Evidence for Self-Medication
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Safety of metamizole superior to comparable OTC analgesics

Waltraud Stromer, Paula Fontanilla and Beata Cywińska-Durczak

Abstract: A meta-analysis involving 20,643 people looked at the risk of side effects after a single dose of metamizole and other non-opioid analgesics. The focus was on serious to potentially life-threatening side effects. Agranulocytosis, for example, is one of the most feared risks associated with metamizole use. Metamizole, at any dose, was found to be a safe drug with even fewer side effects than paracetamol or acetylsalicylic acid.

Introduction

Metamizole, also known as dipyrone or novamine sulphone, has been widely used for 100 years, particularly in Latin America and the EU. Metamizole has a complex mechanism of action that gives it not only an analgesic effect but also an antipyretic effect (**Fig. 1**) [1].

Metamizole is effective for various types of pain and has one of the highest pain reduction rates among non-prescription medicines. A single dose leads to a significant pain reduction (i.e. reduction by at least 50%) in 62% of subjects [1]. Post-operative pain was significantly reduced (i.e. by at least 50%) in 70% of patients who took metamizole and in 30% of patients who took placebo [1]. Despite its proven efficacy in relieving various types of pain, it is not listed in USA clinical guidelines for the use of non-opioid analgesics in palliative care, while paracetamol is the most commonly prescribed drug for cancer pain in palliative care in the USA [1].

Despite the proven effectiveness of metamizole, it is banned in some countries, such as Sweden, UK and the USA, mainly because of the rare but potentially fatal risk of agranulocytosis. However, studies show that metamizole might be safer than COX inhibitors and paracetamol. A meta-analysis of 79 trials and almost 4,000 patients who took metamizole for less than two weeks found no significant differences in the side effects of metamizole compared with COX inhibitors, paracetamol or placebo [3].

Metamizole causes fewer gastric and duodenal ulcers than other nonselective COX inhibitors, and the risk for bleeding is limited. For gastric ulcers, it is unknown whether it is safer than a nonselective COX inhibitor combined with a proton pump inhibitor. Although the drug appears to be safe for renal function in healthy volunteers, data in high-risk patients (e.g., those with heart or renal failure) are lacking. In patients with renal or hepatic impairment, metamizole should only be used after a strict risk-benefit assessment. Appropriate precautions must be taken.

Selective COX-2 inhibitors are associated with increased risk for mortality by cardiac ischemia. In theory, the nonselective COX inhibitor metamizole would not cause an excess of cardiac problems. There are no publications that report increased cardiac risk associated with metamizole. In another large meta-analysis, Paracetamol was associated with a higher risk for hepatic and cardiovascular adverse events [3]. Metamizole was associated with less headache, dizziness and vertigo than COX inhibitors. Serious adverse events (SAEs) were rare and did not differ between metamizole and other nonsteroidal analgesics. Agranulocytosis did not occur [3].

Due to the opioid crisis, metamizole is being considered as a possible alternative or adjunct. This review demonstrates the good tolerability and high safety of metamizole and thus highlights the high value of metamizole in the treatment of acute pain [1].

Almost simultaneously with the publication of the review [1], the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) also reviewed the safety of the analgesic metamizole [4]. The PRAC notes that the risk of agranulocytosis is well known and manageable. The PRAC recommendations follow a review of all available evidence, including data from the scientific literature, post-marketing safety data and information submitted by stakeholders. During the review, the PRAC sought advice from an expert group of pain specialists, haematologists, general

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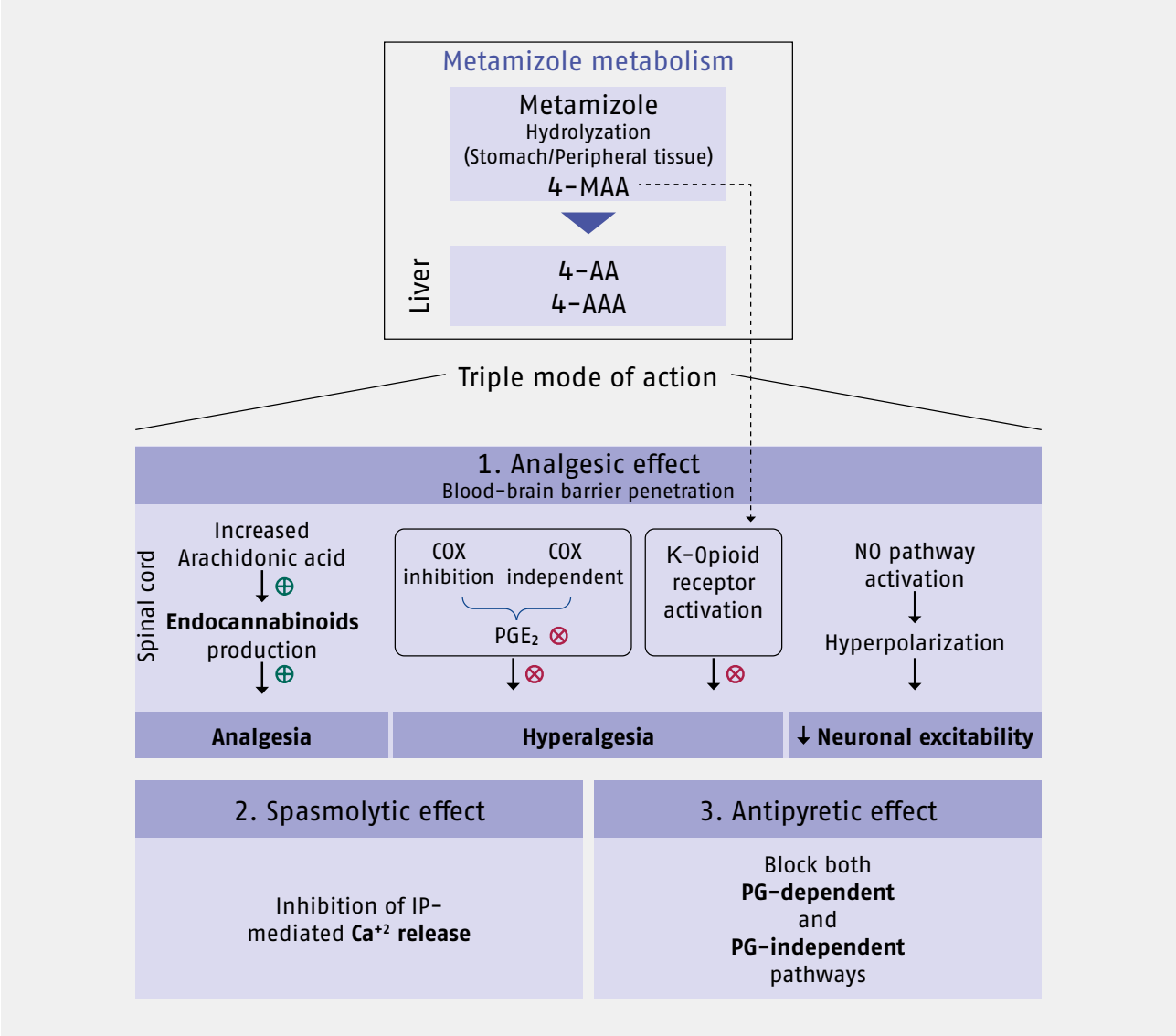

Fig. 1. Metamizole's triple mode of action—analgesic, antipyretic, and spasmolytic. Upon oral ingestion, it is hydrolyzed to produce 4-methyl-amino-antipyrine (4-MAA), which is further metabolized in the liver. The precise mechanism of metamizole's analgesic action remains complex and unclear, likely involving interactions with COX, the cannabinoid system, and the opioidergic system, alongside its anti-inflammatory properties. Endocannabinoid production exerts analgesic effects in the spinal cord and plays an important role in the regulation of pain sensation. The metabolites of metamizole can inhibit hyperalgesia through COX-independent pathways and may activate the endogenous opioidergic system, enhancing pain relief. Metamizole can also directly block nociceptor sensitization via activation of NO signaling pathway that controls neuronal excitability and elicits peripheral analgesic effect. Additionally, metamizole demonstrates spasmolytic effects by reducing intracellular calcium levels in smooth muscle and possesses antipyretic properties, effectively lowering fever. Adapted from [2].
4-AA: 4-amino-antipyrine; 4-AAA: 4-acetyl-amino-antipyrine; COX: cyclooxygenase; IP: inositol phosphate; PG: prostaglandin

practitioners, pharmacists and a patient representative. The PRAC concluded that the benefits of metamizole medicines continue to outweigh the risks. However, the product information for all metamizole-containing medicines will be updated to strengthen the existing warnings to raise awareness among patients and healthcare professionals and to facilitate early detection and diagnosis of metamizole-induced agranulocytosis. [4]. Additionally, in line with current knowledge the product information should be updated to remove any reference to regular blood count monitoring of patients under treatment with metamizole-containing medicinal products, as well as the information that the risk increases after one week of treatment or with long-term use, which is not substantiated by the evidence reviewed [4].

The safety profile of metamizole compared with OTC analgesics

Opioid analgesics are highly effective painkillers, but they carry a risk of side effects (e.g. fatigue, dizziness, nausea, constipation) and, when not used correctly, addiction. In contrast, metamizole and other non-opioid analgesics are non-addictive, provide effective pain relief for acute pain, and can be used as an alternative or adjuvant treatment option [2]. COX inhibitors inhibit prostaglandin synthesis, which often leads to gastrointestinal problems such as ulcers or bleeding. Metamizole, on the other hand, appears to have a significant lower tendency to cause such side effects due to its ability to redirect prostaglandin synthesis [2]. The

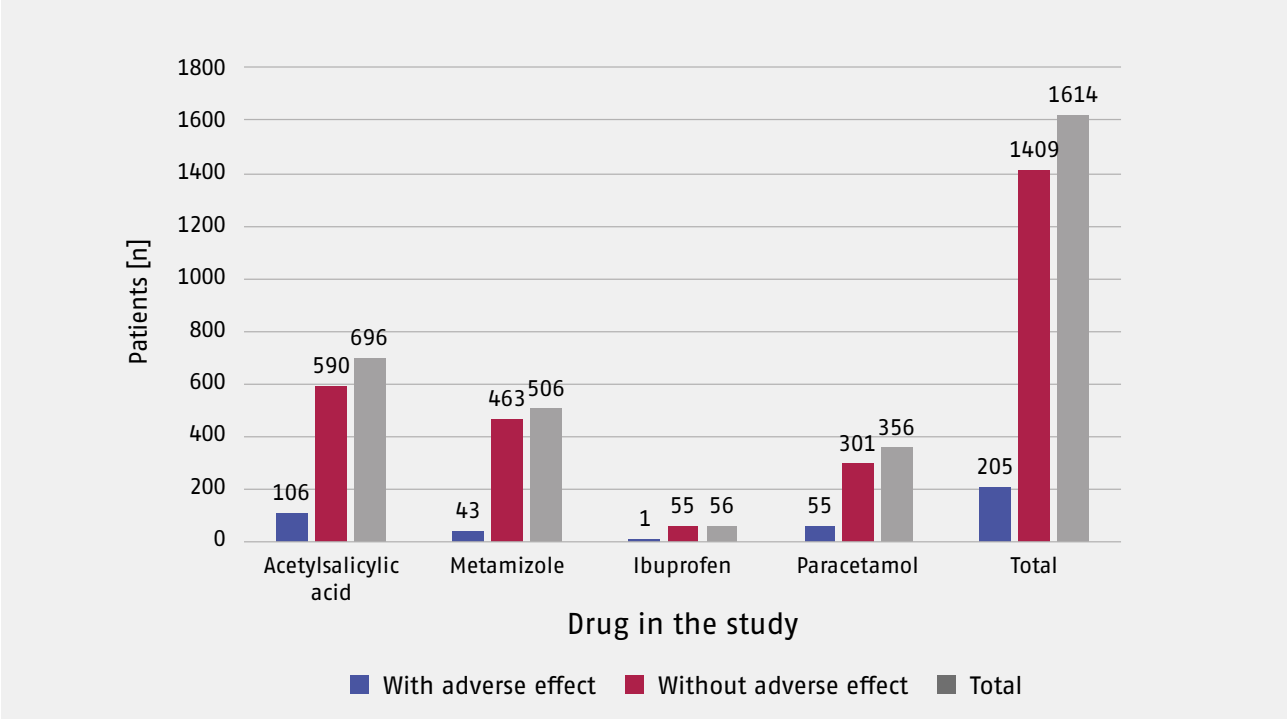

Fig. 2. No serious adverse events were reported at any dose in any of the trials. The probability of mild adverse events was 15.2% (106 of 696 patients) for acetylicsalicylic acid, 8.5% (43 of 506 patients) for metamizole, 1.8% (1 of 56 patients) for ibuprofen, and 15.4% (55 of 356 patients) for paracetamol [1].

analysis in the review [1] focused on the tolerability of non-opioid analgesics. For the first time, the incidence of adverse effects and the safety profile of metamizole were compared with paracetamol, ibuprofen, and acetylsalicylic acid in the treatment of pain after a single, one-time dosage (metamizole 500–2000 mg, paracetamol 500–1000 mg, ibuprofen 200–400 mg, acetylsalicylic acid 500–1000 mg). The key question of the review was: "Are the side effects of metamizole more frequent and more severe compared to paracetamol, ibuprofen, and acetylsalicylic acid in adult patients with mild to moderate pain?" 387 trials were screened. Four systematic reviews from 2006 to 2017 of randomised (RCTs) and non-randomised (NRCTs) clinical trials in adults (aged 18–80 years, N = 20,643) with mild to moderate acute pain who had no known allergy to analgesics (metamizole, ibuprofen, paracetamol, and acetylsalicylic acid) were analysed.

In the trials analysed, metamizole and paracetamol or metamizole and ibuprofen or metamizole and acetylsalicylic acid were also compared regarding the side effects of the drugs. All adverse reactions were recorded, and serious adverse reactions such as agranulocytosis, chronic interstitial nephritis, anaphylaxis, bronchospasm, toxic epidermal necrolysis or death were recorded separately. None of the four studies analysed reported serious adverse events. The reported adverse events (**Fig. 2**) were mild, such as nausea, vomiting, drowsiness, headache, or increased blood pressure. The primary data from the trials that formed the basis of the four reviews were also analysed to identify the safety-relevant results.

The complementary statistical analysis of primary data focussed on metamizole, acetylsalicylic acid and paracetamol. Ibuprofen was excluded because the expected frequency of side effects in the ibuprofen 400 mg group was less than 10. The number of side effects reported was therefore too low to perform a statistically meaningful analysis. In addition, the underlying data relating to ibuprofen showed a high risk of bias. The complementary statistical analysis was performed with 1,558 participants who used "any dose" of metamizole, acetylsalicylic acid, and paracetamol.

First, the odds of experiencing an adverse reaction were analysed for each drug, regardless of the dose taken. It was highest for paracetamol (odds: 0.1827), followed by acetylsalicylic acid (odds: 0.1797) and metamizole (odds: 0.0928). Metamizole was a safer drug compared to paracetamol and acetylsalicylic acid. The comparison showed that metamizole had a lower risk of side effects than paracetamol (odds ratio: 0.508) or acetylsalicylic acid (odds ratio: 0.517), regardless of the dose. In other words, at any dose, metamizole users have a 49% and 48% lower risk of adverse effects than paracetamol and acetylsalicylic acid users, respectively.

The comparison of metamizole with acetylsalicylic acid and paracetamol at a low dose of ≤ 650 mg and a medium dose of > 650 mg to ≤ 1000 mg showed an interesting effect. The adjusted odds ratio for metamizole at a dose of ≤ 650 mg compared to paracetamol and acetylsalicylic acid was 3.24 and 0.2445, respectively; for metamizole at doses between > 650 mg and ≤ 1000 mg, the values were 0.1426 and 0.1545, respectively. This shows that the risk of side effects is up to 85% lower after taking a medium dose (650–1000 mg). For low doses (0–650 mg), the risk of adverse effects is slightly higher than for paracetamol, but this may be due to the small

sample size. As mentioned above, mild side effects such as nausea, vomiting, drowsiness, headache or increased blood pressure have been reported.

In contrast to these dose-related adverse drug reactions, serious immunological reactions can occur rarely with metamizole, regardless of the dose taken. None of the trials analysed reported such serious events as agranulocytosis or epidermal necrosis, suggesting that the risk of such serious adverse reactions with metamizole is low. The incidence of agranulocytosis induced by metamizole is poorly documented in the literature, with most studies failing to distinguish between neutropenia, agranulocytosis, and aplastic anaemia. Several drugs, including antibiotics, antipsychotics, antiplatelet agents, and antithyroid medications, have been associated with agranulocytosis.

One of the limitations of the review is that most of the included studies primarily investigated the analgesic effect of the drugs under review, while systematic analyses of adverse effects were lacking. The lack of comprehensive data on the frequency and distribution of adverse effects, coupled with the absence of detailed documentation on these effects, posed significant challenges to statistical analysis.

Summary

Drug-induced agranulocytosis is a rare but serious adverse event. In the USA, the incidence ranges from 2.4 to 15.4 cases per year per million population, while in Europe the incidence ranges from 3.4 to 5.3 cases per million population [1]. Because of its potentially fatal course, the use of metamizole has been restricted in some countries. Few studies provide clear information on the incidence and often no clear distinction is made between neutropenia, agranulocytosis and aplastic anaemia. Various drugs, such as antibiotics and antipsychotics, have also been associated with agranulocytosis [1].

This systematic review confirmed the favourable safety profile of metamizole among commonly used, similarly effective non-opioid analgesics. Adverse effects were reported less frequently with metamizole than with acetylsalicylic acid and paracetamol. Ibuprofen showed the lowest rate of side effects after a single dose. Metamizole consistently demonstrated a strong safety profile overall. No serious side effects were observed, and the risk of serious side effects may be low. The authors emphasize that more and better-quality studies on agranulocytosis and other potential risks are needed to make a final judgement.

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