Sources

Another source of high rates in the early agranulocytosis literature is the merging of cases from different countries or periods into a single series. When cases taken from another publication are added to the numerator of a series, the rate rises artificially, because the population that produced those cases is not added to the denominator. A historical example of data from other sources and from another drug being transferred to the risk of a single drug is discussed in Section 5.2.

7.1 The logic of the error

An incidence rate is obtained by dividing the number of cases observed in a given population over a given period (the numerator) by the number of people at risk in the same population over the same period (the denominator). Numerator and denominator must come **from the same population and the same period**. When cases taken from the literature, registry or publications of another country are added to the numerator of a local series while only the local number of users is used as the denominator, the rate rises artificially. Any calculation whose numerator grows but whose denominator does not overstates the risk.

A hypothetical example (not real data)

Suppose an author observes 3 cases among 30,000 users in his own region: a rate of 1/10,000.

If the author also adds to his series 7 cases from an article published in the USA as "literature cases" and does not change the denominator: 10 cases / 30,000 users = **1/3,000**.

The rate has more than tripled without any new biological information being added. An error of this kind changes the result decisively, especially in small series where the number of cases is in single figures.

8. A Systematic Analysis of Errors in the Early Studies

8.1 Drug identity: confusing aminopyrine with metamizole

A considerable proportion of the agranulocytosis series published from the 1930s to the 1960s are dominated by aminopyrine: of the 30 cases seen in Montreal between 1946 and 1964, aminopyrine was the sole cause in 8 of the 14 whose aetiology could be determined [128]. When the data of the two drugs are combined under the heading "pyrazolone agranulocytosis", the risk of the far more toxic aminopyrine is carried over to metamizole [2].

8.2 Numerator problems

- **Multiple drug use:** Most cases are taking more than one drug. Levy [151] emphasised that incrimination of a drug often rests on individual judgements

made without objective criteria, and that these judgements are **biased towards incriminating drugs already under suspicion**.

- **Combination products:** For many years metamizole was sold in combination with other active substances; attributing cases with these products to a single active substance is uncertain.
- **Definitional confusion:** Neutropenia, agranulocytosis and aplastic anaemia were not distinguished in the early studies.
- **Stimulated reporting:** After a warning about a drug is published, reports concerning that drug increase (also known as the Weber effect); this distorts time series based on spontaneous reporting.
- **The pooling error:** Division of cases compiled from different sources by a local denominator (Section 7).

8.3 Denominator problems

The largest source of the 800-fold difference between risk estimates is the denominator. "User", "prescription", "treatment", "user-week", "person-day" and "population-year" cannot be converted directly into one another. In countries where non-prescription sale is widespread (Bulgaria, Hungary, Poland) the number of prescriptions does not reflect actual use; when the number of users is estimated from sales data, the assumed average course duration determines the result. For this reason, although the values in Figure 10 are shown on a single axis, they are not biologically equivalent.

Conversions between denominators also carry assumptions. Poland's value of 0.2 cases per million treatment-days can be converted to about 1.4 cases per million use-weeks only if the risk is assumed to be constant throughout treatment; yet a large part of the cases cluster in the first two weeks. The 0.46–1.63 cases per million person-days calculated from Swiss reports (cited in [121]) and the 0.85 cases per million person-weeks of the Spanish cohort cannot be compared directly for the same reason. Similarly, the LATIN study's value of 0.38 per million per year refers to agranulocytosis from all causes, and Barcelona's value of 0.56 to the population incidence attributed to metamizole; neither directly gives the risk for a person using the drug.

8.4 The two-way uncertainty of spontaneous reporting

Schönhöfer argued that spontaneous reporting systems capture only 5–10% of actual events, so that the BGA's value of 1/20,000 actually corresponds to 1/1,000–1/3,000 [133, 145]. This reasoning assumes that the rate of under-reporting is known and constant from drug to drug. Yet as long as the rate of under-reporting is unknown, rates derived from spontaneous reporting are unreliable **in both directions**: stimulated reporting, duplicate reporting and misattribution enlarge the numerator, while under-reporting shrinks it. The right tool for incidence is therefore population-based studies with active case finding.

- Disproportionality analyses carry the same limitation. Zinzi et al. [121] found a reporting odds ratio of 41.7 (95% CI 38.2–45.5) for metamizole versus NSAIDs in EudraVigilance between 2003 and 2024; this value is 5.5 relative to clozapine and 7.3 relative to sulfasalazine. The reporting odds ratio is a measure of signal: it

shows how often metamizole and agranulocytosis are reported together, not the relative incidence among users of the drug. The same review states that the 14 studies it included gave no definitive conclusion on incidence.

8.5 The special case of the Swedish data

Hedenmalm and Spigset [118] are from the Swedish Medical Products Agency; their study was the basis for Sweden's second suspension of metamizole, in April 1999. Because the highest risk estimate of the modern era comes from this study, its full text has been assessed in detail.

Two separate series. The article examines 66 cases of blood dyscrasia reported in Sweden between 1966 and 1999; but these are not a homogeneous series. Most of the 52 cases from the 1966–1994 period had been treated, before the 1974 withdrawal, with combination products containing a spasmolytic for biliary colic (62%); the mean daily dose was 1.2 g and the median cumulative dose 12 g. In the cases reported between 1974 and 1995 the drug had been obtained abroad. In the 14 cases reported after re-authorisation in 1995, on the other hand, the drug had been used for various pains; the mean daily dose was 2.8 g and the median cumulative dose 100 g. All 15 deaths in the series occurred before 1995 (fatality rate 29%); there were no deaths among the 14 cases after 1995, and 9 of these patients received G-CSF. The fatality rate of 23% in the whole series therefore cannot be used as a current risk of death.

Definition and clinical confirmation. The study has strengths. Agranulocytosis was clearly defined as a neutrophil count of $0.5 \times 10^9/L$ or below; neutropenia, anaemia and thrombocytopenia were defined separately. Diagnoses were confirmed by peripheral blood counts and in many cases by bone marrow findings; medical records and forms completed by the patients were reviewed. Those who obtained the drug abroad were excluded from the risk calculation, outpatient cases were related only to outpatient prescriptions, and no separate risk was calculated for hospital use. The interval between last use and agranulocytosis was reported at case level. It would be unfair to characterise this study as a careless collection of reports; it strengthens the clinical evidence that metamizole can cause serious blood dyscrasias.

The basis of the 1/1,439 figure. The risk calculation rests on 8 cases of agranulocytosis reported in outpatient use between 1996 and April 1999 and on the 10,892 prescriptions dispensed by pharmacies in the same period. But dividing these two numbers gives 1/1,362; the value of 1/1,439 given in the article cannot be reproduced from these numbers, and the reason for the difference is not explained. The difference does not change the estimate much, but it shows that the result most frequently quoted in the literature cannot be verified with the numbers in the text; the method used to calculate the confidence interval (1/850–1/4,684) is not given either. In two of the eight cases a contribution from another drug was also considered; when these two cases are excluded the estimate falls to 1/1,820 prescriptions. The denominator is prescriptions, not patients; the authors pointed out that a patient may receive more than one prescription and that the number of prescriptions is an upper limit of the number of patients. The value therefore cannot be interpreted as a risk per patient, per person-day or per single dose. The problem lies not with the authors but with the subsequent literature carrying over this per-prescription estimate as if it were a per-patient risk.

Off-label long-term use. Although the drug was authorised in 1995 only for short-term pain treatment, the total duration of treatment was 13 days or longer in 7 of the 8 cases included in the calculation. Relying on a limited utilisation study from northern Sweden, the authors assumed that about half of the prescriptions covered 13 days or more, and calculated the risk as 1/810 prescriptions for use of 13 days or more and 1/5,230 for use of up to 12 days. These values are not the results of two separately followed patient groups but scenarios obtained by applying a regional distribution of durations to the whole country. Their direction is nevertheless clear: the Swedish figure derives largely from off-label long-term use. It should also be noted that the value calculated for short-term use is still well above that of the IAAAS.

Early onset and additional risk factors. The finding that 92% of cases occurred in the first two months of treatment rests not on all 66 cases but on 33 of the 36 cases for which timing information could be assessed; most patients used the drug intermittently and the duration of treatment could not always be determined. An additional risk factor was found in 36% of cases (24/66), and in 10 another drug capable of causing agranulocytosis was also being used.

The authors' explanations and under-reporting. The authors put forward two reasons to explain the difference from the IAAAS. First, since the drug had been off the market in Sweden for more than 20 years, most users were taking it for the first time; in countries where the drug has long been in use, those who have had agranulocytosis do not use the drug again, so the proportion of susceptible persons declines over time. Second, the IAAAS assumed the risk to be independent of the duration of treatment. The authors also argued that the true risk might be higher because of under-reporting, and, assuming that only 35% of cases were reported, calculated the risk as 1/480 prescriptions. This is not a measured incidence but a correction based on an assumption; for a re-authorised drug attracting attention for its safety, the reporting rate may be higher than that in earlier neutropenia studies. The authors themselves stated that their findings were "not necessarily in conflict" with the IAAAS and that a genetic predisposition in Scandinavians could be neither proposed nor excluded.

Assessment. The study of Hedenmalm and Spigset is a valuable study that clinically confirms that metamizole can cause serious blood dyscrasias. However, the 1/1,439 figure rests on a small group of cases, a prescription-based denominator and a calculation that does not fully agree with the numbers in the text; for the most part it reflects off-label long-term use. Using this figure as a per-patient risk of agranulocytosis valid for all countries is indefensible; nor does it determine the risk of short-term use or of a single parenteral dose. Whether the high rates in northern Europe reflect a genetic predisposition or patterns of use and reporting culture remains unanswered. The reporting in Finland in 2021 of 7 new cases (one fatal) despite strengthened measures was the event that triggered the 2024 EU review [12].

8.6 Geographical heterogeneity

In the IAAAS, conducted with the same protocol, the odds ratio was 0.8 in Budapest and 23.7 in the Western European centres. In the LATIN study in Latin America the incidence of agranulocytosis from all causes was 0.38 per million per year, and no significant association with metamizole exposure was found [137]. Serious cases and deaths have

been reported among British tourists in Spain [152] (the review mentions "more than 100 British tourists"). Shah [112] questioned whether these differences are related to ethnic origin. The EMA [12] left this question open.

9. The Bulgarian Experience

Bulgaria is the country systematically overlooked in the metamizole debate, yet perhaps the most instructive. The drug, widely used for decades under the name Analgin, is still sold **without prescription** today; it is one of only three countries in the EU where metamizole is sold without prescription (together with Hungary and Poland) [12].

- **Its place in the IAAAS:** Bulgaria was one of the seven countries of the IAAAS [147]. An odds ratio specific to the Sofia centre has not been reported separately in the accessible sources; in the published regional analysis the value given for Eastern Europe is Budapest's 0.8.
- **Vlahov et al. [113], Pharmacogenetics 6:67-72,** "Genetic factors and risk of agranulocytosis from metamizol": the first study to investigate HLA associations of metamizole agranulocytosis in Bulgaria. In 9 cases and 180 healthy controls in Sofia, an increased risk with HLA-A24, B7, DQw1 and DQA1*05:01 and a protective association with HLA-A2 were reported (cited in [109]; see Section 4.3). These associations could not be replicated in the Western European cohorts; but it should not be forgotten that HLA associations may be population-specific (Cismaru et al. [114, 115], on the other hand, cite the study as 5 cases; the value of 9 cases/180 controls from the systematic review has been used).
- **Consumption and number of cases:** As we have emphasised before, despite high consumption in Bulgaria and Eastern Europe, the number of reported cases of agranulocytosis has remained extremely limited [146].

10. The Boston Group: BCDSP and the Slone Epidemiology Unit

The term "Boston study" covers two separate entities in the literature, which must not be confused:

- **The Boston Collaborative Drug Surveillance Program (BCDSP):** a comprehensive monitoring programme founded in 1966 by Hershel Jick and Dennis Slone that recorded all drug use and adverse events in hospitalised patients using nurse monitors. Brogden [2] reports that in the BCDSP data dipyrrone was reported among the causes of drug rashes; in this programme the most frequent adverse effects were skin reactions.
- **The Slone Epidemiology Unit:** the unit of Boston University that coordinated the IAAAS (Kaufman, Shapiro et al.).

Micha Levy (Hadassah University Hospital), of the Jerusalem arm of the BCDSP network, is the most consistent advocate of the methodological criticisms concerning metamizole. Levy [153] wrote that "conflicting regulatory decisions" on mild analgesics "are based on indirect evidence", and that only epidemiological studies can form the basis of

scientifically sound judgements. In his 1987 assessment he emphasised that most cases were using more than one drug, that drug attribution was made without objective diagnostic criteria, and that the temporal relationship was inadequately documented.

11. Turkey

Metamizole continues to be widely used in Turkey. Following the EMA's 2024 assessment, the Ministry of Health/TİTCK issued an information letter on metamizole-containing medicines concerning "measures to minimise the serious consequences of the known risk of agranulocytosis", and the Turkish Pharmacists' Association announced it to pharmacists on 25 February 2025 [154].

Published data from Turkey are at the level of case reports and case series. Akyay and Deveci [140] from Malatya studied metamizole-associated granulocytopenia and agranulocytosis in 13 children; the mean duration of exposure was 4.64 days and the mean daily dose 40 mg/kg; agranulocytosis developed in 4 patients who had taken the drug at 30 mg/kg a day or more for 4–7 days, and all patients recovered completely within 2–30 days. A case of hepatosplenic candidiasis developing after metamizole-induced agranulocytosis has also been reported from Akdeniz University.

There is **no population-based incidence study** of metamizole agranulocytosis in Turkey. This means that regulatory decisions rest on the data of other countries rather than of the country itself. Publication of the distribution by year of reports made to TÜFAM (the Turkish Pharmacovigilance Centre), together with sales data, should be the first step.

In our view the agranulocytosis-inducing effect is related to genetic susceptibility, and in the Turkish population this risk is no different from that of other analgesics. This view is consistent with the limited number of cases reported in Turkey despite decades of widespread use; but proving it scientifically requires the population-based incidence and pharmacogenetic data proposed above (see Section 4.3).

12. Current Regulatory Status

12.1 European Medicines Agency

- **2018, Article 31 (referral by Poland):** harmonisation of the maximum dose and of the pregnancy and breastfeeding warnings in the product information (EMA/H/A-31/1469).
- **2024, Article 107i (Finland, 5 June 2024):** an urgent procedure initiated after cases continued in Finland despite the 2021 measures and the marketing authorisation holder of Litalgin withdrew its authorisation. In EudraVigilance, 1,200 cases (99.1% serious) and 120 deaths between January 2014 and May 2024; 44.6% of cases from Germany and 39.5% from Spain.
- **Outcome (September 2024):** Benefit-risk balance positive. A **boxed warning** in section 4.4 of the SmPC; contraindication in previous metamizole agranulocytosis and bone marrow dysfunction; a direct healthcare professional communication.

Because there is no evidence of its effectiveness, **the recommendation for routine blood count monitoring was removed.**

- **Minority opinion:** 11 PRAC members and one independent expert expressed the view that the benefit-risk balance was negative; one member proposed restricting the drug to prescription by pain specialists in hospital.
- **Differences between countries:** The PRAC stated that the differences between incidence estimates could be explained by differences in study design, case ascertainment and patterns of use, but might also reflect real differences in susceptibility between ethnic groups. Because it could neither confirm nor exclude either, it was unable to give a single incidence estimate for the EU as a whole, and it could not identify a genetic or ethnic patient factor with sufficient evidence [12, pp. 12–13, 17]. This conclusion proves neither that the Swedish estimates are wrong nor that ethnic difference is the explanation; it leaves the debate open.

12.2 Other countries

In 2024 Switzerland introduced a red-framed warning on the pack, clarified the second-line indications and recommended avoiding concomitant use with methotrexate [120]. In Spain the AEMPS published measures in 2018 after 79 of 115 adverse reaction reports between 2001 and 2018 concerned agranulocytosis and 10 were fatal (cited in [152]). In Germany the drug has required a prescription since 1987. Metamizole is not on the market in the USA, the UK, Canada or Australia [9].

12.3 Economic context

There is no documentary evidence that rival pharmaceutical companies played a role in the banning of metamizole in some countries. The 1977 decision in the USA rests on the FDA's ground that the products had "not been shown to be safe". The picture that can be documented is different, and it cuts both ways. First, the safety concern that took the drug off the market in the USA and the UK did not prevent the same companies from selling their products in other countries. Silverman and colleagues documented in 1982 that the dipyrone products of the American company Sterling-Winthrop and the German Hoechst were being sold in Indonesia, Malaysia and Singapore without any warning of agranulocytosis, and cited dipyrone as an example of drugs withdrawn in industrialised countries but still sold in the Third World [155]. In 1991 Winthrop was still selling dipyrone in more than 30 countries [156]. In other words, the same risk assessment was applied differently depending on the market. Second, and more importantly, a cheap drug whose patent protection expired long ago has no owner to defend it. No company has funded a new safety study or a dose-response study, and today's dose limits are for this reason not based on a systematic study (Section 3.5). Patented rival analgesics, on the other hand, have research and marketing budgets that influence guidelines and physicians' perceptions. This is a structural imbalance that requires no deliberate intervention: a drug in which no one invests to generate evidence remains defenceless against old and methodologically weak data. Nor is the conflict-of-interest question one-sided; it has been alleged that the largest study favourable to the drug, the IAAAS, was supported by the manufacturer (Section 6.2). The same criterion must be applied in both

directions: it is the method, not the source of funding, that determines the worth of a finding.

13. Comparison with Alternatives

The benefit-risk balance of metamizole must be assessed together with the risks of the drugs that would be used in its place. An international panel convened in Brazil in 2001 concluded that withdrawal of metamizole from the market would increase the indiscriminate use of other analgesics [157].

Parameter	Metamizole	Comparator	Source
Incidence of agranulocytosis (person-weeks)	8.52/10 ⁷	NSAIDs 1.62/10 ⁷ ; opioid-paracetamol 3.72/10 ⁷	Maciá-Martínez [141]
Agranulocytosis HR	Reference	4.40 vs NSAIDs (0.90–21.57); 2.45 vs opioid-paracetamol (0.68–8.83)	Maciá-Martínez [141]
Anaphylaxis	8.1/10,000 exposed (3.5–19)	Diclofenac 7.2/10,000	Cascorbi and Baron [9]
Drug-induced liver injury	1.7-fold vs paracetamol	Paracetamol reference	Cascorbi and Baron [9]
Hypotension	0.1–1%, especially parenteral		Cascorbi and Baron [9]
Gastrointestinal bleeding	Low because it is non-acidic	Known marked risk with NSAIDs	General pharmacological knowledge

Table 11. Selected safety parameters of metamizole and alternative analgesics.

It should be emphasised that the confidence interval of the hazard ratio in the Spanish cohort includes 1, i.e. it is not statistically significant. For neutropenia, on the other hand, the hazard ratio between metamizole and NSAIDs is 2.98 (1.57–5.65) and is significant.

Comparison of excess deaths. Andrade, Martinez and Walker [158] calculated excess deaths per short-term user due to selected serious adverse effects of non-opioid analgesics. The published values are per 100 million users; converted to per million, excess deaths are 0.25 for metamizole, 0.20 for paracetamol, 1.85 for aspirin and 5.92 for diclofenac (Table 12). The calculation is limited to agranulocytosis, aplastic anaemia, anaphylaxis and serious upper gastrointestinal complications; cardiovascular, renal and hepatic harms and the risks of opioids are not included. It is therefore not an all-harm ranking; nevertheless it is a direct comparison showing that in short-term use metamizole causes about 24 times fewer excess deaths than diclofenac.

Analgesic	Excess deaths / million users	Relative to diclofenac	Source
Metamizole	0.25	About 24 times fewer	Andrade [158]
Paracetamol	0.20	About 30 times fewer	Andrade [158]
Aspirin	1.85	About 3 times fewer	Andrade [158]
Diclofenac	5.92	Reference	Andrade [158]

Table 12. Excess deaths due to selected serious adverse effects, per million short-term users [158]. Covers only agranulocytosis, aplastic anaemia, anaphylaxis and serious upper gastrointestinal complications.

Modelled death scenarios. Since an observed comparison exists only in the study above, a scenario calculation was made to show what the different incidence estimates mean in terms of deaths (Table 13). In the metamizole rows the case frequency measured by each study was multiplied by the case fatality of 2.5–10% given by the EMA for the current prognosis of agranulocytosis [12, p. 13]; this is not the fatality rate measured by the studies themselves. In the NSAID rows the 30-day frequency of upper gastrointestinal bleeding observed by Pérez-Gutthann et al. [159] was multiplied by the fatality rate of 7.4–20.9% compiled by Straube et al. [160] from other populations. These values are not observed death rates or deaths attributable to the drug; their denominators (exposure-weeks, prescriptions) cannot be converted into one another either.

Analgesic and data	Observed case frequency	Scenario: deaths / million	Source
Metamizole, IAAAS	1 case / 1.1 million user-weeks	0.023–0.091 (exposure-weeks)	IAAAS [134]; EMA [12], p. 8
Metamizole, Spain	8.52 cases / 10 million person-weeks	0.021–0.085 (exposure-weeks)	Maciá-Martínez [141]
Metamizole, Germany	7.9 cases / million prescriptions	0.20–0.79 (prescriptions)	Hoffmann [119]; EMA [12], p. 7
Metamizole, Sweden	1 case / 1,439 prescriptions	17–69 (prescriptions)	Hedenmalm and Spigset [118]; EMA [12], p. 7
Ibuprofen	40 bleeds / million new prescriptions in 30 days	3–8.4 (prescriptions)	Pérez-Gutthann [159]; Straube [160]
Diclofenac	180 bleeds / million new prescriptions in 30 days	13–38 (prescriptions)	Pérez-Gutthann [159]; Straube [160]
Naproxen	230 bleeds / million new prescriptions in 30 days	17–48 (prescriptions)	Pérez-Gutthann [159]; Straube [160]

Table 13. Modelled death scenarios: case frequency × assumed case fatality (2.5–10% for metamizole, 7.4–20.9% for NSAID bleeding). These are not observed death rates; rows with an exposure-week denominator cannot be compared with prescription rows.

What the scenario says. Viewed in the same unit of measurement (million prescriptions), the scenario value for metamizole with the German estimate (0.20–0.79) is markedly below the NSAID bleeding scenarios (3–48). When the Swedish estimate is used, however, the ranking is reversed (17–69). The result therefore depends largely on which incidence estimate is accepted as correct; the problems in the numerator and denominator of the Swedish data are discussed in Section 8.5. The NSAID scenarios also cover bleeding only; if cardiovascular and renal deaths were added, the NSAID values would rise. The review by Zinzi et al. [121] is not the direct source of these scenarios; it has been used as an additional source showing the uncertainty of the incidence evidence.

Absolute risks of the alternatives. Observational studies show that the comparator drugs are not risk-free either (Table 14). The figures come from different countries, age groups and follow-up periods; they should not be used for a causal ranking. The source of the gastrointestinal bleeding row is Pérez-Gutthann et al. [159].

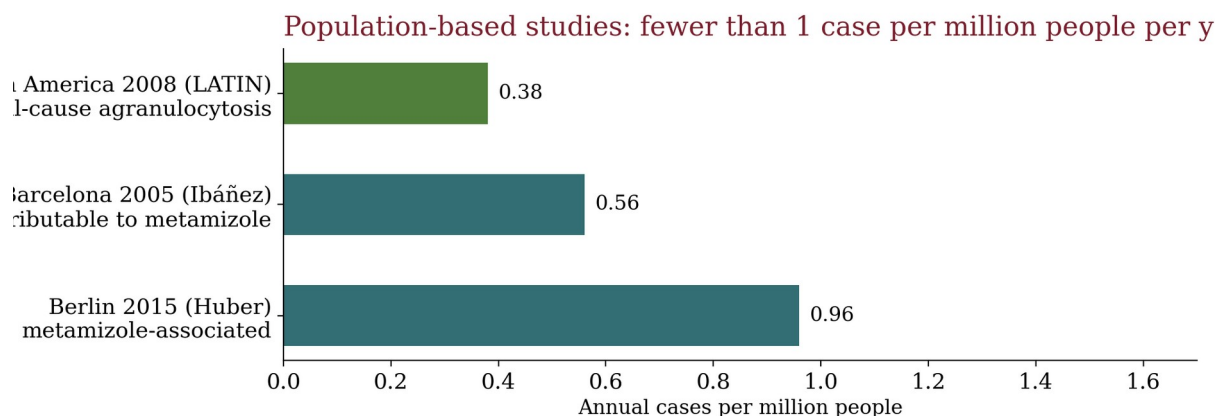
Outcome	Value	Measure	Note
Upper GI bleeding, 30	Ibuprofen 40 (4–130);	Million new prescriptions	No comparable

Outcome	Value	Measure	Note
days	diclofenac 180 (50–460); naproxen 230 (120–420)		absolute value for metamizole; relative risk 1.4–2.7 in observational studies (bleeding frequency: Pérez-Gutthann [159])
Major cardiovascular event, 30 days	Ibuprofen 751; diclofenac 1,069; naproxen 703	Million new users	These are observed events, not excess risk; no data for metamizole
Acute kidney injury, NSAIDs combined	8,242; 5,899 in non-users (difference 2,342)	Million new users, 30 days	Over 66 years of age, prescription longer than 14 days; not by drug; no increase in 30-day mortality
Misuse, poisoning, dependence	Tramadol 37; codeine 18	100,000 person-years	Follow-up over years after the first prescription; does not reflect the short course itself
Overdose (fatal or not)	Tramadol 168; codeine 76	100,000 person-years	Same cohort

Table 14. Selected absolute risks of alternative analgesics. Values left blank or marked "no data" mean "not measured", not "zero".

Differences among NSAIDs. A disproportionality analysis of the US FDA spontaneous reporting system (FAERS, 2004–2023) showed that the gastrointestinal ulcer profiles of NSAIDs differ in frequency, severity and site: non-selective NSAIDs are associated with more frequent but generally milder events, and COX-2 selective ones with rarer but more severe events [161]. Since it is a report analysis without a denominator, it gives no absolute risk; metamizole was not assessed in this analysis.

The conditions for a fair comparison. To compare metamizole correctly with its alternatives, the indication, age, baseline cardiovascular, gastrointestinal and renal risk, concomitant drugs, dose, route of administration, first or repeated exposure, number of days prescribed and the post-treatment case-finding period must be kept the same. Until such a study is done, the absence of death estimates for the vascular harms of ibuprofen, weak opioids, liver failure at therapeutic doses and acute kidney injury means "not measured", not "no risk".



In the LATIN study no significant association was found between metamizole exposure in the last 10 days and agranulocytosis. Sources: Hamerschlag 2008; Ibáñez 2005; F

Figure 11. Annual incidence in population-based studies. The LATIN value shows agranulocytosis from all causes.

14. Recommendations for Clinical Practice

- Metamizole should be used in severe acute pain and in fever unresponsive to other treatments, where other analgesics are contraindicated or insufficient.
- The duration of treatment should be kept as short as possible; if long-term use is needed, the indication should be reassessed regularly.
- Every patient should be told the warning symptoms: **fever, chills, sore throat, mouth ulcers**. With these symptoms the drug must be stopped immediately and a full blood count performed. Symptoms may also appear in the days after the drug is stopped.
- **It should not be used together with methotrexate.**
- **Metamizole reduces the effect of low-dose aspirin on platelets (a similar interaction exists with ibuprofen). In those taking aspirin for cardiovascular prevention, aspirin should be taken at least 30 minutes before metamizole [9].**
- **The drug should not be used again in patients who developed unexplained liver injury during a previous course of metamizole.**
- Previous agranulocytosis due to metamizole or other pyrazolones/pyrazolidines and bone marrow dysfunction are contraindications.
- Intravenous administration should be given **over at least 5 minutes** (about 1 ml per minute for 2.5 g) or diluted as an infusion; rapid injection can cause severe hypotension, syncope and shock (Section 3.2.1).
- There is no evidence that routine blood count monitoring prevents agranulocytosis [12]; the real protective measure is patient education.
- High doses and long-term use should be avoided in children [140].
- In use beyond one week, levels of narrow-therapeutic-range drugs metabolised by CYP3A4, CYP2B6 or CYP2C19 (tacrolimus, ciclosporin, some antidepressants and antipsychotics) should be monitored (Section 3.1.1).
- It should not be used in the last three months of pregnancy; in the first six months a single dose should be considered only if no other analgesic can be used; it should be avoided in breastfeeding mothers, and after an unavoidable single dose breastfeeding should be interrupted for 48 hours (Section 14.1).

14.1 Pregnancy and breastfeeding

The first trimester. Two prospective studies following pregnant women exposed to metamizole in the first trimester showed no increase in the risk of major malformations. In the data of four teratology information services in Israel and Italy, the rate of major malformations was 3% in 108 exposed pregnancies and 2% in a comparison group taking paracetamol (relative risk 1.55; 95% CI 0.26–9.05) [162]. In the German Embryotox cohort, the adjusted odds ratio in 446 exposed pregnancies was 1.15 (95% CI 0.4–3.5) [163]. The results are reassuring, but because the confidence intervals are wide they are not definitive proof of safety.

The second and third trimesters. According to the EMA's 2018 assessment, there is little evidence of a problem in the first six months of pregnancy; single doses are

acceptable if other analgesics cannot be used. In the last three months, however, metamizole, as with all NSAIDs, should be avoided because of evidence of effects on the kidneys and circulation of the fetus [11]. These are the prostaglandin-dependent effects known with NSAIDs: oligohydramnios due to fetal renal dysfunction and constriction of the ductus arteriosus. In the Embryotox cohort, among 1,092 pregnant women using NSAIDs or metamizole in the second and third trimesters, ductus arteriosus constriction occurred in 5 (0.5%) and oligohydramnios in 41 (3.8%; 2.5% in the comparison group; RR 1.5; 95% CI 0.9–2.4); in the second trimester the risk of oligohydramnios was markedly increased (RR 5.1; 95% CI 1.1–24.0). In this study the metamizole results were not given separately from the NSAIDs, and metamizole accounted for only 6.1% of exposures. The authors recommend that use limited to a few days in the second trimester carries no significant risk, and that ductal flow and amniotic fluid be monitored with repeated or prolonged use from late in the second trimester onwards [164].

Drug	1st trimester and up to week 20	After week 20 (2nd trimester)	3rd trimester	Main fetal risk
Metamizole	Evidence limited; single doses acceptable if no other analgesic can be used [11]; no increase in malformations in cohorts [162, 163]	Single doses, if there is no other option [11]	Contraindicated [11]	Prostaglandin-related ductus arteriosus constriction and oligohydramnios; assessed together with NSAIDs in Embryotox [164]
NSAIDs (ibuprofen, diclofenac, naproxen, ketorolac, dexametoprolol)	Should not be used unless clearly necessary [165]	Avoid; if necessary lowest dose, shortest duration; monitor amniotic fluid and ductus with use longer than a few days [165]. FDA: limited use at weeks 20–30, ultrasound if longer than 48 hours [166]	Contraindicated (EU: after week 28, FDA: after week 30) [165, 166]	Oligohydramnios, ductal constriction, maternal bleeding at delivery, suppression of uterine contractions
COX-2 inhibitors (celecoxib, etoricoxib)	Contraindicated throughout pregnancy for some; check product information [165]	Same	Contraindicated [165]	Same as NSAIDs
Acetylsalicylic acid, analgesic dose	As NSAIDs	As NSAIDs	Contraindicated	As NSAIDs; in addition, bleeding risk
Low-dose aspirin (81–150 mg; pre-eclampsia prevention)	No restriction	No restriction [166]	May be used on medical advice [166]	No fetal risk shown at this dose
Paracetamol	First-choice analgesic	First choice	First choice	No proven fetal risk in short-term use; effect of long-term use on neurodevelopment debated

Table 15. Metamizole and other analgesics in pregnancy: regulatory recommendations. The restriction placed on metamizole in the first two trimesters is no stricter than that placed on NSAIDs; the contraindication in the third trimester is common to all drugs that suppress prostaglandin synthesis.

Period	Findings	Approach
First three months	No increase in major malformations in two prospective cohorts (RR 1.55; 0.26–9.05 and adjusted OR 1.15; 0.4–3.5); wide confidence intervals	Should not be used routinely; a single dose acceptable if no other analgesic can be used

Period	Findings	Approach
Second three months	No significant risk shown with short-term use; increased risk of oligohydramnios with prolonged NSAID/metamizole use	A single dose acceptable; with repeated or prolonged use, monitor amniotic fluid and ductal flow
Last three months	Risk of fetal renal dysfunction (oligohydramnios) and constriction of the ductus arteriosus	Should not be used

Table 16. Use of metamizole in pregnancy [11, 162–164].

Transfer into breast milk. In a study in which 10 mothers were given a single oral dose of metamizole 1 g 3–5 days after delivery, all four metabolites were detected in milk; in 8 mothers from whom a single sample was taken 2.5–5.5 hours after the dose, the mean total metabolite concentration was 20.5 mg/L. The mean relative infant dose calculated from the two mothers sampled in detail was 6.8%, and the metabolites became undetectable in milk within 48 hours [167]. Episodes of cyanosis were reported in a 42-day-old infant whose mother had taken 1.5 g metamizole within 16 hours; metamizole metabolites were detected in the infant's serum and urine, and the episodes did not recur after the mother stopped the drug [168]. A case-control study in Brazil reported an approximately twofold association with acute lymphoblastic leukaemia in infants of mothers who used metamizole in the first three months after delivery; this is an observational association and does not show causation [169].

Recommendation. The EMA recommends avoiding metamizole during breastfeeding on the grounds that the infant may receive a large amount of drug through the milk relative to its body weight [11]. One manufacturer recommends interrupting breastfeeding for 48 hours after the dose. Some drug information centres in Israel consider this restriction stricter than necessary [170]. In the breastfeeding mother the first choice is ibuprofen or paracetamol; if metamizole is unavoidable a single dose should be used and, in line with the manufacturer's recommendation, breastfeeding should be interrupted for the next 48 hours [171].

15. Lesser-Known Effects of Metamizole

Metamizole is generally known only as a "painkiller and fever reducer". Yet its smooth muscle relaxant effect covers the blood vessels, kidney, gastrointestinal tract and airways; it also has effects on the central nervous system that have not yet been adequately studied. This section rests largely on studies carried out in the Department of Pharmacology and Clinical Pharmacology of Ankara University Faculty of Medicine.

The spectrum of action of metamizole

Proven: analgesic, antipyretic, smooth muscle relaxant (vascular, renal, gastrointestinal, tracheal).

To be investigated: anticonvulsant (animal data exist), anxiolytic (?), sedative (?).

15.1 Vascular smooth muscle relaxant effect

Rabbit thoracic aorta. Ergün, Ayhan and Tulunay [57] showed that metamizole produces dose- and time-dependent relaxation in rabbit thoracic aorta contracted with phenylephrine. Indometacin, another NSAID, did not produce such relaxation. The effect is independent of the presence of vascular endothelium. Tetraethylammonium (an inhibitor of calcium-activated potassium channels), glibenclamide (an inhibitor of ATP-sensitive potassium channels), indometacin (a cyclooxygenase inhibitor) and methylene blue (a soluble guanylate cyclase inhibitor) did not affect the relaxation. When the preparation was contracted with KCl (30, 60 and 117 mM) instead of phenylephrine, metamizole produced no relaxation. Ouabain (an inhibitor of the Na-K ATPase pump) reduced the relaxation dose-dependently, but no reduction in relaxation was seen in potassium-free medium, the alternative way of blocking the pump. When metamizole was pre-incubated for 2 hours under organ bath conditions, relaxation appeared more rapidly; this indicates that the effect is produced by one of the active products formed by spontaneous breakdown of the drug, probably 4-MAA.

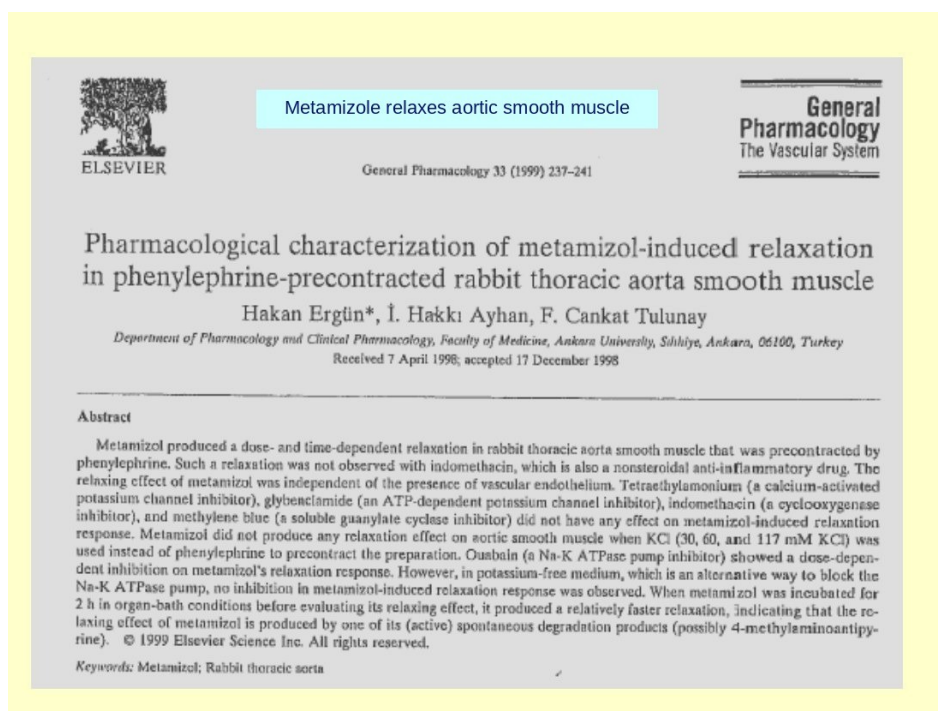
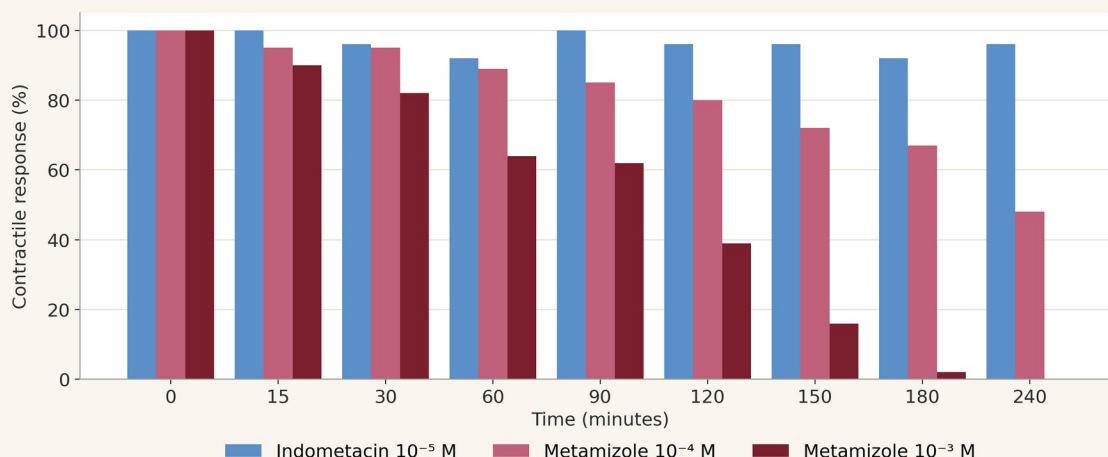


Figure 12. Ergün, Ayhan and Tulunay [57]: first page and abstract of the article. Metamizole produces endothelium-independent, dose- and time-dependent relaxation in rabbit thoracic aorta contracted with phenylephrine; indometacin does not show this effect.

Relaxant effect of metamizole in rabbit thoracic aorta

Aorta contracted with phenylephrine; change in contractile response over time. H. Ergün, İ.H. Ayhan, F.C. Tulunay, 1996



Source: F.C. Tulunay archive (published: Ergün, Ayhan and Tulunay, Gen Pharmacol 1999;33(3):237-241). Values transferred from the original graph.

Figure 13. Time course from the same study: percentage response in phenylephrine-contracted aorta (0–240 minutes). Indometacin 10⁻⁵ M (blue) does not change the contraction, whereas metamizole 10⁻⁴ M (pink) and especially 10⁻³ M (maroon) produce relaxation that increases with time; at 10⁻³ M the contraction has almost completely disappeared by 180 minutes. The slow development of relaxation is consistent with the interpretation that the effect is produced by a spontaneous breakdown product of metamizole (probably 4-MAA).

This finding is of great importance for the mechanism: since relaxation in the aorta was not blocked by glibenclamide or methylene blue, the NO-cGMP-K(ATP) pathway shown in peripheral nociceptors (Section 3.3.6) does not apply in vascular smooth muscle. By contrast, the lack of effect on KCl contraction is consistent with the receptor-mediated inositol phosphate and intracellular Ca²⁺ mechanism shown in the trachea [56]. The mechanism of action of metamizole differs from tissue to tissue.

Human umbilical artery. Ergün and Tulunay [172] showed that in human umbilical artery contracted with 5-HT, metamizole 10⁻³ M produced a marked, time-dependent relaxation, whereas in control preparations relaxation remained limited (unpublished observation).

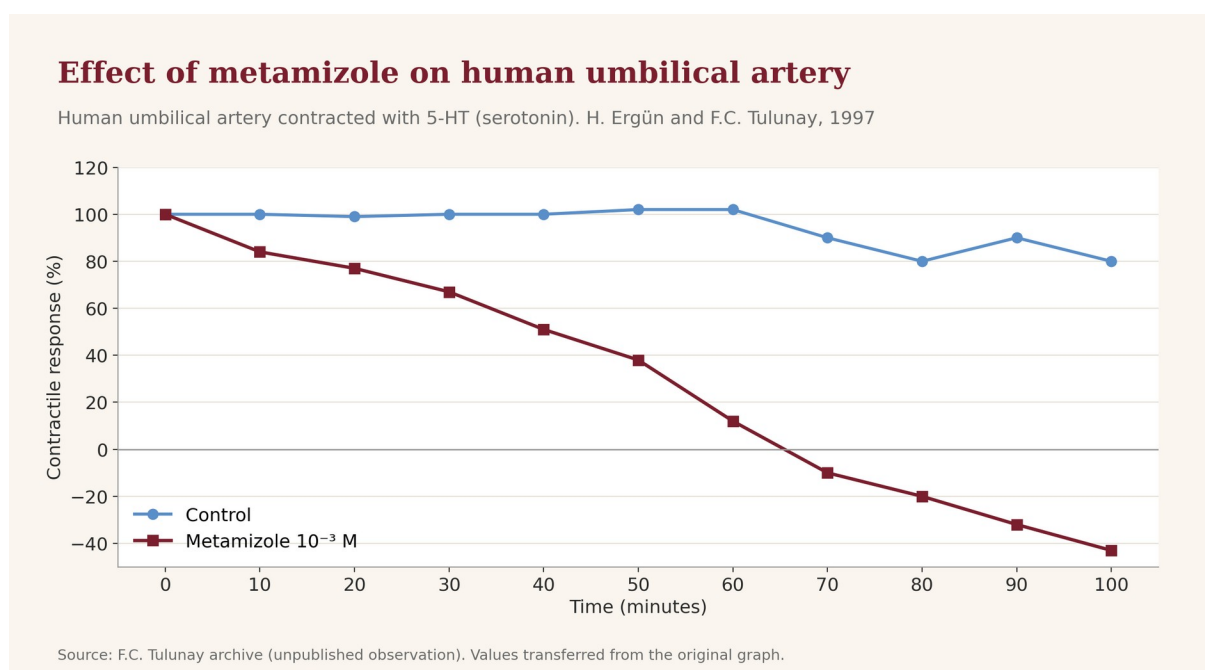


Figure 14. Ergün and Tulunay [172]: effect of metamizole (10^{-3} M) on human umbilical artery contracted with 5-HT (serotonin). In control preparations (blue) the contraction remained at 80–100% over 100 minutes, whereas metamizole (maroon) produced a marked relaxation that increased with time, and after 60–80 minutes the contraction had disappeared completely. The finding shows that the vasorelaxant effect of metamizole also applies in human vascular tissue.

Cerebral vasospasm. Ergün et al. [173] showed that metamizole has a marked spasmolytic effect in a rabbit model of basilar artery vasospasm produced by injecting autologous blood into the cisterna magna. The effect appeared with both local and intravenous administration. Given that cerebral vasospasm after subarachnoid haemorrhage is a clinical problem with high mortality, the authors suggested that metamizole, alone or in combination with other drugs, could potentially be useful in these patients. The same finding was confirmed in a more severe model: Silav et al. [174] used a model in 40 rabbits (20 in each group) in which subarachnoid haemorrhage was induced three times. Metamizole was given first intravenously and then intramuscularly every 8 hours. Basilar artery diameter was followed for 72 hours by digital subtraction angiography. After the haemorrhage the diameter fell to 71% of baseline in the control group and to 68% in the treatment group. Subsequent narrowing was less in the metamizole group at 1 and 72 hours, and endothelial oedema also remained milder. The dose used and the post-treatment diameters are not given in the abstract. Neither rabbit study measured brain tissue perfusion or neurological outcome. The dilating effect of metamizole on cerebral arteries was first observed by our team in the middle cerebral artery in 1999 (Ergün, Temiz, Bağdatoğlu and Tulunay, unpublished observation; Figure 16). This observation was later published in peer-reviewed journals in studies in which we took part [173] and in which we did not [174].

Vasorelaxant effect of metamizole in an
experimental rabbit model of cerebral vasospasm

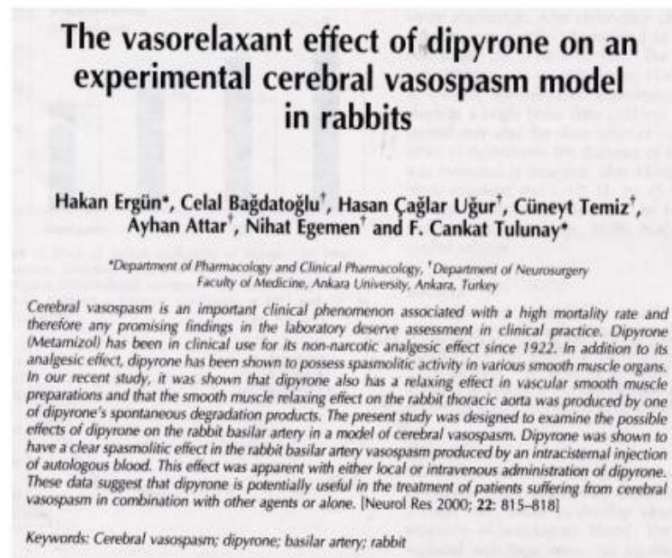


Figure 15. Ergün, Bağdatoğlu, Uğur, Temiz, Attar, Egemen and Tulunay [173]: vasorelaxant effect of metamizole in an experimental rabbit model of cerebral vasospasm. Basilar artery vasospasm produced by injecting autologous blood into the cisterna magna was relieved by both local and intravenous administration of metamizole.

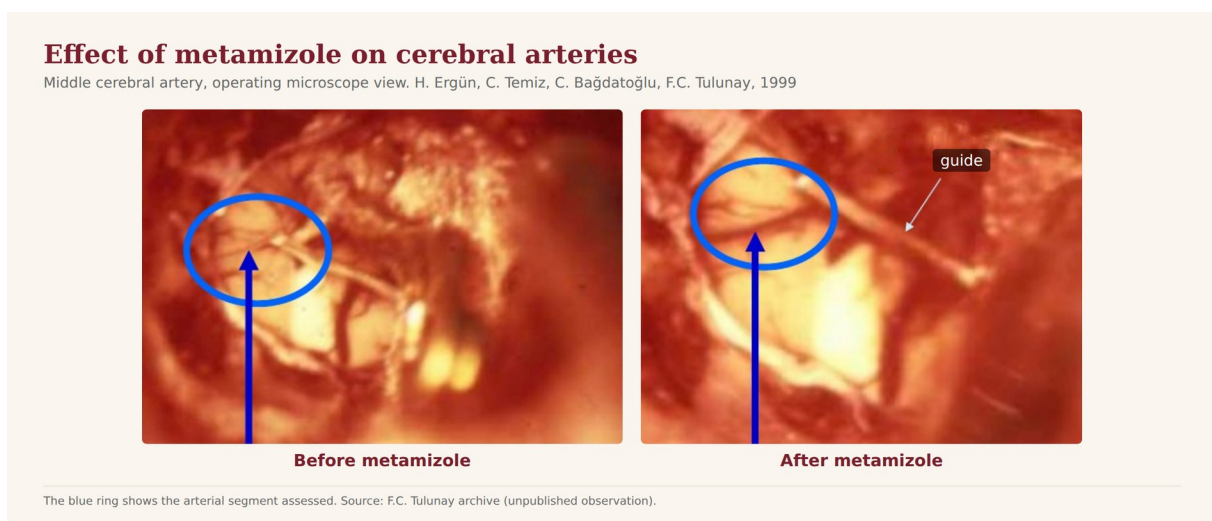


Figure 16. Ergün, Temiz, Bağdatoğlu and Tulunay [175]: operating microscope view of the middle cerebral artery before (left) and after (right) administration of metamizole. The diameter of the arterial segment within the blue ring widened markedly after metamizole.

Clinical data in subarachnoid haemorrhage. The only human data in this field are observational. Solár et al. [176] retrospectively studied 192 patients with aneurysmal subarachnoid haemorrhage. Delayed cerebral ischaemia was less frequent in patients in whom metamizole was used as the main analgesic. In these patients the likelihood of a poor outcome at 2 weeks and at 6 months was also lower. Opioids, by contrast, were associated with worse outcomes; but opioids were mostly used for sedation in severely ill patients on ventilators. Because of the retrospective design the authors claimed no definite benefit and stated that a prospective study was needed. Disease severity and the choice of analgesic may confound this association.

On the other hand, Ianosi et al. [177] monitored 77 patients with severe subarachnoid haemorrhage invasively. These patients received intravenous infusions of non-opioid analgesics and antipyretics. The study found hypotension and falls in cerebral perfusion pressure. Although there were 169 metamizole infusions in total, the results cannot be attributed to metamizole alone because they were given without separating the drugs. Still, this finding is a reminder that in a patient in whom brain perfusion is critical, intravenous metamizole can lower blood pressure.

Vasospasm in microsurgery. Studies along the same line continued in later years. After systemic metamizole had been shown to increase the viability of skin flaps [178] and flap blood flow in the early postoperative period [179] (Section 15.7), Kaya, Işılğan, Serel and Ergün [180] compared metamizole, this time applied topically, with papaverine and lidocaine, which are widely used to relieve vasospasm in microsurgery. In 35 female Wistar rats both femoral arteries were dissected under the microscope; onto the vasospasm produced by the surgical trauma itself, 0.5 ml of normal saline (control, n=8), metamizole (500 mg/ml; n=9), papaverine (20 mg/ml; n=9) or 10% lidocaine (n=9) was dripped. At baseline the mean vessel diameters did not differ between groups (0.565–0.594 mm). Diameters were measured on photographs at 5, 10, 20 and 30 minutes after application.

All three drugs significantly increased vessel diameter compared with the control group at all time points. No difference was found between metamizole and papaverine; both produced significantly greater dilatation than 10% lidocaine at all time points, and the effect persisted throughout the 30-minute observation period. The authors noted that the three drugs have a similar cost in Turkey of about 0.20 dollars per ampoule, and that they believed systemic exposure with topical use would be too low to raise concern about agranulocytosis; however, blood levels were not measured. The limitations of the study are that measurement was made on two-dimensional photographs and that anastomotic patency was not assessed. That metamizole is as potent a vasodilator as papaverine and more potent than lidocaine is consistent with the observation that, unlike lidocaine, it showed no blood "steal" effect with epidural administration (Section 16.3).

There are also experimental studies in which metamizole has been used for vasodilatation in normothermic ex vivo perfusion of rat liver grafts [181]. These findings show that the vascular smooth muscle studies begun in Ankara in the 1990s have extended into the fields of microsurgery and organ perfusion.

Skin flap viability. Ergün et al. [178] showed in an epigastric island flap model in 23 rats that a single intraperitoneal dose of metamizole 50 mg/kg given one hour before the flap was raised significantly reduced ischaemic necrosis ($p < 0.001$). According to the authors, the spasmolytic effect on vascular smooth muscle must be independent of receptors activated by vasoactive substances; metamizole may be useful in the prevention and treatment of flap ischaemia and necrosis.



Figure 17. Ergün, Çilingir, Apaydın, Erçöçen and Tulunay: epigastric island flap in rats not given (left) and given (right) metamizole. The red rings show the area of necrosis; the area of necrosis is markedly smaller in the metamizole group [178].

Peripheral blood flow in Buerger's disease. The effect of epidural metamizole on peripheral blood flow in a patient with Buerger's disease is discussed in a separate section, as it is our original contribution in this field (Section 16).

15.2 The airways

Tracheal smooth muscle. Gülmez, Gürdal and Tulunay [56] showed that metamizole relaxes tracheal smooth muscle contractions induced by histamine and ATP and reduces inositol phosphate accumulation and the ATP-induced rise in intracellular Ca^{2+} , but does not markedly affect KCl contraction (details: Section 3.3.8).

Asthma. Gülmez, Çelik, Mısırlıgil and Tulunay [182] investigated whether their in vitro findings in guinea-pig trachea had a counterpart in patients. In 22 patients aged 18–75 years diagnosed with asthma according to American Thoracic Society criteria and with an indication for metamizole, pulmonary function tests were performed before and 30, 60, 90 and 120 minutes after oral metamizole 1 g; after a washout period of at least 2 days the tests were repeated on a spontaneous-variation day without metamizole. Patients were classified by baseline FEV1 as having mild (80% of predicted or more) or moderate obstruction (60–80%). **Only in patients with moderate obstruction** did metamizole produce significant improvement in FEV1, in flow rates at 25%, 50% and 75% of forced vital capacity and in maximal mid-expiratory flow (MMEF): FEV1 increased by a mean of 0.06 L (5%) at 30 minutes and by a maximum of 0.11 L (8%) at 90 minutes; MMEF improved by 26% at 90 minutes. On the spontaneous-variation day no significant change was seen apart from FEV1. This finding is particularly important: whereas acetylsalicylic acid and other NSAIDs can trigger bronchospasm in some asthmatic patients, metamizole can relax the small airways in asthmatics with moderate obstruction. It should nevertheless be remembered that hypersensitivity reactions to pyrazolones have also been reported [25].

COPD. Gülmez, Tulunay, Beder, Kayacan and Karnak [183] examined the same question in 15 healthy volunteers and 15 patients with stable COPD. Spirometry was performed before and 30, 60, 90 and 120 minutes after oral metamizole 20 mg/kg; in neither group

did any spirometric parameter change significantly from baseline. Metamizole showed no bronchodilator effect in COPD patients or healthy volunteers, but did not impair respiratory function; the authors concluded that metamizole can be used safely in COPD patients when indicated. Read together, the asthma and COPD results indicate that the relaxant effect of metamizole on the airways appears where reversible bronchoconstriction is present.

15.3 Central nervous system: anticonvulsant effect

Ergün, Uzbay, Çelik, Kayır, Yeşilyurt and Tulunay [184] studied the effect of metamizole on ethanol withdrawal and pentylenetetrazol (PTZ) seizures in male Wistar rats. The rats were given 7.2% ethanol in a liquid diet for 21 days; at the 6th hour of withdrawal seizures were induced by a 60-second auditory stimulus. Metamizole (50, 100 and 200 mg/kg) given intraperitoneally 30 minutes before the auditory stimulus significantly and dose-dependently reduced both the frequency and the severity of audiogenic seizures due to ethanol withdrawal. Metamizole also significantly reduced the severity of seizures induced by PTZ (50 mg/kg), but did not change the latency to seizure onset. The same doses did not change locomotor activity in normal rats. The authors suggested that metamizole shows an anticonvulsant effect in both models and might be a new approach in the treatment of seizures.

Anxiolytic and sedative effects remain questions awaiting an answer.

15.4 Local and spinal administration

Local antinociceptive effect. The mouse radiant heat tail-flick test is a model that has repeatedly been found insensitive to the analgesic effect of NSAIDs; the test relies on a strong heat stimulus processed by spinal circuits and supraspinal modulation. Doğrul, Gülmez, Deveci, Gül, Ossipov, Porreca and Tulunay [48] injected diclofenac, metamizole (dipyrone), ketorolac, lysine acetylsalicylate and sodium salicylate intradermally into the tails of mice (3–300 µg) and compared the results with intraperitoneal administration. Each NSAID given intradermally prolonged tail-flick latency dose-dependently; when the same drugs were given intraperitoneally no antinociceptive effect was seen. Naloxone pretreatment did not change the local effect of diclofenac, ketorolac, lysine acetylsalicylate or sodium salicylate, but completely abolished the local antinociceptive effect of metamizole.

This finding is important in two respects. First, it shows that NSAIDs can act locally even against a strong heat-induced pain stimulus. Second, it shows that the endogenous opioid system participates not only in the central (Section 3.3.4) but also in the peripheral antinociceptive effect of metamizole, whereas it plays no role in the effect of the other NSAIDs. In this respect metamizole has a mechanism different from that of classical NSAIDs.

Local antinociceptive effect of metamizole

Doğrul, Gülmez, Deveci, Gül, Ossipov, Porreca and Tulunay, Anesth Analg 2007;104(4):927-935

1 Model

Radiant heat tail-flick test in mice. A model known to be insensitive to systemic NSAIDs.

2 Administration

NSAIDs were injected intradermally into the tail (3-300 µg); the result was compared with intraperitoneal administration.

3 Naloxone test

Whether the local effect depends on endogenous opioids was tested with naloxone pretreatment.

Drug	Intradermal (local)	Intraperitoneal (systemic)	Naloxone pretreatment
Metamizole (dipyrone)	Dose-dependent antinociception	No effect	Local effect completely abolished
Diclofenac	Dose-dependent antinociception	No effect	Unchanged
Ketorolac	Dose-dependent antinociception	No effect	Unchanged
Lysine acetylsalicylate	Dose-dependent antinociception	No effect	Unchanged
Sodium salicylate	Dose-dependent antinociception	No effect	Unchanged

Conclusion: NSAIDs and metamizole also reduce pain when given locally into the tissue. Among these drugs only the local effect of metamizole is abolished by naloxone; that is, endogenous opioids play a role in the peripheral effect of metamizole.

Source: F.C. Tulunay archive; Sections 3.3.4 and 15.4 of the monograph.

Figure 18. Local antinociceptive effect of metamizole [48]. Metamizole and NSAIDs injected intradermally into the mouse tail produced dose-dependent antinociception, whereas the same drugs were ineffective when given intraperitoneally. Naloxone abolished only the local effect of metamizole.

Epidural metamizole in terminal cancer patients. This subject is discussed in Section 16, together with the findings in Buerger's disease.

15.5 Other lesser-known effects

- Enzyme induction (CYP2B6, CYP2C19, CYP3A4) and resulting drug interactions (tacrolimus, ciclosporin, bupropion, efavirenz, sertraline, quetiapine, etc.; Section 3.1.1)
- Drug-induced liver injury (in Hamburg metamizole accounted for 14.9% of cases of drug-induced liver injury, second only to phenprocoumon; in Munich metamizole in 61 of 324 cases; cases of acute liver failure and cases requiring transplantation have been reported; Section 15.7)
- Reduced antiplatelet effect of low-dose aspirin; aspirin should be taken at least 30 minutes before metamizole [9] (Section 14)
- Reddish discolouration of the urine due to metabolites (rubazonic acid)

Calming of the breastfed infant. Linder et al. [185] compared, blind, the infants of mothers given a single dose of metamizole 1 g or placebo for uterine pain at least three days after delivery. Infants in the metamizole group cried less often and for shorter periods over the next 14 hours; the difference was more marked in infants breastfed on demand than in those fed at fixed times. This finding is consistent with the observation that "when the mother takes metamizole the baby becomes calmer", and suggests that metabolites passing into the milk can have a pharmacological effect in the infant. However, these data are not sufficient to separate a direct effect of the metabolites from the indirect effect of the mother's reduced pain on care and breastfeeding. Transfer into milk and recommendations for use during breastfeeding are given in Section 14.1.

Renal ischaemia-reperfusion injury (experimental). Kadar et al. [186] gave metamizole (100 or 200 mg/kg) to 32 male Wistar rats 30 minutes before clamping both renal pedicles for 45 minutes and assessed injury in blood and renal tissue 12 hours later. Compared with the ischaemia-reperfusion control group, metamizole 100 mg/kg

significantly lowered serum IL-18 (86.9 ± 8.3 versus 114.1 ± 12.1 ; $p=0.007$); at 200 mg/kg the difference was not significant (98.8 ± 5.8 ; $p=0.123$). Myeloperoxidase was lowest in the 100 mg/kg group (14.78 ± 2.01). No difference between the groups was seen in NGAL, an early marker of kidney injury. There was an overall difference between the groups in the histopathological (EGTI) score (median: ischaemia control 10.5, both dose groups 9; $p=0.021$), but pairwise comparisons were not reported. The authors concluded that metamizole could be used to prevent ischaemia-reperfusion kidney injury. This conclusion rests on a small animal study, 12 hours of follow-up and biomarkers rather than renal function tests such as creatinine; the unchanged NGAL and the ineffectiveness of the higher dose limit its interpretation. The finding is consistent with the view that metamizole is not harmful to the kidney, but it is no substitute for evidence of renal safety in humans.

15.6 The smooth muscle effect varies by tissue and model

The effect of metamizole and its main metabolite 4-MAA on smooth muscle cannot be explained by a single spasmolytic pathway. The experiments differ in tissue, species, the stimulus initiating contraction, duration of exposure and whether the parent drug or the metabolite is present. A change in tension in an organ bath, a pressure measurement, the distribution of a radioactive tracer or a reduction in pain do not by themselves show that the drug acts directly on smooth muscle. Table 17 separates the published findings by tissue and level of evidence.

Tissue and model	Finding	Level of evidence	Source
Rabbit thoracic aorta	Endothelium-independent, time-dependent relaxation of phenylephrine contraction; no relaxation of KCl contraction; glibenclamide, TEA, indometacin and methylene blue ineffective, ouabain attenuating	In vitro	Ergün [57]
Rat thoracic aorta	Suppresses angiotensin II contraction more strongly than noradrenaline contraction; glibenclamide prevents this effect; K(ATP) current increases at 3 mM	In vitro, patch-clamp	Valenzuela [187]
Human bypass grafts	Internal mammary artery contracts at 1–10 μ M (dependent on endothelium and COX products); saphenous vein relaxes after brief contraction	Ex vivo human tissue	Hoenicka [188]
Rabbit basilar artery, rat femoral artery	Experimental cerebral vasospasm reduced; with topical application arterial diameter increases as much as with papaverine	Animal, in vivo	Ergün [173]; Kaya [180]; Silav [174]
Rat liver graft perfusion	Metamizole added to the perfusion circuit lowers arterial pressure; all groups had received metamizole beforehand	Ex vivo organ	Claussen [181]
Human myocardial scintigraphy (21 patients)	Sestamibi distribution changes after 1 g oral metamizole, blood pressure unchanged; coronary diameter or flow not measured	Human, indirect	Ergün EL [189]
Pulmonary hypertension (4,278 patients)	Metamizole use associated with less ventilation and hospitalisation; pressure and resistance not measured	Database analysis	Hertel [190]
Guinea-pig trachea	Relaxation of histamine and ATP contractions, not of KCl; inositol phosphate accumulation and intracellular Ca^{2+} response reduced	In vitro	Gülmez [56] (Pharmacology)
Asthma (20 patients) and COPD (15 patients)	Small airway flows improve in moderately obstructed asthma; no change in mild obstruction or COPD	Human, open-label	Gülmez [182]; Gülmez [183] (Respir Med)
Swine uterus;	No metamizole-specific dose-response data;	Ex vivo; animal,	Künzel [191]; El

Tissue and model	Finding	Level of evidence	Source
pregnant and non-pregnant sheep	directly administered 4-AA reduces myometrial contractures, PGF ₂ α metabolite falls	in vivo	Badry [192]; Yarrington [193]
Guinea-pig small intestine and ileum	10–100 μ M does not change peristalsis; 100–500 μ M reduces cholinergic and myogenic contractions in ileal strips	In vitro	Herbert [64]; Donnerer [194]
Rat stomach	Gastric compliance increases, liquid emptying delayed; β 2 blockade abolishes the delay	Animal, in vivo	Vinagre [61, 195]
Human sphincter of Oddi (36 patients, 6 groups)	2.5 g IV metamizole lowers basal sphincter pressure (5-minute recording)	Human, manometry	Brandstätter [63]
Opossum biliary tract	No change in biliary pressure compared with control	Animal, in vivo	Coelho [196]
Human upper urinary tract tissue	Metamizole alone up to 1 mM does not change spontaneous activity; the relaxant effect of the combination product belongs to pitofenone	In vitro human tissue	Hertle [197]
Rat and sheep ureter; 5 patients	Intraureteric pressure falls in complete obstruction, motility unchanged at normal pressure (rat); contraction frequency reduced, mean pressure unchanged (sheep); passage of tracer to the bladder slowed (human)	Animal and human, in vivo	Laird [93]; Khater [94]; Schroth [198]

Table 17. Effects of metamizole on smooth muscle and smooth muscle-related physiology: by tissue, model and level of evidence.

Three lessons from the table. First, the response depends on tissue, species, stimulus and concentration; in human internal mammary artery even its direction is reversed. Second, the mechanism is not single: in rabbit aorta glibenclamide does not affect relaxation, whereas in rat aorta it prevents the angiotensin II response; these two findings cannot be reconciled by treating K(ATP) opening as a general mechanism. The lack of response in KCl contractions argues against a general effect related to depolarisation, but does not prove a direct calcium channel target. Third, a physiological smooth muscle response measured in humans exists in two areas: the small airways in moderately obstructed asthma, and sphincter of Oddi pressure.

What it means for colic. The analgesic efficacy of metamizole in renal and biliary colic has been shown in clinical studies (Section 3.5). How much of this effect derives from smooth muscle relaxation is a separate question. The fall in pressure in the sphincter of Oddi has been measured in humans; for the ureter, direct relaxation has not been shown in human tissue, and there is no evidence that it speeds stone passage. Nor has it been proven that the vasorelaxant effect translates into a useful therapeutic effect in patients, or that it has a tocolytic effect in the uterus or a motility-correcting effect in the bowel. Mechanistic claims should therefore be made with the tissue, species, stimulus, exposure and measured end point specified.

The methods of three conflicting studies. Three studies that appear to conflict with the thesis deserve separate methodological assessment. Hertle and Nawrath [197] studied human upper urinary tract tissue in an isolated organ bath. Metamizole is a prodrug; the active metabolites are formed by hydrolysis, and in rabbit aorta relaxation developed only over hours and was accelerated by pre-incubation [57]. A short organ bath exposure measures the effect of the parent compound and can miss a metabolite-mediated effect; in such a study, therefore, the duration of exposure and whether the metabolites were tested separately are decisive for interpreting the result. Moreover, in

renal colic pain part of the pressure rise behind the obstruction is prostaglandin-mediated; the fact that in rats metamizole lowered intraureteric pressure by 25% in 10 minutes during complete obstruction, yet was ineffective in the normal ureter [93] (Section 3.5.1), shows that clinical benefit can be achieved even without direct relaxation of isolated ureteric muscle. Hoenicka et al. [188] used surplus graft segments from coronary bypass surgery (internal mammary artery only 6 samples). The contraction in the artery was abolished by removing the endothelium or by indometacin; that is, it arises not from the smooth muscle itself but from endothelium-derived cyclooxygenase products. In the same study the saphenous vein relaxed. That the samples were taken from patients with advanced atherosclerosis, and the relation of the 1–10 μM concentrations to clinical plasma levels, also need to be considered. Coelho et al. [196] found in the conscious opossum that metamizole neither increased nor decreased biliary pressure. What matters most for biliary colic is that metamizole, unlike opioids, does not contract the sphincter of Oddi; the absence of a fall in pressure under basal conditions without spasm does not contradict a relaxant effect in spasm, and in humans manometry has shown that basal sphincter pressure falls [63]. In conclusion, these three studies do not refute the thesis; but they limit the generalisation that "metamizole directly relaxes smooth muscle in every tissue".

15.7 Tissue perfusion and organ transplantation: the limits of the evidence

The vasorelaxant effect of metamizole has also attracted interest in fields where tissue perfusion is decisive, such as flap surgery and organ transplantation. In this field a change in vessel diameter, pressure measured at constant flow, capillary flow and continued graft function are separate claims, and the evidence must be assessed separately for each.

Skin flaps and microsurgery. In the epigastric island flap model of Ergün et al. [178] in 23 rats, a single dose of metamizole 50 mg/kg given one hour before the flap was raised reduced ischaemic necrosis on day seven ($p < 0.001$); since the accessible abstract does not give the absolute value of the surviving area or the group distribution, the size of the gain cannot be calculated. Gülmez et al. [179] gave metamizole 100 mg/kg a day or normal saline for seven days to 27 male Wistar rats with a 4×10 cm random dorsal flap. Local blood flow measured by laser Doppler was higher in the treatment group only at the measurement immediately after surgery; the area of necrosis on day seven was numerically smaller but did not reach statistical significance ($p = 0.09$). In the study of Kaya et al. [180] topical metamizole increased the diameter of the rat femoral artery as much as papaverine, but flap, anastomosis or patency end points were not examined. There is no controlled study comparing free flap, musculocutaneous flap or microvascular anastomosis success with metamizole.

Liver. Claussen et al. [181] compared dual-vessel (portal vein and hepatic artery) perfusion with single-vessel (portal only) perfusion in six-hour normothermic ex vivo perfusion of explanted rat livers (4 livers per group). In the dual-vessel groups, 100 mg boluses of metamizole were given into the hepatic artery circuit hourly or when arterial pressure reached 110 mmHg. In the dual-vessel circuit without additional metamizole, arterial pressure rose to as much as 190 mmHg by the sixth hour, whereas in the circuits

given metamizole the pressure stayed below the threshold; the difference was significant between hours 3 and 6. This finding shows that circuit resistance fell, but increased flow in the hepatic microcirculation was not measured directly. All donor rats, including the group not receiving additional drug, were given 100 mg/kg subcutaneous metamizole at organ retrieval; the 100 mg bolus given into the circuit is also a local exposure too high to be compared with a clinical dose. The livers were not transplanted, and graft function in a recipient was not followed. The finding therefore shows improved pressure control in a small ex vivo model, not that the transplanted liver is protected.

Liver safety. Any possible benefit for the liver must be weighed together with the negative data. At a reference centre in Hamburg, metamizole was held responsible in 23 of 154 patients with drug-induced liver injury; two of these developed acute liver failure and underwent liver transplantation [199]. Pohl et al. [200] reported two further patients requiring emergency transplantation for metamizole-associated acute liver failure. In Munich, 61 of 324 cases of drug-induced liver injury were associated with metamizole; 16 of these developed acute liver failure, and 8 died or were transplanted [201]. These proportions relate to selected referral cases and do not show the frequency among all users; since the case series may partly overlap, they should not be added together. These data do not invalidate the ex vivo haemodynamic finding, but they do not permit the claim that metamizole protects the liver or is safe in liver recipients.

Kidney. The closest direct human data are not from a transplantation study. In the randomised three-way crossover study of Farker et al. [202], 12 healthy male volunteers were given oral metamizole, diclofenac and placebo for three days; compared with placebo, metamizole (1 g $\times$ 3 for two days, 1 g $\times$ 2 on the third day) did not significantly change PAH clearance, the indicator of effective renal plasma flow, or inulin and creatinine clearance. Blaser et al. [203] compared metamizole (1 g $\times$ 3; 8 subjects) with naproxen (500 mg $\times$ 2; 7 subjects) for seven days in healthy men on moderate salt restriction. Both drugs reduced urinary excretion of the prostacyclin metabolite 6-keto-PGF $_{1\alpha}$, but neither significantly changed inulin or creatinine clearance or sodium excretion; renal blood flow was not measured. These two studies show that short-term metamizole use does not impair renal function in healthy people, but not that it increases renal perfusion or is safer than NSAIDs. The reduction in inflammatory markers in the rat ischaemia-reperfusion model of Kadar et al. [186] (Section 15.5) likewise cannot be interpreted as preserved perfusion or graft function, since renal microcirculation, glomerular filtration and the function of a transplanted graft were not measured.

Myocardium. Ergün EL et al. [189] gave 21 patients oral metamizole 1 g before sestamibi scintigraphy. Uptake improved in 8 of 14 apparently fixed defect segments, and relative uptake increased significantly ($p < 0.001$); blood pressure did not change. Aksoy et al. [204] confirmed the finding with thallium-201. Twenty patients with partially reversible or irreversible defects on routine study were given oral metamizole 1 g, and thallium was injected 45 minutes later. In 26 ischaemic walls uptake was significantly higher than on redistribution and reinjection images ($p < 0.001$). Fourteen walls showed no uptake on either study and were assessed as infarcts. Coronary angiography agreed with the images obtained with metamizole. An asymptomatic but significant fall in blood pressure was seen. These two studies are uncontrolled and measure the relative

distribution of the isotope, not absolute flow. Nevertheless, they are the only published data in humans showing that metamizole affects perfusion in a vascular bed.

Conclusion. There is no controlled study of kidney or liver graft perfusion or graft function with metamizole. An experimental signal of benefit in skin flaps, pressure control in the ex vivo liver and a reduction of inflammatory markers in the kidney have been shown; none of these can be translated into clinical benefit in a transplant patient. Moreover, the tacrolimus and ciclosporin interaction in transplant patients (Section 3.1.1) calls for particular caution.

16. Epidural Metamizole: Our Original Contribution

Metamizole is used today by the oral, intramuscular, intravenous and rectal routes. At the end of the 1990s our team administered the drug by another route, **epidurally**, and studied it in two separate clinical situations: terminal cancer pain and Buerger's disease (thromboangiitis obliterans). This section discusses in detail the finding of the second study in particular, because it reveals a property, not previously shown, that distinguishes metamizole from local anaesthetics, the standard agents for epidural administration.

16.1 Pharmacological rationale

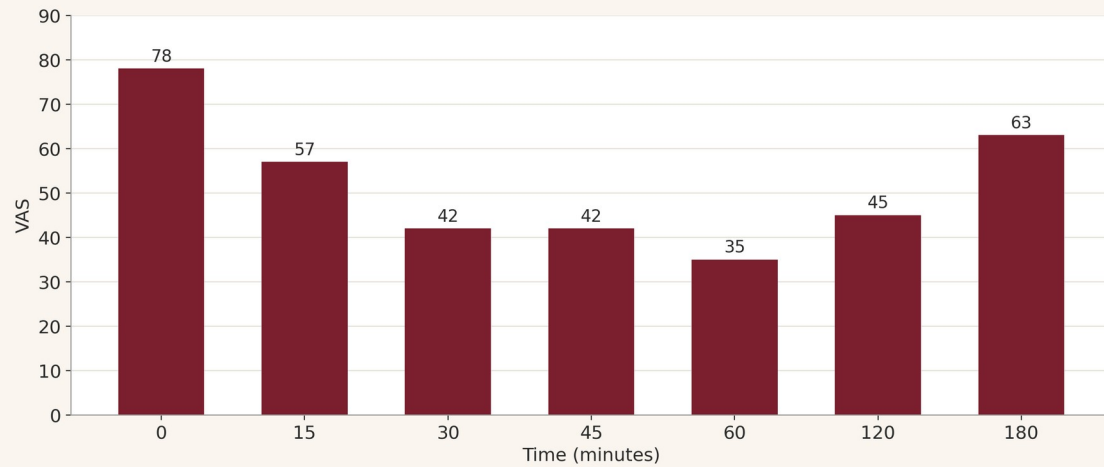
Three pharmacological observations lie behind the idea of epidural metamizole. First, a considerable part of the analgesic effect of metamizole arises at the central and spinal level: descending inhibition starting in the PAG and the endogenous opioid circuits in the raphe magnus and spinal cord mediate the antinociceptive effect of metamizole [39, 46]. Second, metamizole and 4-MAA are very water-soluble and weakly protein-bound; this property suits neuraxial administration. Third, and most important for this section, metamizole relaxes vascular smooth muscle independently of the endothelium and of receptors [57] (Figures 12–16). That is, unlike epidural local anaesthetics, metamizole affects vascular tone not through sympathetic blockade but directly through vascular smooth muscle.

16.2 Terminal cancer pain

Oral, Tulunay, Ergün and Tulunay [205] showed that epidural metamizole markedly reduced pain in patients with terminal cancer. The VAS score, about 78 at baseline, fell to about 42 at 30 minutes and about 35 at 60 minutes; the effect began to wane after 120 minutes and at 180 minutes the VAS had returned to about 63. Percentage pain relative to baseline fell to about 49% at 45 minutes (Figures 19 and 20; values read from the graphs). This is a striking finding as a non-opioid neuraxial option in terminal patients who have developed opioid tolerance or cannot tolerate opioid side effects **(unpublished observation)**.

Effect of epidural metamizole in terminal cancer pain

Pain intensity (VAS, 0-100). M. Oral, M. Tulunay, H. Ergün, F.C. Tulunay, 1998

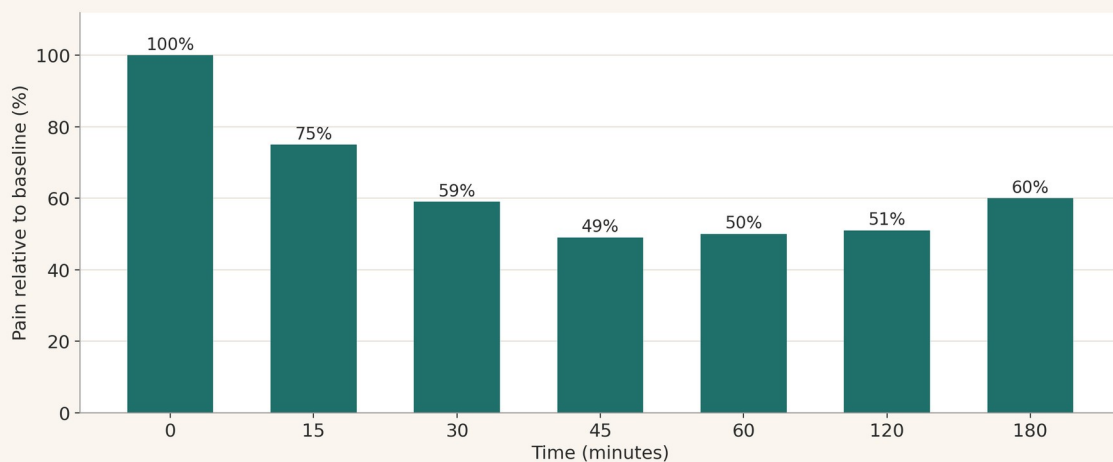


Source: F.C. Tulunay archive (unpublished observation). Values transferred from the original graph.

Figure 19. Oral, Tulunay, Ergün and Tulunay [205]: effect of epidural metamizole on pain intensity (VAS) in terminal cancer patients. The VAS score, about 78 at baseline, fell to about 42 at 30 minutes and about 35 at 60 minutes; the effect began to wane after 120 minutes and returned to about 63 at 180 minutes.

Epidural metamizole: pain relative to baseline

Pain as a proportion of baseline in terminal cancer patients. M. Oral, M. Tulunay, H. Ergün, F.C. Tulunay, 1998



Source: F.C. Tulunay archive (unpublished observation). Values transferred from the original graph.

Figure 20. Percentage pain relative to baseline in the same study: about 75% at 15 minutes and about 49% at 45 minutes; it remained around 50% between 60 and 120 minutes and rose to about 61% at 180 minutes. A preliminary finding suggesting that the epidural route may be a non-opioid option in terminal cancer pain.

16.3 Blood flow in Buerger's disease: the "steal" effect of local anaesthetics and metamizole

Buerger's disease is an inflammatory, occlusive vascular disease affecting small and medium-sized limb arteries in young adult smokers, with a course of ischaemic pain, ulceration and amputation. In these patients pain treatment and preservation of tissue perfusion must be achieved at the same time. Local anaesthetics used for epidural or

sympathetic blockade dilate vessels by abolishing sympathetic tone. Yet this dilatation occurs in healthy vascular beds whose reactivity is preserved; diseased, narrowed or occluded vessels are already maximally dilated and cannot respond. As a result, blood is diverted to the healthy beds and perfusion of the diseased region falls. This is known as the **"steal" phenomenon**.

Oral, Tulunay, Ergün and Tulunay [206] compared the effects of epidural metamizole and epidural lidocaine on blood flow in the tibial artery and the dorsalis pedis artery in a patient with Buerger's disease (a single case). The patient served as his own control, that is, the effects of the two drugs were assessed in the same patient; blood flow was measured by Doppler (Figure 21). The findings are exactly opposite:

Artery and limb	Epidural metamizole	Epidural lidocaine
Tibial artery, control limb	about +16 ml/s	about –1 ml/s
Tibial artery, diseased limb	about +2 ml/s	about –16 ml/s
Dorsalis pedis artery, control limb	about +11 ml/s	about –1 ml/s
Dorsalis pedis artery, diseased limb	about +5 ml/s	about –19 ml/s

Table 18. Effect of epidural metamizole and lidocaine on peripheral arterial blood flow in a patient with Buerger's disease (single case, patient as own control) [206]. Values are approximate changes in flow read from the graph (ml/s).

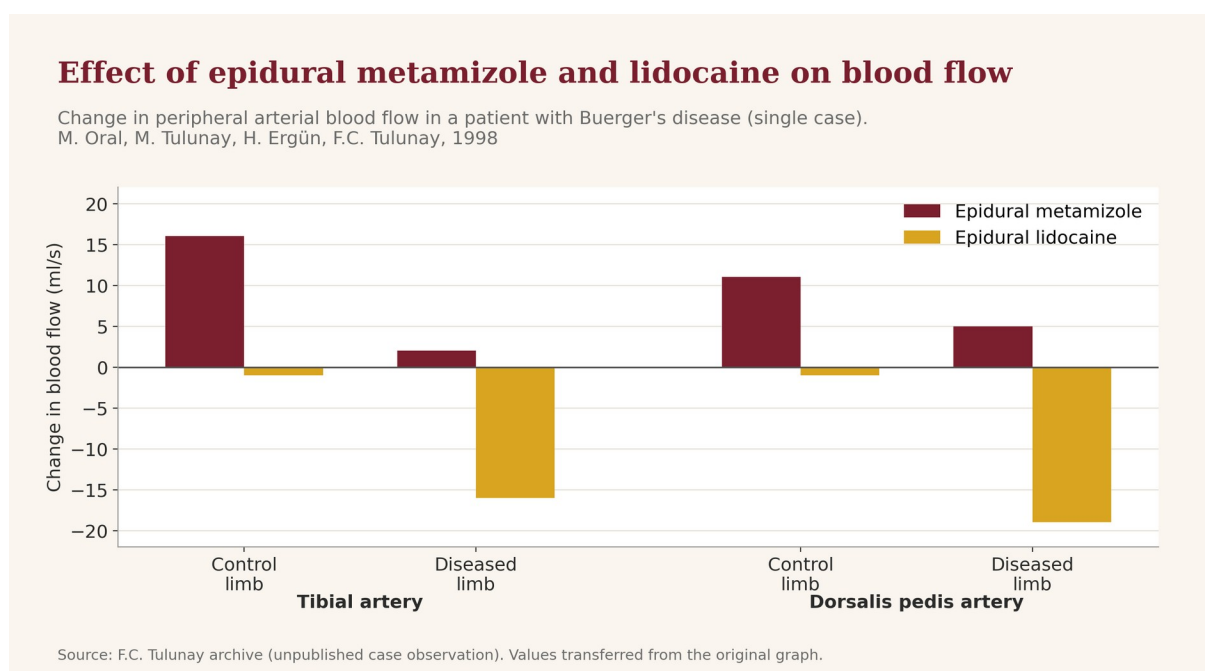


Figure 21. Oral, Tulunay, Ergün and Tulunay [206]: effect of epidural metamizole (maroon) and lidocaine (yellow) on blood flow in the tibial artery and the dorsalis pedis artery (change in ml/s) in a patient with Buerger's disease (single case). Metamizole increased blood flow in the control and the diseased limb, whereas lidocaine caused a fall of about 15–19 ml/s in the diseased limb.

Lidocaine markedly reduced blood flow in the diseased limb in both arteries; this is an example of the steal phenomenon demonstrated by clinical measurement. **Metamizole**, by contrast, increased blood flow in both the control and the diseased limb; no reduction was seen in the diseased limb. That is, metamizole does not show the steal effect seen with local anaesthetics.

The pharmacological explanation of this difference lies in our experimental studies. Local anaesthetics affect vascular tone indirectly, by blocking sympathetic fibres; the

effect therefore appears only in healthy vessels capable of a sympathetic response. Metamizole, on the other hand, relaxes vascular smooth muscle directly: in rabbit aorta the relaxation is independent of the endothelium, is unaffected by potassium channel and guanylate cyclase blockers, and is produced by the active breakdown product 4-MAA [57]; it relieves 5-HT contraction in human umbilical artery and vasospasm in rabbit basilar and middle cerebral arteries [173]; it reduces ischaemic necrosis in skin flaps [178]. A direct smooth muscle effect can also produce some dilatation in diseased vascular segments and prevents blood from being diverted to healthy beds.

A world first

That epidural metamizole increases blood flow in peripheral arterial disease (Buerger's disease) and does not show the "steal" effect seen with epidural lidocaine was, albeit in a single case, **observed for the first time in the world by our team** [206]. The literature search carried out for this monograph found no previously published study examining the effect of epidural metamizole on blood flow in peripheral arterial disease.

Clinical significance: in critical limb ischaemia, epidural local anaesthetic for pain treatment can worsen ischaemia by reducing perfusion of the diseased region. In this case metamizole, by contrast, provided analgesia while preserving and even increasing perfusion. This observation, based on a single case, needs to be confirmed in patient series and controlled studies.

16.4 Limitations and future research

The findings on epidural metamizole are at the level of unpublished observations. The Buerger finding was obtained in a single patient; it is therefore a case observation and cannot be generalised. The rarity of the disease is the main reason for this limitation, but it does not diminish the importance of the observation: the reduction of blood flow in the diseased limb by local anaesthetics (steal) and its increase by metamizole are two opposite responses in the same clinical situation, and this contrast is pharmacologically consistent with the direct vascular smooth muscle relaxant effect of metamizole (Sections 3.3.8 and 15.6). Studying the patient as his own control shows that the contrast between the two drugs does not stem from differences between patients. Both findings should be regarded as preliminary observations. The epidural route is not an authorised route of administration for metamizole; neuraxial safety (neurotoxicity, excipients) must be assessed in controlled studies. Nevertheless, this case observation shows that metamizole may have a unique place in clinical conditions involving both pain and ischaemia (critical limb ischaemia, Buerger's disease, vasospastic conditions), and it deserves to be tested first in case series and then in randomised controlled trials.

Independent literature on peripheral arterial disease. In occlusive or vasospastic peripheral disease the independent literature treats metamizole as a painkiller; there is no perfusion indication. A survey of physicians in Germany reported that metamizole and paracetamol are widely used for chronic ischaemic pain, but blood flow was not measured [207]. In a Buerger case from Spain, finger pain did not resolve with metamizole and nifedipine but improved after treatment including iloprost. The effect of

metamizole on the circulation was not measured in this case [208]. There is no controlled study examining the effect of metamizole on perfusion in Buerger's disease, Raynaud's phenomenon or peripheral arterial disease.

17. Conclusion

Despite its century-long history, metamizole is still a drug whose pharmacology is insufficiently known. The evidence gathered in this monograph shows that metamizole is not merely "a painkiller with controversial side effects" but has a pharmacological profile unlike any other among the non-opioid analgesics. The evidence can be summarised in five main conclusions.

17.1 The most potent non-opioid analgesic

Metamizole is the most potent drug among the non-opioid analgesics and the only non-opioid analgesic that can provide analgesia equivalent to opioids in certain clinical situations:

- **Cancer pain:** oral metamizole 2 g every 8 hours provided analgesia equivalent to oral morphine 10 mg every 4 hours (60 mg a day) and tended to be better tolerated [28, 75].
- **Renal colic:** intravenous metamizole 2.5 g was found more effective than tramadol 100 mg and butylscopolamine 20 mg; rescue medication was needed by 5 patients versus 13 and 11 patients [82].
- **Biliary colic:** intravenous metamizole 2.5 g was significantly more effective than tramadol 100 mg and butylscopolamine 20 mg and was the drug with the fastest onset of action (mean 10.9 minutes versus 15.8 and 25.6 minutes) [29].
- **Postoperative pain:** intravenous metamizole 2.5 g is equivalent to pethidine 50 mg [2]; in intensive care it reduced opioid consumption more than paracetamol [69].
- **Migraine:** oral metamizole 1 g was found to be an effective and well-tolerated treatment for migraine attacks in a multicentre, double-blind, placebo-controlled study [101].

The point to note in single-dose analgesic comparisons (NNT) is **where in its own dose range** each drug was assessed. The 500 mg dose of metamizole, with an NNT of 2.4 in postoperative pain, is **the lowest effective dose** of the drug; the oral single dose can go up to 1 g and the parenteral single dose up to 2.5 g [209]. By contrast, the standard dose of ibuprofen recommended for non-prescription use is 200 mg, and the NNT of this dose is 2.7 (95% CI 2.5–3.0); only 400 mg ibuprofen, twice the standard dose, reaches the level of metamizole's lowest dose, with an NNT of 2.5 [68]. The NNT of 1.8 for etoricoxib belongs to **the drug's highest dose, 120 mg**; this dose is authorised only for acute gouty arthritis and for at most 8 days, and the dose recommended for postoperative dental pain is 90 mg [210].

Drug and dose	Position in the dose range	NNT (95% CI)
Metamizole 500 mg (oral)	Lowest effective dose (oral single dose up to 1 g, parenteral up to 2.5 g)	2.4 (1.8–3.1)

Drug and dose	Position in the dose range	NNT (95% CI)
Ibuprofen 200 mg (oral)	Standard non-prescription dose	2.7 (2.5-3.0)
Ibuprofen 400 mg (oral)	Twice the standard dose	2.5 (2.4-2.6)
Etoricoxib 120 mg (oral)	Highest dose; acute gout only, at most 8 days	1.8 (1.7-2.0)

Table 19. NNTs of single-dose analgesics in acute postoperative pain and the position of the doses in their own dose ranges [67, 68, 211]. NNT: number of patients who need to be treated for at least 50% pain relief; the smaller the value, the greater the effect.

When the position in the dose range is taken into account, the picture changes: **the lowest effective dose of metamizole has a numerically better NNT than the standard dose of ibuprofen and is at the same level as twice that dose.** (Since the confidence intervals overlap, this difference should be assessed not as a statistical superiority but in terms of position in the dose range.) There are no single-dose NNT data for doses in the upper part of metamizole's dose range (1–2.5 g); its superiority at these doses emerges in the cancer pain, renal colic and postoperative pain studies summarised above, in direct comparisons with opioids such as morphine, tramadol and pethidine. In particular, the demonstration in a randomised, double-blind study of equivalence to 60 mg oral morphine a day in cancer pain places metamizole in a category of its own among the non-opioid analgesics.

17.2 Its antipyretic effect is stronger than that of the others

- In a multinational randomised study of 628 children, the rate of return to normal temperature was 82% with metamizole, 78% with ibuprofen and 68% with acetaminophen ($p=0.004$); **at 4–6 hours the mean body temperature remained significantly lower in the metamizole group than in the other two groups** [78]. The antipyretic effect of metamizole lasts longer.
- In intensive care patients a fall in temperature of at least 1 °C at 180 minutes was achieved in 72% of patients with metamizole and 40% with paracetamol ($p<0.001$) [212].
- In a meta-analysis of three randomised trials comparing oral metamizole and ibuprofen in febrile children (547 children), no difference in temperature reduction was found between the two drugs [79].

Together, this evidence shows that the antipyretic effect of metamizole is clearly stronger than that of paracetamol, at least equal to that of ibuprofen, and longer-lasting. Its effect rests on the ability of 4-MAA to suppress both PGE₂-dependent and PGE₂-independent fever [65, 66]; this property is not found in paracetamol or the NSAIDs. In critically ill patients with unstable haemodynamics, however, the fall in blood pressure must be taken into account [212, 213].

17.3 Its smooth muscle relaxant effect is unique

Metamizole is the only non-opioid analgesic that combines analgesic and antipyretic effects with a smooth muscle relaxant effect. NSAIDs and paracetamol have no spasmolytic effect; opioids can contract the sphincter of Oddi in the biliary tract. The studies of our team have established the scope and mechanism of this effect: suppression of receptor-mediated inositol phosphate formation and intracellular Ca²⁺ release in tracheal smooth muscle [56]; improvement of small airway function in asthmatic patients

with moderate obstruction [182]; endothelium-independent relaxation in rabbit aorta [57]; a vasorelaxant effect in human umbilical artery and in a model of cerebral vasospasm [173]; reduction of ischaemic necrosis in skin flaps [178]. This effect makes metamizole unique in renal and biliary colic, in vasospastic conditions and in tissues whose perfusion is at risk.

17.4 It is effective epidurally and, unlike local anaesthetics, does not cause blood steal

Epidural metamizole was found effective in terminal cancer pain. In a patient with Buerger's disease, epidural lidocaine reduced blood flow in the diseased limb (the "steal" phenomenon), whereas epidural metamizole increased blood flow in the control and the diseased limb. Although obtained in a single case, this finding was observed for the first time in the world by our team [206] and is the clinical counterpart of the direct vascular smooth muscle relaxant effect of metamizole (Section 16).

17.5 The risk of agranulocytosis has been overstated

The agranulocytosis story of metamizole is a summary of the history of pharmacoepidemiology itself. A provocation test in a single sensitised patient in 1936, registry data without a denominator in 1964, poorly defined spontaneous reports in the 1970s and case series confused with aminopyrine determined regulatory decisions in many countries for half a century; even the 1977 US decision states no magnitude of risk. None of these data is sufficient for an incidence estimate by today's standards. Population-based studies, on the other hand, show that the absolute risk is below 1 case per million people per year, that it varies up to 30-fold from region to region, and that mortality can be markedly reduced with the right measures. The high estimates from northern Europe have not yet been fully explained and should not be ignored. The risk is real, but it is rare and manageable.

The comparison of excess deaths due to serious adverse effects also supports this picture: per million users, metamizole 0.25, paracetamol 0.20, diclofenac 5.92 [158] (Section 13). Since this comparison does not cover vascular and renal harms, it very probably understates the difference to the disadvantage of NSAIDs.

17.6 Final word

With its potent analgesic, potent and long-lasting antipyretic, unique spasmolytic and vasorelaxant effects, metamizole is a drug without equal among the non-opioid analgesics. At a time when the opioid crisis has become a global public health problem, the unavailability in a large part of the world of a drug that can reduce opioid requirements and in some situations replace opioids, because of a largely exaggerated perception of risk, is a serious loss for rational drug policy. Unfortunately, because of the agranulocytosis story told in studies built on some incorrect information and flawed methodology, this drug has been banned in some countries, and in others the public and health professionals have been frightened. Like every drug, metamizole has very serious side effects, but these side effects are no more frequent than those of similar drugs. Because it is an old drug without patent protection, it does not attract the interest of pharmaceutical companies, yet millions of people around the world still use it. The right

policy is not a ban; **it is ensuring that the drug is used with the right indication, the right dose, the right route and rate of administration, and the education of physicians, pharmacists and patients.** The most urgent need for Turkey is to identify the side effects through its own population-based and pharmacogenetic research, and to inform the public and health professionals.

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