ORIGINAL ARTICLE

Metamizole (Dipyrone) as an Alternative Agent in Postoperative Analgesia in Patients with Contraindications for Nonsteroidal Anti-Inflammatory Drugs

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■ **Abstract**

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) play an important role in multimodal pain management. In patients with a contraindication for NSAIDs, pain management is challenging. A recent Dutch anesthesiology guideline propagates the use of metamizole (dipyrone) in these patients. Metamizole is a controversial drug, its use being previously discouraged because of the risk for agranulocytosis. We discuss whether metamizole could be an alternative to classical NSAIDs and opioids in postoperative pain management despite this drawback.

Method: Literature review and pharmacovigilance research based on World Health Organization adverse effect registrations.

Results: Metamizole causes fewer gastric and duodenal ulcers than other nonselective NSAIDs, and the risk for bleeding is limited. It is unknown whether it is safer than a nonselective NSAID combined with a proton pump inhibitor. Although the drug appears to be safe for renal function in healthy volunteers, data in high-risk patients (eg, those with heart or renal failure) are lacking. The incidence of metamizole-induced agranulocytosis is controversial, but the risk is likely to be limited with short-term postoperative use in this selected group of patients.

Conclusion: Although firm evidence is lacking, metamizole may be safer for the upper intestinal tract and kidneys than other NSAIDs, and could alternatively be used in patients with an increased risk for stomach or renal problems. Hereby, improved postoperative pain relief can potentially be achieved. The risk for metamizole-induced agranulocytosis is judged to be acceptable. ■

Key Words: analgesia, anti-inflammatory agents, nonsteroidal, pain, postoperative, opioids, metamizole

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INTRODUCTION

Despite using analgesics, 15% of patients indicate severe postoperative pain,[1] while the Dutch National Safety management system (landelijk veiligheidssysteem, VMS) states that fewer than 5% of patients should experience severe pain postoperatively (pain score 8/10 or higher, source: www.vmszorg.nl). In patients with a contraindication for nonsteroidal anti-inflammatory drugs (NSAIDs), pain management is challenging. The most common contraindications are a history of gastric or duodenal ulcers or bleeding, or renal impairment. In current practice, patients in whom NSAIDs are contraindicated receive more opioids postoperatively than other patients. Although these agents can be effective, they frequently cause adverse events (drowsiness, nausea, vomiting, constipation). Dangerous adverse events such as respiratory depression and hypotension occur after postoperative opioid use in 1% and 5% of patients so treated, respectively.[2] These adverse events can be dose limiting, in which case adequate analgesia cannot be achieved. The weak opioid tramadol provides a poor substitute and is rarely used postoperatively, as it is associated with more adverse events such as nausea with equipotent dosing.[3] In the guidelines of the Dutch Association of Anaesthesiology (NVA), the NSAID metamizole (World Health Organization [WHO] name: metamizole; American and British name: dipyrone) is propagated as an alternative to other NSAIDs.[4] By adding metamizole to the analgesic arsenal for patients with gastric and/or renal function risks as contraindications for other NSAIDs, better postoperative analgesia may be achieved. Simultaneously, the use of opioids and the related adverse events could possibly be decreased. Metamizole is a prostaglandin synthetase inhibitor that strongly inhibits COX-1 and COX-2, making it a nonselective NSAID. It has analgesic, antipyretic, spasmolytic, and weak anti-inflammatory effects.[5] The adverse event profile of metamizole differs from that of other NSAIDs. The use of metamizole is controversial, mainly because of metamizole-induced agranulocytosis.[6]

In this study, we review current literature regarding efficacy and safety of metamizole and perform a safety analysis using a WHO database to discuss whether metamizole can be a safe alternative in postoperative pain management when other NSAIDs are contraindicated.

METHODS

Relevant literature was searched on PubMed using a nonsystematic approach, using MeSH terms such as *dipyrone, non-steroidal anti-inflammatory agents, in combination with postoperative pain, adverse effects, renal insufficiency, acute kidney injury, ulcer, agranulocytosis, gastrointestinal hemorrhage, hemorrhage, myocardial ischemia, bone fractures, surgical anastomosis,* and *anastomosis leak*. In addition, the WHO database (VigiBase) was used to calculate reporting odds ratios (RORs). VigiBase is the largest and most comprehensive pharmacovigilance database in the world. VigiBase data are collected from over 110 countries participating in the WHO Programme for International Drug Monitoring. VigiBase includes over 10 million individual case safety reports (https://tools.who-umc.org/webroot/ [access restricted]). We searched this database using the following MedDRA system organ class (SOC) terms: *cardiac disorders, gastro-intestinal disorders,* and *renal and urinary disorders*. Furthermore, the database was searched using the following preferred terms: *agranulocytosis, fracture malunion,* and preferred terms containing *haemorrhage/bleeding/haematoma,* and *anastomotic complication*. Reports in relation to celecoxib, diclofenac, etoricoxib, ibuprofen, meloxicam, metamizole, and naproxen (all these drugs are available by multiple manufacturers wordwide) that were entered into the database up to July 2014 were included. Using the extracted lists of reported adverse events, relevant reports were collected and RORs were calculated. The ROR is calculated in the same way as the odds ratio (OR) in a patient–control study: $(A \times D)/(B \times C)$, where A is the number of reports of the adverse effect after use of the drug, B is the number of reports of other adverse effects after use of the drug, C is the number of reports of the adverse effect after the use of other drugs, and D is the number of reports of other adverse effects after the use of other drugs. The ROR was calculated as a measure of disproportionality. The ROR represents the extent to which the association between the adverse drug reaction and suspect drug stands out in respect to its background frequency in the database. If the ROR is statistically significant, then the adverse drug reaction is significantly associated with the suspect drug in reference to other reports in the database.

Table 1. Efficacy Several Analgesics Commonly Used for Postoperative Pain Management

Drug	Dose (mg)	NNT (50% Relief 4–6 hours)*	95% CI	Ref.	T_{max} (Oral)†	$T_{1/2}$ (Oral)†	*F* (Oral), %†
Aspirin	600/650	4.2	3.9–4.8	22	10–20 minute	Depending on dose,	100
	1000	3.8	3.0–5.1	22		1–3 g/day $T_{1/2}$ 2–3 hour	
	1200	2.7	2.0–3.8	22			
Celecoxib	200	4.2	3.4–5.6	23	2–3 hour	8–12 hour	22–40[28]
	400	2.6	2.3–3.0	23			
Diclofenac potassium	25	2.4	2.0–2.9	24	0.5–2 hour	1–2 hour	50
	50	2.1	1.9–2.5	24			
	100	1.9	1.7–2.3	24			
Diclofenac sodium	50	6.6	4.1–17	24	0.5–4 hour	1–2 hour	50
Etoricoxib	120	1.8	1.7–2.0	25	1 hour	22 hour	100
Ibuprofen	200	2.7	2.5–3.0	26	1–2 hour (regular formula)	1.5–2.5 hour	80
	400	2.5	2.4–2.6	26			
	600	2.7	2.0–4.2	26			
Metamizole	500	2.4	1.9–3.2	7	1.2–2 hour [8]	2.6–3.5 hour [8,‡]	85[8]
Naproxen	400/440	2.7	2.2–3.5	26	1–2 hour (sodium salt) 2–4 hour (regular formula)	10–16 hour	100
	500/550	2.7	2.3–3.3	26			
Oxycodon + paracetamol	10/650	2.7	2.4–3.1	26	See separate drug text		
	10/1000	1.8	1.6–2.2	26			
Oxycodon	15	4.6	2.9–11	27	1.5 hour	2–3 hour	60–87
Paracetamol (acetaminophen)	500	3.5	2.7–4.8	26	0.5–2 hour	1–4 hour	100
	600/650	4.6	3.9–5.5	26			
	975–1000	3.6	3.2–4.1	26			

NNT, number needed to treat; CI, confidence interval; T_{max}, time of maximum concentration; $T_{1/2}$, half-life; F, bioavailability.
*NNT reflects data in combined dental and nondental surgery. In most drugs, data are insufficient to analyze the NNT in nondental surgery patients.
†Sources: Micromedex, Truven Health Analytics, Inc., Greenwood Village, CO, available at www.micromedexsolutions.com, and KNMP Kennisbank, available at kennisbank.knmp.nl (drug database by the Royal Dutch Pharmacists Association).
‡Half-life of the active metabolite.

RESULTS

Efficacy

The efficacy of metamizole compared to other analgesics is shown in Table 1. Many studies have reported good efficacy with metamizole as a postoperative analgesic. However, these studies are difficult to compare due to varying quality and differences in patient groups and dosing regimens. A meta-analysis shows that after an oral dose of 500 mg metamizole, 70% of patients experience at least 50% pain relief over 4 to 6 hours (number needed to treat: 2.4, 95% confidence interval (CI): 1.9 to 3.2), comparable to other NSAIDs.[7] Oral metamizole has a high bioavailability (F = 85%) and is absorbed quickly (time of maximum concentration [T_{max}] = 1.2 to 2.0 hours).[8] As expected based on pharmacokinetic data, reported results suggest similar efficacy after intravenous administration and oral administration.

Safety: Agranulocytosis

After years of being widely used in a number of countries, including the Netherlands, metamizole was taken off the Dutch market as a result of reports of agranulocytosis. In the 1950s, it was noticed that amidopyrin (chemically closely related to metamizole) could provoke agranulocytosis, which at the time had a mortality rate of 40% to 60%. Subsequently, a number of greatly varying incidences of metamizole-induced agranulocytosis were reported: 1:1,439 to 1:16,666,667. All studies performed on the subject have been methodologically criticized. Some of the investigators based incidence estimates on spontaneous reports of agranulocytosis after metamizole use in adverse effect registrations. However, because of incomplete and selective reporting, adverse effect registrations cannot be used to produce reliable incidence rates. In other studies, patients with agranulocytosis (spontaneously reported or systematically researched) are checked for having used metamizole previously. The number of cases of metamizole-related agranulocytosis is plotted against the amount of metamizole prescribed in total, by which the number of metamizole users is estimated. These estimates use assumptions that have not been validated in control groups but do have a great impact on the incidence estimate. Two larger case–control studies reported an incidence of 1:1.1 million[9] and 1:1.8 million,[10] respectively. Altogether, it is clear that metamizole-induced agranulocytosis (even after short-

term use[10]) can occur, but the actual incidence remains uncertain.

Metamizole has not been withdrawn in all countries and has remained popular worldwide, with frequent use in Germany, Spain, Poland, Israel, Brazil, and Mexico, among others. Metamizole is freely available in some countries, and it is among the top 5 most commonly sold over-the-counter drugs worldwide.[11] In hospitals in Berlin, 10 metamizole-related cases of agranulocytosis were reported between 2000 and 2010 via active monitoring; extrapolating this number to the total German population would calculate a total of 300 cases in 10 years.[12] More than 110 million daily doses of metamizole were prescribed in Germany in 2010 alone. Given the large-scale use of metamizole worldwide, the true incidence of metamizole-induced agranulocytosis is very unlikely to be as high as the highest estimates. Also, the mortality rate of agranulocytosis has decreased to 10% to 20%.

Safety: Peptic Ulceration and Bleeding

Prostaglandins produced by COX-1 have a protective role in the upper gastrointestinal tract; COX-1 inhibitors (nonselective NSAIDs) increase the risk for ulcers and bleeding. Therefore, NSAIDs are not prescribed to patients with a history of gastric or duodenal ulcers.

Because metamizole is a strong COX-1 inhibitor, one would expect a similar adverse event profile. However, in animal studies, human volunteer studies, and human clinical studies, metamizole was shown to be much more stomach friendly. In equipotent doses, it causes fewer ulcers and less bleeding than other nonselective NSAIDs, comparable to acetaminophen.[13,14] A single study showed minimal elevated risk for bleeding after metamizole.[15]

Gastric or duodenal ulcers are not reported more often than would be expected by chance alone after metamizole use (ROR [95% CI]: 0.9 [0.7 to 1.2]), in contrast to other nonselective NSAIDs (ROR [95% CI] for diclofenac 14.3 [13.8 to 14.9], ibuprofen 8.3 [7.8 to 8.7], and naproxen 10.7 [10.2 to 11.1]), and also less often than after selective NSAIDs (ROR [95% CI] for meloxicam 18.9 [17.4 to 20.5], celecoxib 6.9 [6.5 to 7.3], and etoricoxib 7.2 [6.4 to 8.2]). Marginally increased incidence of upper gastrointestinal tract bleeding has been reported in metamizole users (ROR [95% CI] 1.5 [1.3 to 1.7]); however, this number is lower than for other nonselective NSAIDs (ROR [95% CI] for diclofenac 9.1 [8.8 to 9.3], ibuprofen 8.2 [8.0 to 8.5], and naproxen 7.9 [7.7 to 8.1]) or selective NSAIDs (ROR [95% CI] for meloxicam 13.1 [12.4 to 14.0], celecoxib 5.9 [5.7 to 6.1], and etoricoxib 5.8 [5.2 to 6.4]).

Based on available data, we conclude that metamizole is relatively safe for the stomach and the duodenum. The reason for the safety of metamizole compared to other classic NSAIDs is unknown. It is unknown whether metamizole is safer than a nonselective NSAID combined with a proton pump inhibitor. It is also unknown whether in patients with high risk for NSAID-induced gastrointestinal bleeding a proton pump inhibitor should be added to metamizole.

Safety: Renal Impairment

Prostaglandins regulate the glomerular blood flow, especially with decreased effective circulating volume. Inhibiting this process by COX inhibition could cause (progression of) renal failure.[16] Therefore, NSAIDs are not prescribed to patients with increased risk for renal impairment.

Metamizole is a strong COX inhibitor, and in theory, it could also cause kidney problems. In healthy volunteers with good renal function and a normal hydration status, metamizole does not cause renal function limitation.[17] In healthy individuals, however, renal function is hardly prostaglandin dependent.

There are no studies about the effects of metamizole on renal function in patients with a decreased effective circulating volume. In clinical trials, renal impairment is not mentioned as an adverse effect of metamizole. The effect of metamizole on renal function in patients with pre-existent renal impairment is unknown in all published trials, patients with pre-existent renal impairment were excluded, so the efficacy and safety of metamizole have not been demonstrated in this patient group.

We also studied the WHO database with regard to renal safety. Loss of renal function after metamizole use is reported marginally more than can be expected based on coincidence alone (ROR [95% CI] 1.2 [1.0 to 1.3]). Loss of renal function is reported more after other NSAIDs (ROR [95% CI] for diclofenac 2.3 [2.2 to 2.4], ibuprofen 2.4 [2.3 to 2.5], naproxen 1.2 [1.1 to 1.3], meloxicam 1.9 [1.7 to 2.2], celecoxib 2.1 [2.0 to 2.2], and etoricoxib 1.9 [1.7 to 2.2]).

Based on the available data, metamizole might be relatively safe for kidney function. However, data in patients at risk for renal failure on NSAIDs (patients with heart or renal failure, patients with dehydration) are lacking.

Safety: Other Risks

Thrombocyte Dysfunction. Like other nonselective NSAIDs, metamizole reversibly inhibits thrombocyte aggregation by decreased thromboxane production through COX-1 inhibition.[18] In theory, postoperative nonselective NSAID use could increase bleeding risk; in practice, however, this is controversial. In adverse effect registrations, no increase has been reported after the use of nonselective NSAIDs, including metamizole (ROR not significantly different from 1 for all nonselective NSAIDs).

Cardiovascular Risk. 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 adverse effect registrations, no increase in the occurrence of ischemic heart disease is reported for metamizole (ROR [95% CI] 0.5 [0.4 to 0.5]), in contrast to the selective COX-2 inhibitors (ROR [95% CI] for celecoxib 8.5 [8.3 to 8.7] and etoricoxib 1.9 [1.7 to 2.2]).

Postoperative Recovery. The effect of COX inhibition on postoperative recovery is controversial. In some studies, postoperative NSAID use is associated with a negative impact on bone healing[19] and with more leakage of intestinal anastomoses.[20] On this basis, some surgeons are reticent in respect to postoperative NSAID use. In literature, no information was found regarding the effects of postoperative metamizole use on bone healing or intestinal anastomoses. No increase in complications were reported to the WHO after NSAID use, including metamizole.

DISCUSSION

Using the OR in a patient–control study, the relative risk (RR) can be approximated. In theory, this can also be done with the ROR, assuming the degree of (in)completeness of reporting is similar for all kinds of adverse effects. The ROR corrects for spontaneous background reporting in a control population, and so ideally the ROR reflects occurrence of side effects in the population. However, as spontaneous reports of adverse events are both incomplete and subjective (e.g, because of the attention of a registration authority or the media for a certain adverse effect), bias because of over- or underreporting should be taken into account. Also, in the WHO database multiple adverse event registrations and other sources worldwide are bundled, and the likelihood that a suspected adverse reaction is drug related is not the same in all cases. For this reason, the ROR cannot be used to estimate relative risk. The ROR has a signaling function and can be used in pharmacovigilance in large databases of adverse effects and spontaneous reports. The information provided does not represent the opinion of the WHO.

What is, taken together, the place of metamizole in pain management? First of all, even though many uncertainties remain, its analgesic efficacy has been clearly demonstrated. Because of its relatively mild adverse event profile regarding the upper gastrointestinal tract, the agent stands out against other NSAIDs. It is at present unknown whether metamizole is safer compared to a classic NSAID combined with gastric protection (adding a proton pump inhibitor). It is also unknown whether a proton pump inhibitor should be added to metamizole in patients at high risk for NSAID-induced gastrointestinal bleeding. As for the kidney, although there is circumstantial evidence that metamizole may be safer than other NSAIDs, data in patients at risk for renal failure on NSAIDs are lacking. Interestingly, cardiovascular disease was less often reported in metamizole users, which might point to a protective role for metamizole. However, future research should confirm this finding, since as stated above ROR is not suitable to estimate relative risks.

The benefits of metamizole should be weighed against the risk for metamizole-induced agranulocytosis. The incidence and clinical consequences of this specific adverse event remain questionable. Based on the available incidence estimates (weighed down by methodological issues), the intended deployment (only short-term use in postoperative clinical setting), and the current mortality of this condition, the risk seems acceptable in comparison with the alternative of increased usage of opioids and concurrent side effects. The risk for fatal side effects with metamizole, including agranulocytosis, is estimated to be comparable to acetaminophen and much lower than, for instance, in diclofenac, mainly because of lower incidence of gastric ulceration and bleeding (25, 20, and 592 fatalities per 100 million users, respectively).[21] In the Netherlands, each year 1,400,000 operations are performed, 700,000 of which are undertaken during clinical admission

(source: http://statline.cbs.nl/statweb). If metamizole would be administered after every clinical operation in which other NSAIDs are contraindicated (assuming a high estimate of 50%), and an agranulocytosis incidence of 1:1,000,000 is assumed (in accordance with the larger case–control studies mentioned earlier in this article) with a mortality rate of 15%, in the Netherlands there would be 1 case of metamizole-induced agranulocytosis every 3 years, and 1 death every 20 years. For this calculation, assumptions were used that cannot be validated at this time.

Based on the available data, we conclude that metamizole might indeed be an effective and safe alternative to other NSAIDs. A practical problem in the Netherlands is that metamizole is only registered for intravenous use, which limits its application in the ambulant setting.

Finally, it is upsetting that so little is known about a drug that is so massively used. Future research should firstly be aimed at assessing its safety in high-risk patients, including those with heart failure, renal dysfunction, and dehydration. Secondly, it would be interesting to know the gastrointestinal safety of metamizole compared to classical NSAIDs plus a proton pump inhibitor. If metamizole would appear to have better cardiac and renal safety than other NSAIDs and would be similar compared to a classical NSAID plus a proton pump inhibitor with respect to gastrointestinal side effects, it would deserve a more prominent role in pain management in vulnerable patients.

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