Metamizole (Dipyrone) and the Liver:
A Review of the Literature

Mathias Lutz, MD

Abstract
Metamizole, also known as dipyrone, was introduced to the market nearly a century ago. Due to its excellent analgesic, antipyretic, and spasmolytic properties combined with its mostly favorable gastrointestinal tolerability, the drug was extensively applied worldwide during the first decades after its market introduction. Although rare, agranulocytosis is a well-known adverse event of metamizole and led to its withdrawal from the market in a number of countries beginning in the 1960s. Nevertheless, metamizole is still a frequently used drug worldwide either legally (by prescription in some countries, over the counter in other countries) or without official approval (especially by immigrants knowing the drug from their home countries) or even illegally (due to its growing application as an adulterant in illicit drugs). Metamizole undergoes extensive metabolism in the liver and cases of potential metamizole-associated hepatotoxicity have been described. Here, the literature is extensively reviewed for the first time regarding hepatic effects associated with the use of metamizole.

Keywords
dipyrone, hepatotoxicity, liver, liver disease, drug-drug interactions, drug metabolism, metamizole

Nearly 100 years have passed since metamizole, also known as dipyrone, was introduced to the market in 1922.1,2 Due to its chemical structure belonging to the class of pyrazolones and its analgesic, antipyretic, and (however weak) antiphlogistic effects, metamizole is classified as a nonsteroidal anti-inflammatory drug (NSAID).3–5 Compared to the other agents of this heterogeneous group, metamizole also offers additional spasmolytic properties.6,7 In combination with its mostly favorable gastrointestinal tolerability, this profile led to an extensive clinical application of metamizole during the initial period after its market introduction.8–10

However, an increasing number of side effects of metamizole have been reported over the following decades affecting the cardiovascular system (ie, hypotension and arrhythmia), the respiratory system (ie, bronchospasm, especially in asthmatic patients), and the skin (ie, maculopapular rash), among others.11–15 While most of these side effects rapidly disappear after discontinuation of the drug and/or are manageable in a clinical setting, metamizole-induced agranulocytosis, whose first description dates back to 1936, poses a serious threat to the patient’s life.16,17 Defined as a granulocyte count of <500/µL and thought to be mediated by immunological processes,18–20 metamizole-induced agranulocytosis can emerge independently of the drug’s dose or way of administration and, therefore, is not predictable.21,22 Furthermore, although about half the cases occur during the first week of metamizole therapy, there can be a latency of up to several months, making it difficult to identify the association.17,23 Reported incidences of metamizole-induced agranulocytosis show a wide variation. While a first international study calculated a risk of 1.1 agranulocytosis cases per 1 million patients per week of metamizole treatment, other studies found much higher incidences, including a Swedish analysis reporting 1 case of agranulocytosis per at least 1439 prescriptions of metamizole.17,24–26 Either way, many fatal cases of metamizole-induced agranulocytosis have been reported over the decades.17,27 Beginning in the 1960s, metamizole was therefore withdrawn from the market or never got approved in a number of countries, including Australia, Canada, France, India, Japan, the Scandinavian countries, the United Kingdom, and the United States.6,28–31

Nevertheless, metamizole is still available in many countries worldwide either by prescription (ie, Belgium,
Beginning in the 1960s, metamizole was banned (or never got approved) in a number of countries (depicted in dark red) following an increasing number of reports of agranulocytosis induced by the drug. 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 could be found for countries depicted in white.

Germany, Italy, Portugal, Spain, and Switzerland) or over the counter (ie, Brazil, China, Israel, Mexico, Poland, Turkey, and Russia). In these countries, the drug is still commonly used for indications such as cancer pain, colic pain, postoperative pain, headache, or pain resulting from acute injuries, among others. For instance, metamizole was the third most prescribed analgesic drug in Switzerland in the period between 2006 and 2013, and in Germany it was the most prescribed analgesic substance in 2012, with more than 140 million defined daily doses. In countries where metamizole is sold over the counter, the drug is used as a common self-medication and is the most taken analgesic agent in patients with chronic pain. A cross-sectional population-based study performed in Brazil, where metamizole is sold over the counter, analyzed 41,433 individuals and revealed that metamizole is the most used self-medication. A new appearance of metamizole, especially in the United States, is associated with its growing application as an adulterant in illicit drugs. For instance, metamizole has recently been detected in illegal fentanyl samples (which itself is often used to cut heroin) by different chromatography-based analyses. It has been known for quite some time that metamizole is also used as an adulterant to cut cocaine for street-level consumption.

Metamizole still is a frequently used drug worldwide, either legally or without official approval or even illegally. The drug undergoes extensive metabolism in the liver. However, no one has ever extensively reviewed the literature regarding potential hepatic effects associated with the use of metamizole.

### Hepatic Metabolism of Metamizole

Metamizole is available for oral, rectal, and intramuscular administration. Due to its good solubility in water, it can also be administered intravenously. While metamizole can be detected in the plasma for approximately 15 minutes after intravenous administration, it is nearly untraceable after oral administration. The reason of this divergence is the nonenzymatic hydrolysis of metamizole in the gastrointestinal tract to its first metabolite, 4-methylaminoantipyrine (4-MAA), leading to its fast and nearly complete absorption when given orally. Mediated by its active metabolites, metamizole achieves an oral bioavailability of almost 100%.

A single-site analysis in a US urban pediatric hospital revealed that over one-third of all Spanish-speaking Latino families had used metamizole before. Therefore, metamizole has received the (politically incorrect) nickname “Mexican aspirin” in some regions of the United States.
published decades ago, it was assumed that food intake does not influence the absorption of metamizole. In this trial in 12 healthy male volunteers aged between 24 and 30 years, metamizole was delivered once after fasting for 8 hours and once immediately after a breakfast standardized within the study. While the administration of metamizole with food led to a significant delay in the mean time to peak plasma concentration and to a slower absorption rate, there was no significant difference in the area under the plasma concentration–time curve (AUC), the peak plasma concentration, and the elimination rate. Hence, the authors assumed that metamizole could be given orally regardless of food intake.60 However, Moore et al61 concluded in a more recently published systematic review analyzing metamizole and other NSAIDs that early plasma concentrations of the administered analgesic drug lead to an improvement of early and overall pain relief as well as to longer lasting pain relief and subsequently to a lower rate of remedication. Therefore, oral administration of metamizole with or shortly after food intake may undermine its efficacy. In summary, the authors suggested a rethinking process regarding the advice given to physicians as well as to patients. Either way, the absorption rate, the time to peak plasma concentration, and the peak plasma concentration of metamizole seem to be similar regardless of age following the results of a study performed in a group of younger (21-30 years) and a group of elderly (73-90 years) healthy volunteers.62

As the first active metabolite of metamizole, 4-MAA reaches its peak plasma concentration within 1 to 2 hours and is further metabolized in the liver to both a second active metabolite, 4-aminoantipyrine (4-AA), via N-demethylation, and a first inactive metabolite, 4-formylaminoantipyrine (4-FAA), via C-oxidation.15,63

Up to now, hepatic metabolism of 4-MAA was known to be mediated by the cytochrome P450 (CYP) 3A4 system.64 However, Bachmann et al65 recently published their experimental work showing that (besides a postulated potential extrahepatic metabolism via myeloperoxidase in granulocytes and granulocyte precursor cells) other CYPs are also involved in N-demethylation of 4-MAA, namely, CYP2B6, CYP2C8, and CYP2C9. Consistently, another experimental study performed over 10 years ago analyzing liver microsomes of patients treated with metamizole revealed not just a selectively higher expression of CYP3A4 (2.8-fold), but also of CYP2B6 (3.8-fold) in comparison to untreated individuals.66 As a consequence, it has to be hypothesized that metamizole could interact with other substances metabolized via these CYP systems, including frequently applied agents such as aspirin or immunosuppressants such as tacrolimus.67–71 For instance, a small trial in patients on long-term cyclosporin (CsA) treatment after heart or kidney transplantation could indeed show an association between short-course administration of metamizole and a mild decrease in CsA plasma concentrations, especially in the first hours after metamizole intake. However, no dose adjustment of CsA was necessary in this small cohort of patients.72

Compared to 4-MAA, 4-AA as the second active metabolite of metamizole has a markedly weaker analgesic effect and a longer time to peak plasma concentration, but a longer pharmacological half-life. The combination of these properties of 4-MAA and 4-AA is leading to both the fast and long-lasting efficacy of metamizole.15,73 Further metabolism of 4-AA to another inactive metabolite, 4-acetylaminoantipyrine (4-AAA), via acetylation is mediated by a polymorphic N-acetyltransferase system.74 Accordingly, AUC and formation rate of 4-AAA are highly correlated with the acetylator phenotype of each individual.75 However, increasing doses of metamizole do not lead to a deviation from linearity in AUC or formation rate in slow acetylators compared to rapid acetylators. Therefore, it must be assumed that despite the increasing plasma concentrations of 4-AA associated with increasing metamizole doses, no saturation of acetylation capacity from 4-AA to 4-AAA occurs even if it is genetically low, as in slow acetylators.76,77

Besides the metamizole metabolites mentioned above, which have been known for decades, 2 further metabolites have been identified more recently by liquid chromatography–mass spectrometry–based analyses after oral administration of metamizole to mice: arachidonoyl-4-MAA and arachidonoyl-4-AA, representing the arachidonoyl amides of 4-MAA and 4-AA, respectively.73,78 Furthermore, a total of 6 metabolites of metamizole could be detected in the urine of healthy volunteers after oral administration of metamizole. Four of them could be identified as the main metabolites mentioned above (4-MAA, 4-AA, 4-FAA, and 4-AAA) while the other 2 up to then unknown metabolites included conjugated 4-hydroxyantipyrine, supposedly a glucuronide. Therefore, the existence of further (in all likelihood inactive) metabolites of metamizole could be hypothesized.79 Figure 2 depicts the known metabolites of metamizole.

Considering the chemical structure of metamizole and its metabolites containing a phenyl ring as well as a heterocyclic ring with amine and carbonyl groups, a certain potential for interactions via their reactive groups seems to be conceivable.

One interaction is mediated by CYP metabolism, which has been shown in both animal and human in vitro trials. In each case, the major metabolites of metamizole could be identified as inducers of different CYP enzymes.65,66,80,81
Another manner of interaction might be mediated by covalent binding of reactive groups. Indeed, albeit relatively low, an older trial showed a plasma protein binding for the major metabolites of metamizole.\(^8\) However, the character of these bindings is still not fully clarified. Results of an in vitro study performed by Lüthy et al.\(^8\) suggest that metamizole does not inhibit cyclooxygenase by binding covalently to the enzyme. On the contrary, Ariza et al.\(^5\) recently could establish a basophil activation test to identify selective anaphylaxis for metamizole and its metabolites and assumed that molecules inducing such reaction require covalent binding to plasma proteins.\(^4\) Furthermore, several trials found strong evidence that development of the metamizole-induced agranulocytosis mentioned above is mediated by drug-dependent antineutrophil antibodies requiring covalent binding of the drug or its metabolites to neutrophils.\(^2\),\(^5\)

Another interaction potential for metamizole might occur through the fact that it has been identified as a highly potent scavenger of reactive nitrogen species such as nitric oxide and peroxynitrite. The authors of this trial interpreted these results in the context of an anti-inflammatory potential of the drug, but it seems to be conceivable that there exist further interactions based on this mechanism.\(^8\) However, an extensive literature search did not reveal further trials investigating this mechanism.

In patients with chronic impairment of liver function, metabolism of the above-mentioned metabolites of metamizole is reduced. For instance, Zylber-Katz et al.\(^7\) investigated plasma concentrations for 4-MAA, 4-AA, 4-FAA, and 4-AAA following a single dose of metamizole in hospitalized patients with known liver cirrhosis (aged between 25 and 65 years) and compared them to 2 groups of healthy volunteers (a younger
group aged between 21 and 40 years and an elderly group aged between 73 and 90 years) having received the same dose of metamizole. They could show that the disposition of all 4 metabolites was reduced in cirrhotic patients compared to the healthy volunteers regardless of the age of the latter, although there were some differences in subgroup analyses with regard to the acetylation phenotype. The same group could also demonstrate an impairment of metamizole metabolism in asymptomatic carriers of hepatitis B virus, although having normal liver function tests. In detail, oxidative pathways producing 4-AA and 4-FAA were significantly impaired compared to healthy individuals, while metabolism of 4-AAA seemed to be unaffected. Hence, the authors concluded that hepatitis B infection has an effect on the oxidation but not on the acetylation of metamizole metabolites. All subjects of this study displayed the slow acetylation phenotype. Some years later, the authors performed another trial examining the same issue in rapid acetylators. In this case, they found no difference in metabolism of the metamizole metabolites between asymptomatic carriers of hepatitis B virus and healthy volunteers.

Potential Hepatotoxicity Associated With the Use of Metamizole

Considering the extensive hepatic metabolism of metamizole mentioned above, a hepatotoxic potential of the drug seems to be at least conceivable. Results of a recently published experimental trial could possibly substantiate this theory. Benesic et al. developed a test applying monocyte-derived hepatocyte-like (MH) cells obtained from patient blood samples to identify drugs causing liver injury based on their toxic potential to these MH cells. A total of 300 patients were enrolled in the trial, and the results of 40 patients are presented in the publication. In total, 10 drugs could be identified showing toxicity to MH cells from 13 patients. Among these drugs, metamizole was involved in 1 case. As a liver reinjury could be shown in all 13 patients mentioned above after reexposure to these drugs and the MH test correctly identified the provoking drug in 12 of these 13 cases again, the test seems to be valid (sensitivity of 92.3% and specificity of 100%). Therefore, a hepatotoxic potential of metamizole seems to be possible.

Furthermore, experimental data in a rat model showed at least an increase in alanine aminotransferase (ALT) activity after a subchronic metamizole treatment. In this study, 14 rats received 60 mg/kg of metamizole twice daily for 14 days. Compared to a control group with the same sample size, a significant increase in ALT activity (65.8 ± 4.2 U/L compared to 48.0 ± 2.1 U/L; \( P < .01 \)) was seen after metamizole treatment. However, this short-term application of metamizole was surely too short to draw definite conclusions about potential development of drug-induced liver injury (DILI). Additionally, no significant differences between the experimental and control groups were observed in this trial regarding aspartate aminotransferase (AST), gamma-glutamyltransferase, and alkaline phosphatase.

Most published clinical reports about metamizole-associated liver toxicity describe single cases, and several pathomechanisms have to be differentiated.

Hepatotoxicity might be interpreted in the context of multiple organ failure due to metamizole intoxication. In a case of metamizole-induced suicide, a 70-year-old female patient with chronic pain due to rheumatoid arthritis died 4 days after hospitalization due to acute kidney failure with secondary multiple organ failure including the liver.

Metamizole-associated hepatotoxicity might also be induced by allergic mechanisms. In one case, a 50-year-old patient presented with acute jaundice and elevation of liver enzymes (ALT, AST, gamma-glutamyltransferase and alkaline phosphatase) after accidental reexposure to metamizole. A lymphocyte transformation test (LTT) performed 5 times over a period of 232 days could demonstrate sensitization to 4-AA and therefore the allergic genesis of this reaction.

In another case, a 66-year-old patient was hospitalized with generalized exanthema and elevation of hepatic blood parameters after application of metamizole. Since liver biopsy revealed a drug-induced hepatitis, an association with the metamizole medication was suspected. LTT was performed and confirmed sensitization to metamizole and 3 of its metabolites (4-MAA, 4-FAA, and 4-AAA).

Regarding the latter 2 case reports described, it must be noted that LTT is not always reliable in diagnosis of DILI due to technical aspects such as time of testing and influence of treatment leading to false-positive results.

Table 1 summarizes details of the 3 case reports mentioned above. It must be noted that none of these case reports provides enough details to classify the hepatotoxicity observed as DILI according to standardized nomenclature.

Larger trials analyzing potential hepatotoxic effects of metamizole are nearly missing, and most available data are from retrospective studies. In an older trial, Okonek and Reinecke analyzed 23 cases of pyrazolone intoxications reported to a German poison information center and concluded that metamizole might induce hepatotoxic effects in this situation (usually occurring with a latency of at least 24 hours). However, the incidence of liver toxicity seemed to be lower compared to the other pyrazolones.
### Table 1. Published Case Reports on Metamizole-Associated Hepatotoxicity

| Reference                  | Patient Details                  | Current Condition                                      | Treated With Metamizole | Duration of Current Metamizole Treatment | Development of Jaundice or Other Liver-Specific Symptoms | Initial Values of Hepatic Serum Parameters | Peak Values of Hepatic Serum Parameters | Confirmation of Metamizole Toxicity | Confirmation of DILI According to Standardized Nomenclature |
|----------------------------|---------------------------------|--------------------------------------------------------|--------------------------|-----------------------------------------|----------------------------------------------------------|--------------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------------------|
| Federmann et al.93          | 50 y Male, Acute postoperative pain after cholecystectomy | Single application of 300 mg metamizole | Chronic (for years), but with high doses taken over the few days before developing toxicity signs | Not reported | Not reported | ALT: 4.4 × ULN; bilirubin: 36.6 × ULN | By LTT demonstrating sensitization to 4-AA | Not possible | Not possible |
| Haase et al.92              | 70 y Female, Chronic pain due to rheumatoid arthritis | Chronic (for years), but with high doses taken over the few days before developing toxicity signs | Single application of 250 mg metamizole | ALT: 35.3 × ULN; bilirubin: within reference range | Not reported | ALT: 160.1 × ULN; bilirubin: within reference range | By metamizole serum concentration measurement (initial value of 524 mg/L with potential toxicity beginning from 20 mg/L) | Not possible | Not possible |
| Herdeg et al.94             | 66 y Male, Flulike symptoms with fever, headache, and sore throat | Single application of 250 mg metamizole | Single application of 250 mg metamizole | Not reported | Not reported | ALT: 6.6 × ULN; bilirubin: within reference range | By LTT demonstrating sensitization to 4-MAA, 4-FAA, and 4-AAA | Not possible | Not possible |

4-AA, 4-aminoantipyrine; 4-AAA, 4-acetylaminoantipyrine; 4-FAA, 4-formylaminoantipyrine; 4-MAA, 4-methylaminoantipyrine; ALT, alanine aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.

In another historic study, 118 young adults (35 women and 83 men) were treated for their measles symptoms during an outbreak either with acetaminophen (paracetamol; total drug dose, 10.1 ± 5.5 g; n = 43) or with metamizole (total drug dose, 3.9 ± 1.7 g; n = 13) or with acetaminophen first and metamizole afterwards (total drug dose of acetaminophen, 5.1 ± 3.7 g; total drug dose of metamizole, 3.6 ± 2.7 g; n = 62). While 58% of patients treated with acetaminophen had an elevation of ALT and AST concentrations, only 15% of patients treated with metamizole showed an elevation of these enzymes (P < .01 for ALT and P < .02 for AST). Furthermore, mean concentrations of AST and bilirubin were significantly higher in the patients treated with acetaminophen compared to those treated with metamizole (P < .02 for AST and P < .01 for bilirubin).99 Results of this trial do not seem to support significant hepatotoxicity for metamizole, especially since the drug’s dosing was too brief to draw further conclusions. Furthermore, among other potential biases of this evaluation, it must be considered that measles can also cause hepatitis,100 and the authors interpreted their results in the context of a combined drug-virus effect.99 However, this effect might play a significant role in the future because the incidence of measles infections has been increasing over the past several years, even in Western countries.101,102

A more recently published study analyzed the potential hepatotoxic effects of metamizole, among others: Sabaté et al103 identified a total of 126 patients with acute liver injury from 12 hospitals in Barcelona (Spain) and evaluated their drug consumption within 15 days (in terms of hepatocellular pattern) or within 30 days (in terms of acute cholestatic or mixed pattern) using patient interviews. Regarding NSAIDs, metamizole showed the lowest estimated relative risk (RR) of 3.1 (99% confidence interval [CI], 0.4-11.4) compared to acetaminophen (RR, 7.0; 99%CI, 3.3-13.9), diclofenac (RR, 7.6; 99%CI, 1.8-22.0), and aspirin (RR, 5.4; 99%CI, 2.0-12.3). However, the results of this study are surely limited by different biases, including the missing analysis of potential confounding factors as well as the potential recall bias due to evaluation of drug consumption by patient interviews as already criticized by Andrade et al.27

A German case-control surveillance study evaluating drug-induced liver injury published in 2014 revealed a significantly higher odds ratio of 5.2 (95%CI, 2.0-13.4) in 122 outpatients treated with metamizole compared to 708 outpatient controls. However, this significant difference could not be seen in 76 inpatient cases compared to 377 inpatient controls (odds ratio, 1.0; 95%CI, 0.4-2.2). Besides metamizole, an increased risk for drug-induced liver injury was found.
for other drugs seldom associated with hepatotoxic effects. Hence, the authors demanded further postauthorization safety trials regarding this matter.104

In some prospective trials analyzing the analgesic use of metamizole, preexisting liver injury was defined as an exclusion criterion. In 2017, Gaertner et al performed a systematic review evaluating the application of metamizole for relief of cancer pain. They analyzed 4 studies (3 randomized controlled trials and 1 cohort study with a total of 252 patients) revealing a favorable toxicity profile without any hepatotoxic effects. However, because liver impairment was defined as an exclusion criterion by 3 of these trials and liver metastases by the fourth one,105–108 no definite conclusion can be drawn regarding the potential hepatotoxicity of metamizole in patients with preexisting liver impairment.

The most comprehensive analysis of adverse events associated with the use of metamizole was performed by Kötter et al and published in 2015. Within a systematic review and meta-analysis, they identified 79 trials with a total of 3716 patients receiving a short-term course of metamizole with a maximum duration of 14 days. While they found no significant differences in reports of any adverse event for metamizole compared to placebo, acetaminophen, and NSAIDs, more adverse events of any kind were reported for opioids compared to metamizole (RR, 0.79; 95% CI, 0.65-0.96). Hepatotoxicity was presumably subsumed in the category “other digestive adverse events,” and no significant differences were seen between metamizole and any of the other substances mentioned above. However, the authors had to note limitations of their results mostly due to the mediocre overall quality of the trials evaluated. Subsequently, they stressed the need for further high-quality studies investigating potential adverse events of metamizole, especially in the intermediate- to long-term setting.

Conclusions

Although introduced to the market nearly a century ago, metamizole still is a common analgesic and spasmylytic drug used nearly worldwide even in countries where it got banned or was never approved. Metamizole undergoes an extensive metabolism in the liver mediated by CYP isoenzymes, among others. Subsequently, interactions with other drugs such as immunosuppressants have been reported. While results of several experimental and clinical studies make some hepatotoxic potential of metamizole at least conceivable, further evidence is missing to draw definite conclusions. However, some cases of even lethal metamizole-induced hepatotoxicity have been reported, and one should be suspicious in situations where liver injury is seen during metamizole treatment and no other obvious cause can be identified. Finally, high-quality postauthorization safety studies are needed to further assess the relevance of potential hepatotoxicity associated with the use of metamizole.

Conflicts of Interest

The author declares no conflicts of interest.

References

1. Vuik FE, Koehestanie P, Herbers AH, Terhaar Sive Droste JS. Chronic use of metamizole: not so safe after all? Ned J Med. 2017;75(2):81-83.
2. Gaertner J, Stamler UM, Remi C, et al. Metamizole/dipyrone for the relief of cancer pain: a systematic review and evidence-based recommendations for clinical practice. Palliat Med. 2017;31(1):26-34.
3. Miljkovic M, Dragojevic-Simic V, Rancic N, et al. Metamizole utilization and expenditure during 6-year period: Serbia vs Croatia. Front Public Health. 2018;6:213.
4. Bagarn J, Lopez Arranz JS, Valencia E, et al. Clinical comparison of dextroketoprofen trometamol and dipyrone in postoperative dental pain. J Clin Pharmacol. 1998;38(S1):S55-S65.
5. Tsutsui MA, Carvalho WM, Silva CV, Miranda AE, Ferreira SH, Francisci IN. Analgesic and antiinflammatory effects of dipyrone in rat adjuvant arthritis model. Inflammation. 2014;18(4):399-405.
6. de Leeuw TG, Dirckx M, Gonzalez Candel A, Scoones GP, Huygen F, de Wildt SN. The use of dipyrone (metamizol) as an analgesic in children: what is the evidence? A review. Paediatr Anaesth. 2017;27(12):1193-1201.
7. Drobnik L. [Metamizol in relieving perioperative pain - contemporary look at the traditional medicine]. Anestezjologia i Ratownictwo. 2010;4:40-48.
8. Nikolova I, Tencheva J, Voinikov J, Petkova V, Benbasat N, Deanche N. Metamizole: a review profile of a well-known “forgotten” drug. Part I: Pharmaceutical and nonclinical profile. Biotechnol Biotechnol Eq. 2012;26(6):3329-3337.
9. Sanchez S, Alarcon de la Lastra C, Ortiz P, Motilva V, Martin MJ. Gastrointestinal tolerability of metamizol, acetaminophen, and diclofenac in subchronic treatment in rats. Dig Dis Sci. 2002;47(12):2791-2798.
10. Hinz B, Cheremina O, Bachmukov J, et al. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. J FASEB J. 2004;21(10):2343-2351.
11. Kötter T, da Costa BR, Fassler M, et al. Metamizole-associated adverse events: a systematic review and meta-analysis. PLoS One. 2015;10(4):e0122918.
12. Rodriguez-Martín S, Martin-Merino E, Lerma V, et al. Active surveillance of severe cutaneous adverse reactions: a case-population approach using a registry and a health care database. Pharmacoeconomics Drug Saf. 2018;27(9):1042-1050.
13. Achilles A, Mohring A, Dannenberg L, et al. Analgesic medication with dipyrone in patients with coronary artery disease: Relation to MACCE. Int J Cardiol. 2017;236:76-81.
14. Bellegrandi S, Rosso R, Mattiacci G, et al. Combined intermediate- and delayed-type hypersensitivity to metamizole. Allergy. 1999;54(1):88-90.
15. Ariza A, Garcia-Martín E, Salas M, et al. Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. Sci Rep. 2016;6:23845.
16. Benjamin JE, Biederman JB. Agranulocytic leukopenia induced by a drug related to aminopyrine. JAMA. 1936;107(7):493-494.
17. Rollason V, Desmeules JA. Use of metamizole in children and the risk of agranulocytosis: is the benefit worth the risk? *Eur J Anaesthesiol*. 2015;32(12):837-838.

18. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146(9):657-665.

19. Blaser L, Hassna H, Hofmann S, et al. Leucopenia associated with metamizole: a case-control study. *Swiss Med Wkly*. 2017;147:w14438.

20. Curtis BR. Non-chemotherapy drug-induced neutopenia: key points to manage the challenges. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):187-193.

21. Garbe E. Non-chemotherapy drug-induced agranulocytosis. *Expert Opin Drug Saf*. 2007;6(3):323-335.

22. Huber M, Andersohn F, Bronder E, et al. Drug-induced agranulocytosis in the Berlin case-control surveillance study. *Eur J Clin Pharmacol*. 2014;70(3):339-345.

23. Blaser LS, Tramonti A, Egger P, Haschke M, Krahenbuhl S, Huber M, Andersohn F, Bronder E, et al. Drug-induced agranulocytosis in the Berlin case-control surveillance study. *Eur J Clin Pharmacol*. 2015;71(2):209-217.

24. Risks of agranulocytosis and aplastic anemia. A first report of the risk of agranulocytosis: is the benefit worth the risk? *Ann Intern Med*. 2015;32(12):837-838.

25. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol*. 2002;58(4):265-274.

26. Kiatooonsri P, Richter J. Dipyrone trials in Thailand. *Lancet*. 1989;2(8654):107.

27. Andreade S, Bartels DB, Lange R, Sandford L, Gurwitz J. Safety of metamizole: a systematic review of the literature. *J Clin Pharm Ther*. 2016;41(5):459-477.

28. Preissner S, Sirmashetty VB, Dunkel M, Steinborn P, Luft FC, Preissner R. Pain-prescription differences - an analysis of 500,000 discharge summaries. *Curr Drug Abuse Rev*. 2018;11(1):58-66.

29. WITHDRAWN: a resource for withdrawn and discontinued drugs. Metamizole–legal status. http://cheminfo.charite.de/withdrawn/metamizole.html. Published September 2015. Accessed April 15, 2019.

30. Nikolova I, Petkova V, Tencheva J, Benbasat N, Voinikov J, Danchev V. Metamizole: a review profile of a well-known “forgotten” drug. Part II: Clinical profile. *Biotechnol Biotechnol Eq*. 2013;27(2):3605-3619.

31. Bhauimik S. India’s health ministry bans pioglitazone, metamizole, and flupentixol-melitracen. *Funct Neurol*. 2015;5(4):593-598.

32. Reist L, Erlenwein J, Meissner W, Stammschulte T, Stuber LM, Turner MA. Suspected adverse drug reactions reported for Brazilian children: cross-sectional study [published online ahead of print July 18, 2018]. *J Pediatr (Rio J)*. https://doi.org/10.1016/j.jped.2018.05.019.

33. Lima EDC, Matos GC, Vieira JML, Goncalves I, Cabral LM, Turner MA. Suspected adverse drug reactions reported for Brazilian children: cross-sectional study [published online ahead of print July 18, 2018]. *J Pediatr (Rio J)*. https://doi.org/10.1016/j.jped.2018.05.019.

34. Prado MA, Francisco PM, Bastos TF, Barros MB. Use of prescription drugs and self-medication among men. *Rev Bras Epidemiol*. 2016;19(3):594-608.

35. Lima EDC, Matos GC, Vieira JML, Goncalves I, Cabral LM, Turner MA. Suspected adverse drug reactions reported for Brazilian children: cross-sectional study [published online ahead of print July 18, 2018]. *J Pediatr (Rio J)*. https://doi.org/10.1016/j.jped.2018.05.019.

36. Wertli MM, Reich O, Signorrell A, Burgstaller JM, Steurer J, Held U. Changes over time in prescription practices of pain medications in Switzerland between 2006 and 2013: an analysis of insurance claims. *BMC Health Serv Res*. 2017;17(1):167.

37. Pastore GP, Goulart DR, Pastore PR, Prati AJ, de Moraes A. Self-medication among myofascial pain patients: a preliminary study. *Open Dent J*. 2018;12:347-353.

38. Arrais PS, Fernandes ME, Pizzol TD, et al. Prevalence of self-medication in Brazil and associated factors. *Rev Saude Publica*. 2016;50(suppl 2):13s.

39. da Silva Dal Pizzol T, Turmina Fontanella A, Cardoso Ferreira MB, Damaso Bertoldi A, Boff Borges R, Serrate Mengué S. Anagclesc use among the Brazilian population: results from the National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM). *PLoS One*. 2019;14(3):e0214329.

40. Ly N. Account for all medications, even if they’re banned. *J Fair Pract*. 2016;65(7):437.

41. Garcia S, Canoniero M, Lopes G, Soriano AO. Metamizole use among Hispanics in Miami: report of a survey conducted in a primary care setting. *South Med J*. 2006;99(9):924-926.

42. Dorr VJ, Cook J. Agranulocytosis and near fatal sepsis due to “Mexican aspirin” (dipyrone). *South Med J*. 1996;89(6):612-614.

43. Bonkowsky JL, Frazer JK, Buchi KF, Byington CL. Metamizole use by Latino immigrants: a common and potentially harmful home remedy. *Pediatrics*. 2002;109(6):e98.

44. Hearns R, Derry S, Moore RA. Single dose dipyrone (metamizole) for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2016;4:CD011421.

45. Bensenor IM. Dipyrone and blood dyscrasia revisited: “non-evidence based medicine.” *Sao Paulo Med J*. 2005;123(3):99-100.

46. Ruiz-Argeuilles GJ, Alarcon-Segovia D. “Mexican Aspirin”—a derogatory term. *Am J Hematol*. 1990;34(2):159-160.

47. Weinert PL, Pezza L, Pezza HR. A simplified reflectometric method for the rapid determination of dipyrone in pharmaceutical formulations. *J Braz Chem Soc*. 2007;18(4):846-854.

48. Chotimah C, Sudjadi, Rianto S, Rohman A. Simultaneous determination of metamizole, thiamin and pyridoxin using UV-spectroscopy in combination with multivariate calibration. *Adv Pharm Bull*. 2015;5(4):593-598.

49. Isaacs RCA, Harper MM, Miller EC. Analytical challenges in the confirmative identification of dipyrone as an adulterant in illicit drug samples. *Forensic Sci Int*. 2017;270:185-192.

50. Broseus J, Gentile N, Esspeva P. The cutting of cocaine and heroin: a critical review. *Forensic Sci Int*. 2016;262:73-83.

51. Fucci N, De Giovanni N. Adulterants encountered in the illicit cocaine market. *Forensic Sci Int*. 1998;95(3):247-252.

52. Marcelo MCA, Fiorentin TR, Mariotti KC, Ortiz RS, Limberger RP, Ferrão MA. Determination of cocaine and its main adulterants in seized drugs from Rio Grande do Sul, Brazil, by a Doehlert optimized LC-DAD method. *Anal Methods*. 2016;8:5212-5217.

53. Giorgi M, Lebkowska-Wieruszewska B, Lisowski A, et al. Pharmacokinetic profiles of the active metamizole metabolites after four different routes of administration in healthy dogs. *J Vet Pharmacol Ther*. 2018;41(3):428-436.

54. Ergün H, Uzbay IF, Celik T, Kayir H, Yesilyurt O, Tulunay FC. Dipyrone inhibits ethanol withdrawal and pentylentetrazol-induced seizures in rats. *Drug Res Dev*. 2001;53:254-259.

55. Malvar Ddo C, Luguier S, Vaz Ade L, et al. Dipyrone metabolite 4-MAA induces hypothermia and inhibits PG2-dependent and -independent fever while 4-AA only blocks PG2-dependent fever. *Br J Pharmacol*. 2014;171(15):3666-3679.
56. Vlahov V, Badian M, Verho M, Bacracheva N. Pharmacokinetics of metamizol metabolites in healthy subjects after a single oral dose of metamizol sodium. *Eur J Clin Pharmacol*. 1990;38(1):61-65.
57. Konijnenberg-Peters J, van der Heijden C, Ekhart C, Bos J, Bruhn J, Kramers C. Metamizole (dipyrone) as an alternative agent in postoperative analgesia in patients with contraindications for nonsteroidal anti-inflammatory drugs. *Pain Pract*. 2017;17(3):402-408.
58. Artaza MA, Puerta JL, Ortiz R, Laporte JR. Bioavailability of two metamizole (dipyrone) solutions as single doses of 2 g versus metamizole capsules. *Int J Clin Pharmacol Ther*. 2002;40(7):322-326.
59. Taylor J, Mellstrom B, Fernaud I, Naranjo JR. Metamizol potentiates morphine effects on visceral pain and evoked c-Fos immunoreactivity in spinal cord. *Eur J Pharmacol*. 1998;351(1):39-47.
60. Flusser D, Zylber-Katz E, Granit L, Levy M. Influence of food on the pharmacokinetics of dipyrone. *Eur J Clin Pharmacol*. 1988;34(1):105-107.
61. Moore RA, Derry S, Wiffen PJ, Straube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review. *Br J Clin Pharmacol*. 2015;80(3):381-388.
62. Zylber-Katz E, Granit L, Stessman J, Levy M. Effect of age on the pharmacokinetics of dipyrone. *Eur J Pharmacol*. 1989;165(5):513-516.
63. Suarez-Kurtz G, Ribeiro FM, Estrela RC, Vicente FL, Struchiner CJ. Limited-sampling strategy models for estimating the pharmacokinetic parameters of 4-methylaminoantipyrine, an active metabolite of dipyrone. *Braz J Med Biol Res*. 2001;34(11):1475-1485.
64. Cohen O, Zylber-Katz E, Caraco Y, Granit L, Levy M. Cerebrospinal fluid and plasma concentrations of dipyrone metabolites after a single oral dose of dipyrone. *Eur J Clin Pharmacol*. 1998;54(7):549-553.
65. Bachmann F, Duthaler U, Rudin D, Krahenbuhl S, Haschke M. N-demethylation of N-methyl-4-aminoantipyrine, the main metabolite of metamizol. *Eur J Pharm Sci*. 2018;120:172-180.
66. Saussele T, Burk O, Blievernicht JK, et al. Selective induction of human hepatic cytochromes P450 2B6 and 3A4 by metamizol. *Clin Pharmacol Ther*. 2007;82(3):265-274.
67. Lampl C, Likar R. [Metamizole (dipyrone): mode of action, drug-drug interactions, and risk of agranulocytosis]. *Schmerz*. 2014;28(6):584-590.
68. Cazacu I, Mogosan C, Loghin F. Safety issues of current analgesics: an update. *Chilul Med*. 2015;88(2):128-136.
69. Pfrepper C, Deters S, Metze M, Siegemund R, Gockel I, Petros S. Metamizole inhibits arachidonic acid-induced platelet aggregation after surgery and impairs the effect of aspirin in hospitalized patients. *Eur J Clin Pharmacol*. 2019.
70. Sigaroudi A, Jetter A, Mueller TF, Kullak-Ublick G, Weiler S. Severe reduction in tacrolimus concentrations with concomitant metamizole (dipyrone) therapy in transplant patients. *Eur J Clin Pharmacol*. 2019.
71. Martinez C, Andrei I, Amo G, et al. Gender and functional CYP2C and NAT2 polymorphisms determine the metabolic profile of metamizole. *Biochem Pharmacol*. 2014;92(3):457-466.
72. Caraco Y, Zylber-Katz E, Fridlander M, Admon D, Levy M. The effect of short-term dipyrone administration on cyclosporin pharmacokinetics. *Eur J Clin Pharmacol*. 1999;55(6):473-478.
73. Rogosch T, Sinning C, Podlewski A, et al. Novel bioactive metabolites of dipyrone (metamizol). *Bioorg Med Chem*. 2012;20(1):101-107.
74. Levy M, Flusser D, Zylber-Katz E, Granit L. Plasma kinetics of dipyrone metabolites in rapid and slow acetylator. *Eur J Clin Pharmacol*. 1984;27(4):453-458.
75. Zylber-Katz E, Granit L, Levy M. Formation and excretion of dipyrone metabolites in man. *Eur J Clin Pharmacol*. 1992;42(2):187-191.
76. Vlahov V, Lüthy C, Multhaupt M, Oetliker O, Perisic M. Differential effect of dipyrone in peripheral tissue involves two different mechanisms: neuronal K(ATOM) channel opening and CB1 receptor activation. *Eur J Pharmacol*. 2014;741:124-131.
77. Volz M, Kellnner HM. Kinetics and metabolism of pyrazolones (prophenazone, aminopyrine and dipyrone). *Br J Clin Pharmacol*. 1980;10(Suppl 2):299S-308S.
78. Kraul H, Pasanen M, Sigusch H, et al. Immunohistochemical properties of dipyrone-induced cytochromes P450 in rats. *Hum Exp Toxicol*. 1996;15(1):45-50.
79. Geisslinger G, Bocker R, Levy M. High-performance liquid chromatographic analysis of dipyrone metabolites to study their formation in human liver microsomes. *Pharm Res*. 1996;13(8):1272-1275.
80. Zylber-Katz E, Granit L, Levy M. Plasma protein binding of dipyrone metabolites in man. *Eur J Pharmacol*. 1985;29(1):67-71.
81. Lüthy C, Multaupt M, Oetliker O, Perisic M. Differential effect of acetylsalicylic acid and dipyrone on prostaglandin production in human fibroblast cultures. *Br J Pharmacol*. 1983;79(4):849-854.
82. Uramaru N, Shigematsu H, Toda A, Eyanagi R, Kitamura S, Ohta S. Design, synthesis, and pharmacological activity of nonallergenic pyrazolone-type antipyretic analgesics. *J Med Chem*. 2010;53(24):8727-8733.
83. Costa D, Vieira A, Fernandes E. Dipyrone and aminopyrine are effective scavengers of reactive nitrogen species. *Redox Rep*. 2006;11(3):136-142.
84. Levy M, Leibowich I, Zylber-Katz E, et al. Impairment of the metabolism of dipyrone in asymptomatic carriers of the hepatitis B virus. *Clin Pharmacol Ther*. 1997;62(1):6-14.
85. Levy M, Safadi R, Zylber-Katz E, Granit L, Caraco Y. Impairment of the metabolism of dipyrone in asymptomatic carriers of the hepatitis-B virus does not occur in rapid acetylator. *Eur J Clin Pharmacol*. 2001;57(6-7):461-465.
86. Basiecka A, Maslanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Pol J Vet Sci*. 2014;17(1):207-214.
87. Benesic A, Rotter I, Dragoi D, Weber S, Buchholz ML, Gerbes AL. Development and validation of a test to identify drugs that cause idiosyncratic drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2018;16(9):1488-1494 e1485.
88. Haase D, Hübner S, Kremilis S, Kotzerke G, König H. Metamizol suicide - lethal outcome despite maximum therapy. *Toxichem Krimtech*. 2012;79(2):71-80.
89. Federmann G, Becker EW, Tautrat H, Penschuck C, Berg PA. [Demonstration by lymphocyte transformation test of
the allergic genesis in a case of acute hepatitis. *Dtsch Med Wochenschr.* 1988;113(43):1676-1679.

94. Herdeg C, Hilt F, Buchtemann A, Bianchi L, Klein R. Allergic cholestatic hepatitis and exanthema induced by metamizole: verification by lymphocyte transformation test. *Liver.* 2002;22(6):507-513.

95. Elzagallaai AA, Rieder MJ. In vitro testing for diagnosis of idiosyncratic adverse drug reactions: implications for pathophysiology. *Br J Clin Pharmacol.* 2015;80(4):889-900.

96. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy.* 2007;62(12):1439-1444.

97. Fontana RJ, Seeff LB, Andrade RJ, et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology.* 2010;52(2):730-742.

98. Okonek S, Reinecke HJ. Acute toxicity of pyrazolones. *Am J Med.* 1983;75(5A):94-98.

99. Ackerman Z, Flugelman MY, Wax Y, Shouval D, Levy M. Hepatitis during measles in young adults: possible role of antipyretic drugs. *Hepatology.* 1989;10(2):203-206.

100. Dinh A, Fleuret V, Hanslik T. Liver involvement in adults with measles. *Int J Infect Dis.* 2013;17(12):e1243-e1244.

101. Thornton J. Measles cases in Europe tripled from 2017 to 2018. *BMJ.* 2019;364:l634.

102. Sundaram ME, Guterman LB, Omer SB. The true cost of measles outbreaks during the postelimination era. *JAMA.* 2019;321(12):1155-1156.

103. Sabaté M, Ibanez L, Perez E, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. *Aliment Pharmacol Ther.* 2007;25(12):1401-1409.

104. Douros A, Bronder E, Andersohn F, et al. Drug-induced liver injury: results from the hospital-based Berlin Case-Control Surveillance Study. *Br J Clin Pharmacol.* 2015;79(6):988-999.

105. Duarte Souza JF, Lajolo PP, Pinczowski H, Del Giglio A. Adjunct dipyrone in association with oral morphine for cancer-related pain: the sooner the better. *Support Care Cancer.* 2007;15(11):1319-1323.

106. Rodríguez M, Barutell C, Rull M, et al. Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. *Eur J Cancer.* 1994;30A(5):584-587.

107. Yalcin S, Guluß IH, Tekuzman G, Savas C, Firat D. A comparison of two nonsteroidal antiinflammatory drugs (diflunisal versus dipyrone) in the treatment of moderate to severe cancer pain: a randomized crossover study. *Am J Clin Oncol.* 1998;21(2):185-188.

108. Yalcin S, Gulüß I, Tekuzman G, Savas C. Ketorolac tromethamine in cancer pain. *Acta Oncol.* 1997;36(2):231-232.