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Metamizole: A comprehensive approach to its benefit–risk profile

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Metamizole is a drug with many years of use in some countries, and a large number of patients are exposed to its pharmacologic effects. The safety assessments have been done decades ago; therefore, it is worth summarizing the current state of knowledge of its benefit–risk profile.

Metamizole (dipyrone) was first introduced into the market in 1922, and it rapidly became widely used throughout the world due to its excellent analgesic, antipyretic, and spasmolytic properties. Metamizole has been extensively used as a nonopioid analgesic (NOA) in Europe and Latin America [1], although for years, it was claimed to belong to nonsteroidal anti-inflammatory drugs (NSAIDs). It offers additional spasmolytic properties that differentiates it from other drugs in this heterogenous class of non-opoid analgesics [2].

Profile of action differs from classic nonsteroidal anti-inflammatory drugs

The mechanism of action of metamizole is not fully understood. As its chemical structure belongs to the class of pyrazolones [3], the drug is not a typical cyclooxygenase (COX) inhibitor, although it inhibits peripheral and central prostaglandin (PG) synthesis via action on COXs. Inhibition of COX-1 and COX-2 by metamizole is weak compared with classic NSAIDs, which explains the missing effects on thrombocyte aggregation and the minor side effects by COX-2 inhibition [4]. Another possible analgesic effect of metamizole is by activating the endogenous opioid and endocannabinoid systems. It activates the cannabinoid type 1 (CB1) receptor increasing the action of the descending pain inhibitory pathway [4, 5]. Metamizole blocks not only PG-dependent but also PG-independent (indomethacin-insensitive) pathways that suggests an antipyretic mode of action that differs from other COX inhibitors and might be advantageous in the treatment of fever [6].

Metamizole and its effect on pain reduction

A meta-analysis by the Cochrane Collaboration showed a high success rate of metamizole in dental pain relief with 62% of patients showing at least 50% of the maximum possible pain relief with metamizole over 4 to 6 h compared with placebo (**Fig. 1**) [7]. The number needed to treat (NNT) for at least a 50% reduction in acute pain after oral administration of 500 mg metamizole was 2.3 (95% confidence interval [CI]:

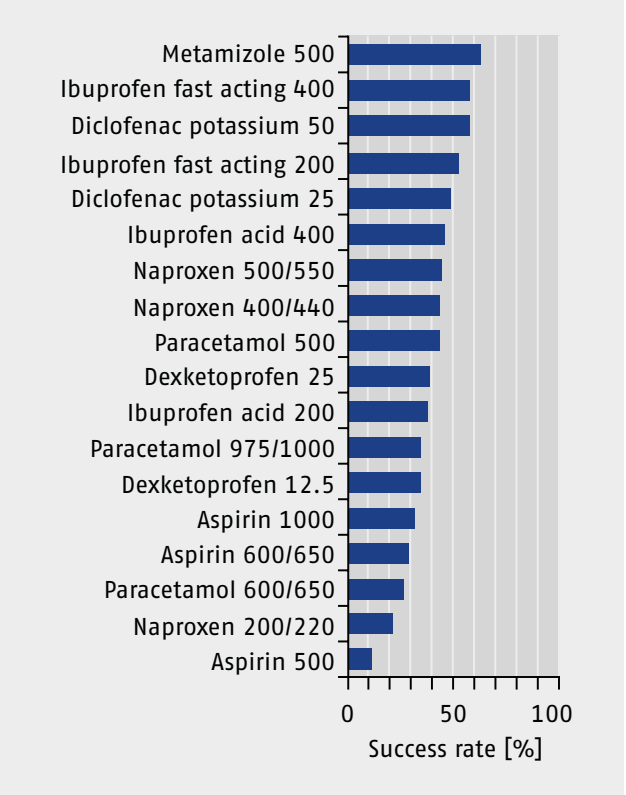

Fig. 1. Success rate: Percentage of subjects who achieved at least 50% of the maximum achievable pain relief with analgesic treatment, minus the percentage of subjects who had achieved the same effect with placebo. (Adapted from Moore et al. [7])

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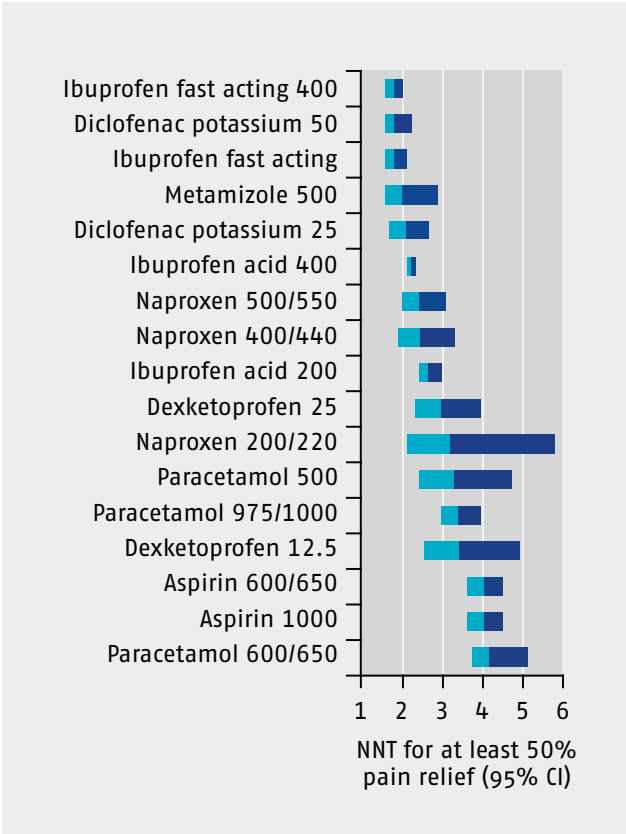

Fig. 2. NNT to achieve a pain reduction of at least 50% over 4 to 6 h compared with placebo in a setting of acute nociceptive pain (tooth extraction). The bars show 95% confidence interval (CI), and the color change is the point estimator. (Adapted from Moore et al. [7])
CI, confidence interval; NNT, number needed to treat.

1.8–3.1), which is in the upper-middle range of common COX inhibitors (**Fig. 2**). Among single drugs investigated, metamizole had best the NNT values compared with other single drugs [7].

Pharmacokinetics independent of the route of administration

The key pharmacokinetic characteristics of metamizole after oral or parenteral administration are rather similar [4]. Peak analgesia is attained approximately 1 h after the administration of metamizole tablet, independent of the dose. With dental pain elicited by electrical stimulation of the dental pulp, a dose-dependent increase in the peak effect was observed, but the increase was less marked with doses >1500 mg, and the time until onset of action was independent of the administered dose [4]. By contrast, in the case of postoperative pain, increasing the dose led not only to a greater effect but also to a faster onset. To date, a clear dose-effect relationship – in particular, covering all indications – has therefore not been established.

Dosage

Based on the available data, the recommended single dose (oral or parenteral) for adults and adolescents aged ≥15 years is 500 to 1000 mg. A single dose can be repeated up to four times daily at intervals of 6 to 8 h, corresponding to a maximum daily dose of 4000 mg. The recommended dose of metamizole for children and adolescents up to 14 years old is 8 to 16 mg/kg body weight. This can also be given up to four times a day [4].

Indication and tolerability

Metamizole has analgesic, antipyretic, spasmolytic, and weak anti-inflammatory effects. For moderate and severe pain, metamizole is used alone or in combination with opioid or other analgesics, leading to an increased analgesic effect and a possible opioid reduction. The treatment experience with metamizole in Europe between 2006 and 2018 was around 8 million patient-years [4].

In terms of tolerance, a meta-analysis of randomized controlled studies with almost 4000 patients showed significantly fewer adverse events with metamizole than opioids [8]. Several studies have shown that metamizole has a favorable gastrointestinal [9, 10], cardiovascular, and cerebrovascular profile compared with NSAIDs [11]. Some studies included were too small to estimate the occurrence of rare severe events. The most serious complication of metamizole treatment is agranulocytosis, but this occurs rarely to very rarely. Estimates of the incidence vary from 1 : 1500 to >1 : 1,000,000 [8]. The median latency between the start of treatment and the occurrence of undesirable hematological reactions is 7 days (**Fig. 3**); agranulocytosis can appear after 2 days. About 96% of all cases occur during the first 2 months of treatment. Thereafter, the risk of treatment-emergent hematological reactions decreases rapidly [8]. During a 4-year study in Latin America, after a minimum 30-day follow-up, 6 (11.5%) of 52 patients with agranulocytosis had died. Diagnostic measures for the early

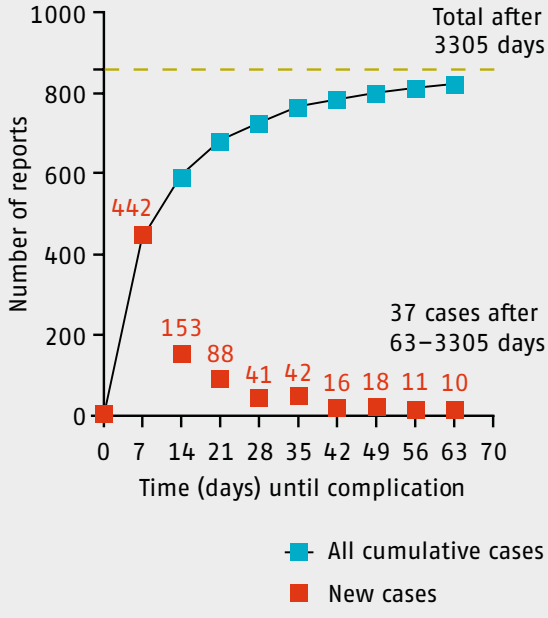

Fig. 3. Latency between start of metamizole treatment and occurrence of undesirable hematological reactions including agranulocytosis for 858 internationally reported cases. (Adapted from Malvar et al. [6])

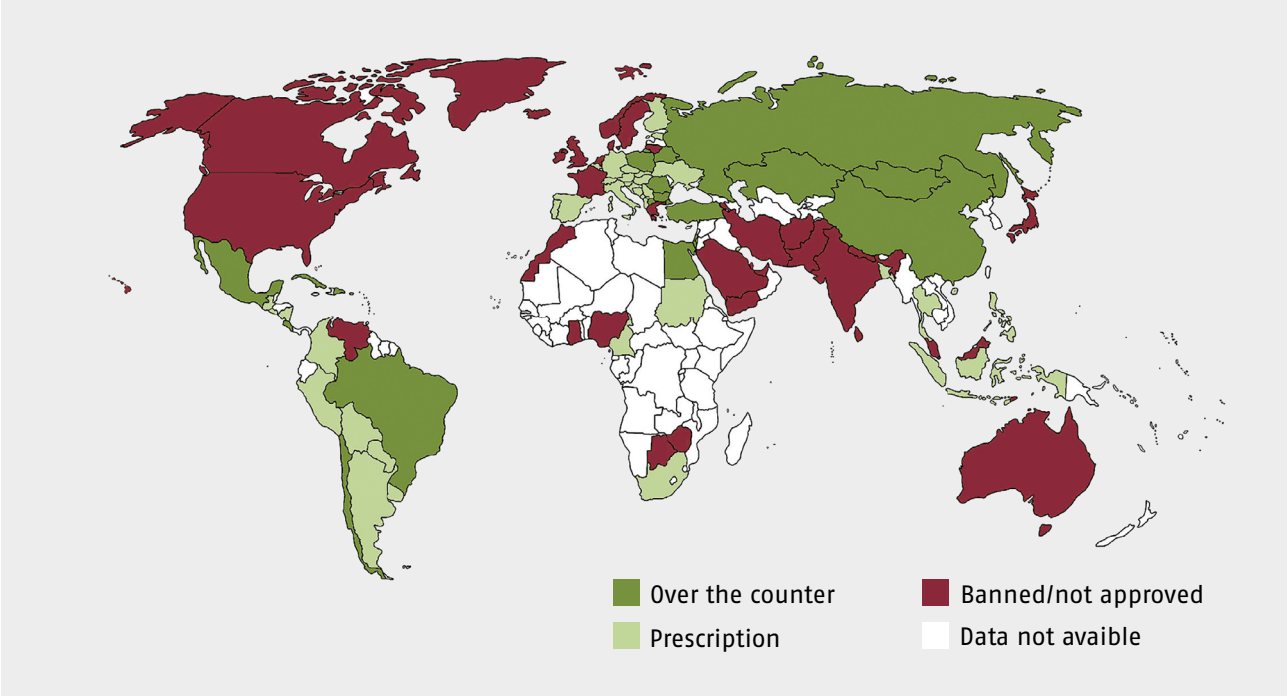

Fig. 4. Legal status of metamizole worldwide.
Beginning in the 1960s, metamizole was banned in several countries (depicted in dark red) following an increasing number of reports of adverse events, such as agranulocytosis. Nevertheless, metamizole is still available in many countries either by prescription (depicted in light green) or over the counter (depicted in dark green). No data are available for countries depicted in white. (Adapted from [2])

detection of this side effect, therefore, appear adequate to ensure that the population is protected [12]. Providing patients and medical staff with better information about early symptoms of agranulocytosis could be a sensible way to prevent complications. Any suspicion of agranulocytosis should immediately lead to a differential blood count and to the withdrawal of all drugs possibly associated with agranulocytosis. Patients should be monitored and treated according to the severity of their symptoms.

Practical use of metamizole

Metamizole is widely used in many countries, either by prescription or as an over-the-counter medicine. However, it has been withdrawn in some countries (**Fig. 4**) [2]. The antipyretic and analgesic effects of COX inhibitors are comparable with metamizole when the underlying pathology is driven by prostaglandins. In terms of their antipyretic and analgesic effect, non-selective COX inhibitors and coxibs are comparable with metamizole, where their analgesic, antipyretic, and anti-inflammatory effect is due to their influence on the synthesis of prostaglandins and leukotrienes in peripheral tissues and the central nervous system by inhibiting cyclooxygenase [13, 14]. Unlike paracetamol and metamizole, non-selective COX inhibitors more often lead to gastrointestinal bleeding and ulcers (**Tab. 1**). Non-selective COX inhibitors (apart from aspirin and naproxen) and coxibs are more frequently associated with cardiovascular events and impaired renal function. Due to the well-known safety profile, NSAIDs as well as coxibs should be prescribed only in the lowest effective dosage and for as short time as possible. Notably, the risks of non-selective COX inhibitors and coxibs for cardiovascular and renal events are statistically considerably higher than the risk of metamizole-associated agranulocytosis [15]. Therefore, metamizole is frequently used for treatment of moderate to severe acute and chronic pain in all age groups [8], either as first line of treatment in few countries or as second line of treatment if other therapeutic measures are contraindicated.

Increasing comorbidities lead to increasing polypharmacy, which can make the choice of suitable analgesics significantly more difficult because the risk of interactions that may cause adverse effects increases. While prescribing NSAIDs, special attention should be paid to possible polypharmacy. Metamizole is a broad CYP inducer via its major metabolite, 4-methylaminoantipyrine, and an inhibitor of CYP1A2 [16]. However, interaction with the constitutive androstane receptor is needed for the CYP induction [16]. In recent years, there has been considerable debate over the safety of administration of metamizole. However, several studies have shown that compared to NSAIDs, metamizole is considered equally potent and safer, without contra-indications such as cardiovascular, renal or gastrointestinal comorbidities [17], and with an acceptable and favorable benefit-risk profile [18].

Summary

The analgesic effect of metamizole is complex and at least comparable to most of the other non-opioid analgesics with widespread use per the EMA guidelines. The risk of agranulocytosis is statistically very low and can be further reduced by monitoring the blood count during treatment. In contrast to COX inhibitors, metamizole has fewer effects on kidney function and is less likely to cause gastrointestinal or cardiovascular side effects. Hence, it is particularly suitable

Tab. 1. Characteristics of COX inhibitors

Drug group/drug	Profile of action	Important ADR
Non-selective COX inhibitors (NSAIDs) ▪ Diclofenac ▪ Ibuprofen ▪ Indometacin ▪ Aspirin ▪ Naproxen	▪ Analgesic ▪ Antipyretic ▪ Anti-inflammatory ▪ Inhibition of platelet aggregation	▪ Gastric and intestinal ulcers ▪ indometacin > aspirin / diclofenac > ibuprofen ▪ Renal side effects ▷ Acute renal failure ▷ Exacerbation of chronic renal failure ▷ Chronic analgesic nephropathy ▪ Increase in cardiovascular risk (apart from aspirin and naproxen)
Selective COX-2 inhibitors (coxibs) ▪ Celecoxib ▪ Etoricoxib ▪ Parecoxib	▪ Analgesic ▪ Anti-inflammatory ▪ Antipyretic	▪ Increase in cardiovascular risk ▪ Renal side effects ▷ Acute renal failure ▷ Exacerbation of chronic renal failure ▷ Increase in blood pressure ▪ 50% fewer gastrointestinal side effects than non-selective COX inhibitors
Paracetamol (acetaminophen)	▪ Analgesic ▪ Antipyretic	▪ Hepatotoxicity ▪ Acute liver failure in the case of intoxication
Metamizole	▪ Analgesic ▪ Antipyretic ▪ Spasmolytic	▪ Allergic reactions, in extreme cases anaphylactic shock ▪ Changes in blood count (agranulocytosis)

COX, cyclooxygenase; ADR, adverse drug reaction; NSAIDs, nonsteroidal anti-inflammatory drugs

for patients with renal dysfunction or at increased risk of bleeding. In conclusion, owing to its excellent analgesic and antipyretic properties along with its mostly favorable gastrointestinal tolerability, metamizole is used as a self-medication or prescription drug worldwide.

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