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SHORT COMMUNICATION

Pharmacology and relevant drug interactions of metamizole

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Metamizole is a frequently prescribed analgesic because of its favourable benefit/risk ratio compared with classic NSAIDs. However, increasing research shows that metamizole displays several drug interactions that are relevant to clinical practice. We reviewed the literature to summarize the pharmacology and most clinically relevant drug interactions of metamizole. Metamizole has a fast analgesic effect but a short half-life and duration of action. The exact mechanism of action of metamizole is currently not fully known. Studies showed that metamizole appears to be a moderate to strong inductor of the enzymes CYP3A4, CYP2B6 and CYP2C19; a weak inductor of CYP2C9; and a moderate inhibitor of CYP1A2. Furthermore, metamizole inhibits the effect of acetylsalicylic acid when taken simultaneously. Metamizole should be cautiously used together with other drugs that can cause agranulocytosis. If metamizole is prescribed in a high dosage (1000 mg three or four times daily) for more than 1 day, these pharmacokinetic and dynamic interactions should be taken into account.

KEYWORDS
acetylsalicylic acid, CYP, dipyrone, interactions, metamizole, pharmacology

1 | INTRODUCTION

Metamizole (also known as dipyrone) is a common and generally well-tolerated non-steroidal anti-inflammatory drug (NSAID) that is mainly prescribed in Latin America, Russia and parts of Europe and Asia. Metamizole is popular because of its analgesic, antipyretic and spasmolytic effects; low dependence potential; and favourable risk/benefit ratio compared with classic NSAIDs such as diclofenac and ibuprofen.[1] Because of the availability of an intravenous form of administration, the drug is often used in the perioperative and oncologic setting when oral intake is limited. In both Germany and the Netherlands, the use of metamizole has increased substantially over the past 10 years.[2,3] A known but very rare side effect of metamizole is agranulocytosis, which has a probability of less than one per million daily doses.[4] The incidence of agranulocytosis may be reduced by short-term use and careful consideration when prescribing to specific patient categories. Because of this rare but serious side effect, the drug is not approved in the United States, the United Kingdom and Canada. Besides agranulocytosis, there is a growing body of research showing that metamizole has a number of relevant drug interactions that are important for practice. This article discusses the pharmacology and the most relevant drug interactions of metamizole.

2 | METHODS

Employing a systematic search, relevant articles on drug interactions with metamizole were retrieved from the PubMed database. Combinations of the search terms 'metamizole', 'dipyrone' and 'interaction' were used, resulting in 208 articles. We selected articles (clinical studies, meta-analyses, reviews, editorials, letters and case-reports) from the earliest date up to 31 March 2025 that were written in

Dutch, German, English or Spanish. References of the retrieved articles were scanned for relevant citations. The Dutch KNMP Knowledge Bank and Dutch Medicines Information Bank were also searched for drug interactions with metamizole.[5,6] Finally, 30 articles were selected after reading the full text. The citations of included articles were also screened for relevant articles that did not lead to new inclusions. Of the 30 selected articles, 10 addressed the pharmacology and 20 pertained to drug interactions of metamizole.

3 | RESULTS

3.1 | Pharmacokinetics

Metamizole belongs to the pyrazole derivatives and is available for both oral and intravenous administration. After oral administration, the prodrug metamizole is non-enzymatically hydrolysed in the gastrointestinal tract to the active metabolites 4-methylaminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA) and a number of inactive antipyrins.[5] Eighty-five percent of the metabolites are absorbed, and maximum concentration (T_{max}) is reached after 1.4–2 h.[7] Following intravenous administration, this conversion takes place in the liver.[8] In the liver, 4-MAA is further metabolized by cytochrome (CYP)-3A4, 2B6, 2C8 and 2C9 and potentially an extrahepatic metabolism via myeloperoxidase to inactive antipyrins.[9,10] The elimination half-life of 4-MAA is 2–3 h and that of 4-AA is 5–6 h.[5] The analgesic effect of the active metabolites starts within 30 min and persists for about 4 h. Because of its short half-life and duration of action, metamizole is usually dosed three to four times a day. The volume of distribution of 4-MAA is 0.4 L/kg after intravenous administration, and excretion occurs via the kidneys (90%) and faeces (10%) in the form of inactive metabolites.

TABLE 1 Articles about the pharmacokinetic interactions of metamizole.

Publication year	Author	Study design	Substrate	Plasma concentration of substrate	Metamizole dosage	Measurement day	CYP enzyme	Effect
1999	Caraco et al.[17]	Placebo-controlled	Cyclosporine	mPC −14% (4–36)	Oral TID 500 mg	Day 3	3A4	No effect
2012	Qin et al.	Cohort	Bupropion	AUC −31% (23–38)	Oral TID 500 mg	Day 2	2B6	Weak induction
2012	Domeque Valiente et al.[19]	Case report	Methadone	Unknown	Unknown	Unknown	2B6, 3A4, 2C19, 2D6	Undefined induction
2018	Morath et al.[20]	Case report	Valproic acid	Plasma concentration −59%	Oral/IV TID 1000 mg	Day 4	2A6, 2B6, 2C9, 2C19	Moderate induction
2019	Sigaroudi et al.[21]	Case report	Tacrolimus	Unknown	Unknown	Unknown	3A4/5	Undefined induction
2021	Gaebler et al.[22]	Case control	Sertraline	mDAPC −74% (74, 91)	Unknown	Unknown	2C19, 3A4, 2B6	Moderate induction
2020	Kliem et al.[23]	Case report	Valproic acid	Plasma concentration −58%	Oral QID 1000 mg	Day 9	2A6, 2B6, 2C9, 2C19	Moderate induction
2021	Bachmann et al.[15]	Cohort	Efavirenz	AUC −79% (74–80)	Oral QID 1000 mg	Day 7	2B6	Moderate induction
2021	Bachmann et al.	Cohort	Midazolam	AUC −68% (59–76)	Oral TID 1000 mg	Day 7	3A4/5	Moderate induction
2021	Bachmann et al.[15]	Cohort	Omeprazole	AUC −66% (66–67)	Oral TID 1000 mg	Day 7	2C19	Moderate induction
2021	Bachmann et al.[15]	Cohort	Flurbiprofen	AUC −22% (20–24)	Oral TID 1000 mg	Day 7	2C9	Weak induction
2021	Bachmann et al.[15]	Cohort	Caffeine	AUC +79% (38–132)	Oral TID 1000 mg	Day 7	1A2	Moderate inhibition
2023	Breithaupt et al.[15]	Cohort	Midazolam	AUC −82% (84–86)	Oral TID 1000 mg	Day 6	3A4/5	Strong induction
2024	Watermeyer et al.[24]	Case control	Quetiapine	mDAPC −69% (56, 71)	Oral daily dose >1500 mg	Unknown	3A4, 2D6	Moderate induction

Abbreviations: AUC, area under the curve (95% CI); CYP, cytochrome; IV, intravenous; mDAPC, median dose-adjusted plasma concentration (Q1, Q3); mPC, mean plasma concentration (SD); QID, four times a day; TID, three times a day.

3.2 | Pharmacodynamics

The exact mechanism of action of metamizole has not yet been fully elucidated. Initially, it was thought that the active metabolites, especially 4-MAA, have an inhibitory effect on the enzymes cyclooxygenase (COX)-1 and 2, although to a lesser extent than classical NSAIDs.[9] Reduced production of prostaglandins and prostacyclins via COX-2 provides an analgesic, spasmolytic and antipyretic effect, whereas reduced production of thromboxane A2 via COX-1 provides an antithrombotic effect. Although still a topic of debate, more recent in vitro and animal studies showed that metamizole might also have an analgesic effect via several other mechanisms including COX-3,[11] the 'transient receptor potential ankyrin-1 (TRPA-1)' receptor,[12] the cannabinoid[13] and the endogenous opioid system.[14] Further studies are needed to determine the extent to which these mechanisms play a role in the action of metamizole in humans.

3.3 | Pharmacokinetic interactions

In recent years, more and more research has been published assessing the effect of metamizole on the CYP450 system in the liver. In fact, it appears to be a moderate to strong inductor of the enzymes CYP3A4, CYP2B6 and CYP2C19; a weak inductor of CYP2C9; and a moderate inhibitor of CYP1A2 (Table 1).[15,16] Enzyme induction is most likely related to a direct or indirect activation of the constitutive androstane receptor (CAR) by the main metabolite 4-MAA, which is similar to the effect that is attributed to phenobarbital.[15,16] In 1999, for the first time, a low dosage of metamizole (500 mg three times daily for 4 days) was shown to reduce the plasma concentration of the CYP3A4 substrate cyclosporine, leading to a higher risk of rejection after organ transplantation (Table 1).[17] Over a decade later, new case reports appeared showing that metamizole may also have an effect on the plasma concentration of other drugs such as bupropion,[18] methadone[19] and valproic acid[20] (Table 1). More recent research in healthy volunteers showed that metamizole at higher doses (1000 mg three times daily) is even a moderate to strong inducer of CYP3A4 and CYP2B6, similar to carbamazepine and St. John's wort.[16,25] In fact, it lowered the area under the curve (AUC) of the CYP3A4 substrate midazolam by 73% and 82% after 3 and 6 days, respectively.[25] Enzyme induction occurs as early as after a single dose of metamizole, reaches its maximal after 5 days and persists for several weeks after discontinuation. A single dose of metamizole had no significant effect on enzyme activity, and a dose duration shorter than 1 day displayed a limited effect.

3.4 | Pharmacodynamic interactions

In addition to the pharmacokinetic interactions, metamizole also has several pharmacodynamic interactions that are relevant for clinical practice. In platelets, metamizole binds reversibly to COX-1, whereas acetylsalicylic acid does so irreversibly. Thus, the effect of acetylsalicylic acid lasts throughout the entire life span of the platelet (approximately 10 days). When both drugs are used simultaneously, metamizole may reduce the effect of acetylsalicylic acid by preventing the binding of acetylsalicylic acid to COX-1 (Figure 1). This competitive pharmacodynamic interaction is comparable with the interaction

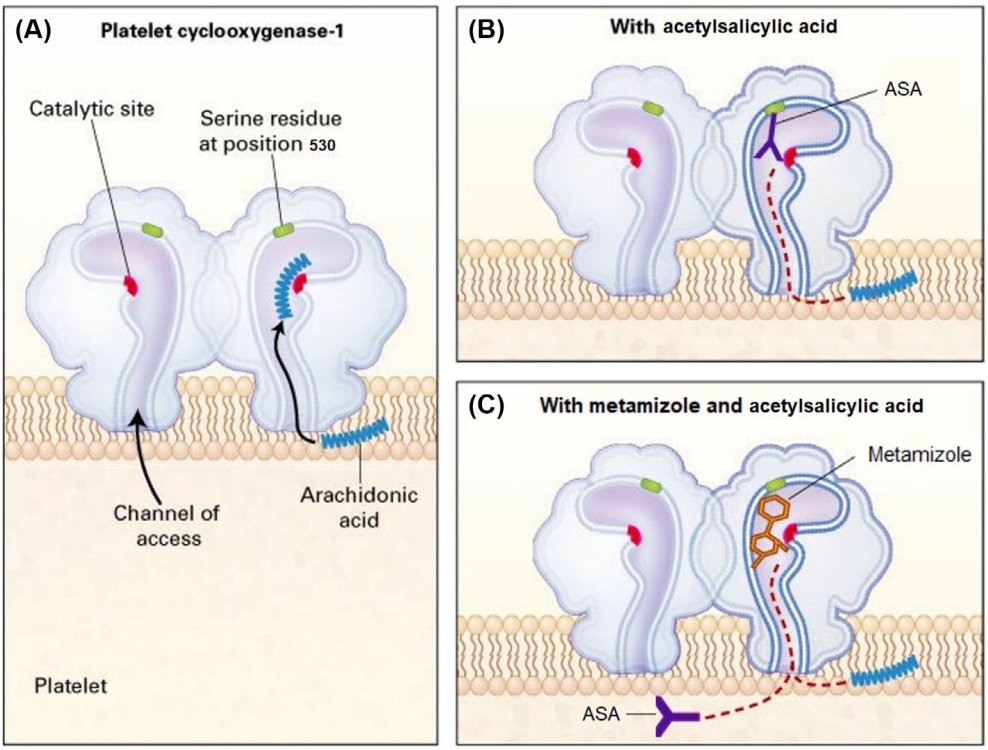

FIGURE 1 Interaction between metamizole and acetylsalicylic acid in the COX-1 enzyme of the thrombocyte. (A) Arachnidonic acid binds to the active core of the COX-1 enzyme and is converted to prostaglandins. (B) Acetylsalicylic acid (ASA) prevents the binding of arachnidonic acid by binding to the protein serine 530. (C) Metamizole binds to the same serine 530, preventing the binding of acetylsalicylic acid and arachnidonic acid. Adapted from Catella-Lawson et al.[26]

TABLE 2 Recommendations for pharmacokinetic interactions of metamizole when used for more than 1 day in high dosage (1000 mg three or four times daily).

Drug group	CYP enzyme	Recommendations
Immunosuppressants		
Cyclosporine	3A4	Stop metamizole and determine plasma concentration of the coadministered drug, choose alternative to metamizole if possible. At lower dose monitor effect.
Tacrolimus	3A4/5	
Psychotropics		
Valproic acid	2A6, 2B6, 2C9, 2C19	Stop metamizole and determine plasma concentration of the coadministered drug, choose alternative to metamizole if possible. At lower dose monitor effect.
Sertraline	2C19, 3A4, 2B6	Avoid combination, choose alternative to metamizole if possible.
Midazolam	3A4/5	Reduce dosage of metamizole or titrate dosage of the coadministered drug based on effect, choose alternative to metamizole if possible.
Quetiapine	3A4, 2D6	Avoid combination, choose alternative to metamizole if possible.
Analgesics		
Methadone	2B6, 3A4, 2C19, 2D6	Reduce dosage of metamizole or titrate dosage of the coadministered drug based on effect, choose alternative to metamizole if possible.
Fentanyl	3A4	
Oxycodone	3A4, 2D6	
Piritramide	3A4	
Direct oral anticoagulant		
Rivaroxaban	3A4, 2 J2	Avoid combination, choose alternative to metamizole if possible.
Edoxaban	3A4/5	
Apixaban	3A4/5	
Antivirals for HIV		
Efavirenz	2B6	Avoid combination, choose alternative to metamizole if possible.
Nevirapine	2B6	
Etravirine	3A4, 2C9, 2C19	
Maraviroc	3A4/5	
Dolutegravir	3A	
Rilpivirine	3A	
Doravirine	3A4	
Bictegravir	3A	
Fostemsavir	3A4	
Lenacapavir	3A	
Nirmatrelvir/ritonavir	3A4	
Others		
Omeprazole	2C19	Reduce dose of metamizole or titrate dose of the coadministered drug based on effect, choose alternative to metamizole if possible.
Oral contraceptives	1A2, 3A4	Avoid combination and warn patient for decreased contraceptive reliability for at least 4 weeks.

between ibuprofen and acetylsalicylic acid. Previous studies showed that the interaction between acetylsalicylic acid and metamizole is dose-dependent and may be prevented when acetylsalicylic acid is administered at least 30 min before metamizole.[27,28] This way, acetylsalicylic acid binds to COX-1 before metamizole could. However, a recent study showed that despite the order of intake, this competitive interaction cannot always be prevented.[29] For example, 26% of patients who took acetylsalicylic acid 30 min before metamizole still had an excessive platelet activation status and thus no adequate anticoagulation. Since acetylsalicylic acid has a relatively short half-life (20 min *vs.* 3 h) compared with metamizole, plasma levels of acetylsalicylic acid might become too low (after four to five times the half-life, i.e., within 2 h), enabling metamizole to bind to newly produced platelets (about 10% renewal per day) when the next dose is administered.[29–31] Blood coagulation is already normalized when 20% of platelets have a normal COX activity.[32] Next to comedication, other factors such as diabetes, renal failure and recent surgery may also contribute to an excessive platelet activation status.

TABLE 3 Recommendations for pharmacodynamic interactions of metamizole.

Drug group	Recommendations
Analgesics	
Aminopyrine	Be cautious with metamizole due to increased risk of agranulocytosis.
Diflunisal	
Acetylsalicylic acid	Avoid combination with metamizole in patients with an increased cardiovascular risk. Choose an alternative for metamizole or acetylsalicylic acid.
NSAIDs and COX-2 inhibitors	Avoid combination with metamizole due to increased risk of acute renal and hepatic injury and agranulocytosis.
Antiarrhythmics	
Disopyramide	Be cautious with metamizole due to increased risk of agranulocytosis.
Procainamide	
Quinidine	
Anti-infective drugs	
Ampicillin	Be cautious with metamizole due to increased risk of agranulocytosis.
Carbenicillin	
Cefotaxime	
Cefuroxime	
Flucytosine	
Fusidic acid	
Imipenem–cilastatin	
Nafcillin	
Oxacillin	
Penicillin G	
Quinine	
Ticarcillin	
Anticonvulsants	
Phenytoin	Be cautious with metamizole due to increased risk of agranulocytosis.
Antineoplastics	
Amygdalin	Be cautious with metamizole due to increased risk of agranulocytosis.
Antirheumatics	
Infliximab	Be cautious with metamizole due to increased risk of agranulocytosis.
Levamisole	
Antithyroid drugs	
Propylthiouracil	Be cautious with metamizole due to increased risk of agranulocytosis.
Cardiovascular drugs	
Clopidogrel	Be cautious with metamizole due to increased risk of agranulocytosis.
Methyldopa	
Ramipril	
Spironolactone	
Gastrointestinal drugs	
Cimetidine	Be cautious with metamizole due to increased risk of agranulocytosis.
Metoclopramide	
Psychotropics	
Chlorpromazine	Be cautious with metamizole due to increased risk of agranulocytosis.
Clozapine	
Perazine	
Flupentixol	
Fluoxetine	

(Continues)

TABLE 3 (Continued)

Drug group	Recommendations
Others	
Calcium dobesilate	Be cautious with metamizole due to increased risk of agranulocytosis.
Mebhydrolin	

Note: This list of drugs with increased risk of agranulocytosis is based on Andersohn et al.[36]
Abbreviations: COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drugs.

In line with these results, clinical studies showed that the use of acetylsalicylic acid together with metamizole is associated with an increased risk of cardiovascular complications in patients with coronary artery disease,[33] a recent stroke[34] and after percutaneous transluminal angioplasty.[35] However, in these studies, it is not clear when precisely acetylsalicylic acid and metamizole were taken by the patients. Lastly, an additive pharmacodynamic interaction applies to the risk of agranulocytosis, when metamizole is used together with other drugs that can cause agranulocytosis such as clozapine, phenytoin and perazine.[36] This risk of agranulocytosis is not dose-dependent and can occur at any time during treatment or shortly after stopping the drug and also when metamizole was previously used without problems.[37]

4 | DISCUSSION

The pharmacokinetic and dynamic interactions of metamizole have several implications for our daily clinical practice. Since CYP3A4 (~30%), CYP2C19 (~13%) and CYP2B6 (~7%) enzymes are involved in the metabolism of more than half of the available drugs,[38] enzyme induction by metamizole has important consequences. If metamizole is continued longer than 1 day in a high dosage (1000 mg three or four times daily), we have listed several recommendations in Table 2. In certain cases, it might be better to choose another analgesic instead of metamizole such as a COX-2 inhibitor. Since enzyme induction is dose-dependent, another option is to lower the dosage of metamizole or to increase the dosage of coadministered drugs with a large therapeutic window. However, attention has to be paid to decrease the dosage of the coadministered drug when metamizole is discontinued; otherwise, the risk of adverse events and toxicity is increased. For agents with a narrow therapeutic window such as cyclosporine and tacrolimus, the combination with metamizole should be avoided or therapeutic drug monitoring should be employed. In addition to being an inducer for various CYP enzymes, metamizole actually has a moderate inhibitory effect on CYP1A2 and can increase the plasma concentrations of several drugs including amitriptyline and duloxetine.[15] Regarding perioperative care, interactions with analgesics including fentanyl, oxycodone, methadone and piritramide and direct-acting oral anticoagulants (DOACs) including apixaban and rivaroxaban are of particular interest.

Besides pharmacokinetic interactions, several recommendations concerning the pharmacodynamic interactions of metamizole are summarized in Table 3. We recommend to avoid metamizole together with acetylsalicylic acid in patients with a high cardiovascular risk such as after a recent stroke or after high-risk cardiovascular surgeries such as a carotid endarterectomy. Since the intake of acetylsalicylic acid 30 min before metamizole is not reliable, a recommendation for a safe time interval cannot be provided. A single perioperative bolus of metamizole has a negligible effect on the binding of acetylsalicylic acid. Alternatively, an analgesic other than ibuprofen can be chosen instead of metamizole or another platelet aggregation inhibitor instead of acetylsalicylic acid such as dipyridamole. Another option is to decrease the dosage of metamizole since the interaction is dose-dependent. As mentioned earlier, metamizole by itself has an anticoagulatory effect via COX-1, but whether this is clinically relevant action needs further investigation. Lastly, we recommend to use metamizole cautiously together with other drugs that can lead to agranulocytosis (Table 3).

5 | CONCLUSION

Metamizole is an analgesic that is frequently prescribed worldwide. It has a number of relevant pharmacokinetic and dynamic interactions that should be known in clinical practice. If metamizole is prescribed in a high dosage (1000 mg three or four times daily) for more than 1 day, these interactions should be taken into account.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, data collection and analysis and writing of the report. All authors contributed to data interpretation and approved the final version of the submitted report. The authors confirm that the PI for this paper is David Brinkman.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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