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Maricela Piña-Pozas *

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Suspected Adverse Reactions Associated with Metamizole Prescription in the Mexican Population: A Scoping Review of the Literature published between 2009-2022

[#]Eunice Rodriguez [1], [#]Leonel González-González [2], Lina Sofia Palacio-Mejía [3], Maricela Piña-Pozas [4*]

[1]School of Public Health of Mexico. National Institute of Public Health. Cuernavaca, Morelos, Mexico.

[2]Planning Director, National Institute of Public Health. Cuernavaca, Morelos, Mexico.

[3]Research Center for Evaluation and Surveys, National Institute of Public Health. Cuernavaca, Morelos, Mexico.

[4]Information Center for Public Health Decisions, National Institute of Public Health. Mexico City, Mexico.

[#]These authors have contributed equally to this work and share first authorship.

[*]**Corresponding Author:** Maricela Piña-Pozas, Information Center for Public Health Decisions, National Institute of Public Health. Mexico City, Mexico.

Received date: June 24, 2024; Accepted date: July 05, 2024; Published date: July 30, 2024

Citation: [#]Eunice Rodriguez, [#]González- González EL, Palacio Mejía LS, Piña-Pozas M, (2024), Suspected Adverse Reactions Associated with Metamizole Prescription in the Mexican Population: A Scoping Review of the Literature published between 2009-2022, *Clinical Research and Studies*, 3(4); **DOI:10.31579/2835-2882/057**

Abstract

Background: Metamizole is a widely used analgesic, but potentially life-threatening adverse drug reactions (ADRs), such as agranulocytosis, have been associated with it, leading to its withdrawal from the market in some countries. In Mexico, the incidence of these events remains unclear. Aim: To explore the frequency and types of adverse drug reactions associated with metamizole prescriptions reported in the Mexican population between 2009 and 2022, with a specific focus on agranulocytosis and other blood dyscrasias.

Material and Methods: We searched six databases (Medline/PubMed, Lilacs, Cochrane, Redalyc, Scopus, and Medigraphic) and supplemented them with free Google searches. Articles published between 2009 and 2022 reporting adverse drug reactions associated with the prescription of metamizole in the Mexican population were selected, with no restriction on the type of study.

Results: Four studies were selected for inclusion in the review. Three of these studies provided information on the frequency of ADRs associated with metamizole, and one study specifically identified the observed reaction types. The proportion of ADRs related to metamizole ranged from 0.8% to 3.8% of all recorded ADRs, in studies where calculations were possible. One study reported a case of agranulocytosis potentially linked to metamizole consumption.

Conclusions: Adverse drug reactions related to metamizole are relatively common in the Mexican population, but severe reactions like agranulocytosis are infrequent. The available information makes causal relationships between the suspected drug and clinical manifestations difficult to establish. The incidence of agranulocytosis in Mexico appears to be low, although the available evidence is insufficient to conclude in this regard. Metamizole is a widely used drug in this country and is generally considered a safe pain reliever.

Keywords: Metamizole; analgesics; adverse drug reactions; agranulocytosis; blood dyscrasias; Mexico

Introduction

Metamizole (dipyrone) is a non-opioid analgesic with antipyretic and antispasmodic effects [1]. It is prescribed for conditions such as fever, acute or chronic pain, severe pain, post-traumatic and surgical pain, headache and migraine, tumor pain, and certain visceral pain associated with spasmodic pain in the gastrointestinal region, biliary tract, kidneys, and lower urinary tract. It also reduces refractory fever when conventional methods are insufficient [2]. In Mexico, metamizole is included as an essential analgesic drug in the health sector's drug catalog [3].

Several studies have documented the efficacy of metamizole, confirming its analgesic effect in clinical practice. It exhibits comparable analgesic efficacy to non-steroidal anti-inflammatory drugs (NSAIDs), but a reduced likelihood of inducing adverse effects on the gastrointestinal tract, cardiovascular

system, and renal function [4]. As a result, its use is widespread in countries like Mexico, Brazil, and Germany, and prescription frequency has increased in recent decades [1]. However, reports associating metamizole with liver injury, anaphylaxis, agranulocytosis, and other blood dyscrasias have raised concerns [5-7]. Some countries, including Japan, the United States, the United Kingdom, Sweden, Australia, and Iran, have withdrawn the drug from the market [5,8].

Reported risk estimates for agranulocytosis and other life-threatening adverse drug reactions associated with metamizole are widely divergent. In Mexico, the incidence of these events remains unclear. In 2004, a consensus among Mexican experts concluded that metamizole is a safe and effective medication for the symptomatic treatment of pain. While they acknowledged a low potential for causing blood dyscrasias, they argued that its nearly negligible potential for inducing gastrointestinal adverse effects makes metamizole one of the safest analgesics [1].

A multinational case–control study published in 2008 and designed to estimate agranulocytosis incidence and to identify risk factors in Latin American countries including Mexico, Brazil, and Argentina, reported a low overall agranulocytosis incidence rate (0.38 cases per 1 million person/years). However, metamizole was the most frequently reported drug exposure by the cases within the 10 days prior to the unset of symptoms [9].

In this context, this review aimed to explore the frequency and types of adverse drug reactions (ADRs) or suspected adverse drug reactions (SADRs) associated with metamizole prescriptions reported in the Mexican population between 2009 and 2022, with a specific focus on agranulocytosis and other blood dyscrasias.

Material and methods

We conducted a scoping review of the literature to map the available evidence related to the frequency and types of adverse drug reactions associated with metamizole in the Mexican population after 2008.

Eligibility criteria

Studies meeting the following criteria were included: studies of any design, without language restrictions, published between January 2009 and December 2022 in scientific journals, providing relevant evidence on the characteristics and/or frequency of ADRs or SADRs associated with metamizole prescription in the Mexican population. Conference presentations and unpublished documents were excluded.

For these purposes, we understand an ADR as an unwanted response to a drug that can be reasonably attributed to its administration; meanwhile, a SADR is defined as any unwanted clinical or laboratory manifestation occurring after drug intake, following the Official Mexican Standard NOM-220-SSA1-2016 about installation and operation of pharmacovigilance [10].

Search strategy

We searched Medline/PubMed, Lilacs, Cochrane, Redalyc, Scopus, and Medigraphic. Free Google searches were also performed. Additionally, the reference lists of selected studies were reviewed.

The search terms and controlled language MeSH descriptors used were “adverse drug reactions,” “adverse effects,” “metamizole,” “dipyrone,” “agranulocytosis,” “blood dyscrasia,” and “Mexico”. All searches were completed in March 2023.

Document selection and data extraction

The selection of studies involved two levels: title and abstract screening and full-text evaluation. Two teams, each consisting of two reviewers (ER, MP, MA, LP), independently and blindly selected the studies.

Duplicate articles were first identified and removed. Subsequently, the two review teams (ER, MP, MA, and LP) independently reviewed the titles and abstracts to identify potentially eligible studies. They then independently evaluated the full texts of the potentially eligible articles to confirm whether they met the inclusion criteria. Disagreements were resolved through discussion with another author (LG) for both teams. The reasons for study exclusion and removal were documented. A flowchart summarizing the document selection process was created following the PRISMA guidelines [11] (Figure 1).

Data extraction and synthesis

For data extraction, the authors independently reviewed the full texts of the selected studies. Relevant information was recorded using a pre-designed and standardized form, including the complete reference of the document, geographic area, study date, study design, study objective, outcomes of interest, drugs analyzed, types of ADRs reported, number of cases, and other pertinent results. The authors' findings were compared, and any discrepancies were resolved through discussion with a third author (LG).

Results

Selection and characteristics of included studies

Following the search strategy, 385 records containing information on ADRs and SADRs associated with metamizole prescriptions were identified. After 49 duplicate articles49 duplicate articles were eliminated, and 290 were excluded based on the review and analysis of their titles and abstracts as they did not meet the eligibility criteria.

The full texts of the remaining 46 potentially eligible studies were thoroughly reviewed (references provided in the supplementary material). After a detailed reading, 42 articles were excluded because they did not meet the criteria for inclusion in this study. The primary reason for exclusion was that the information did not pertain to adverse reactions associated with the prescription of metamizole in Mexican patients. Four studies were selected for inclusion in the analysis [12-15]. Figure 1 shows a flowchart detailing the study selection process.

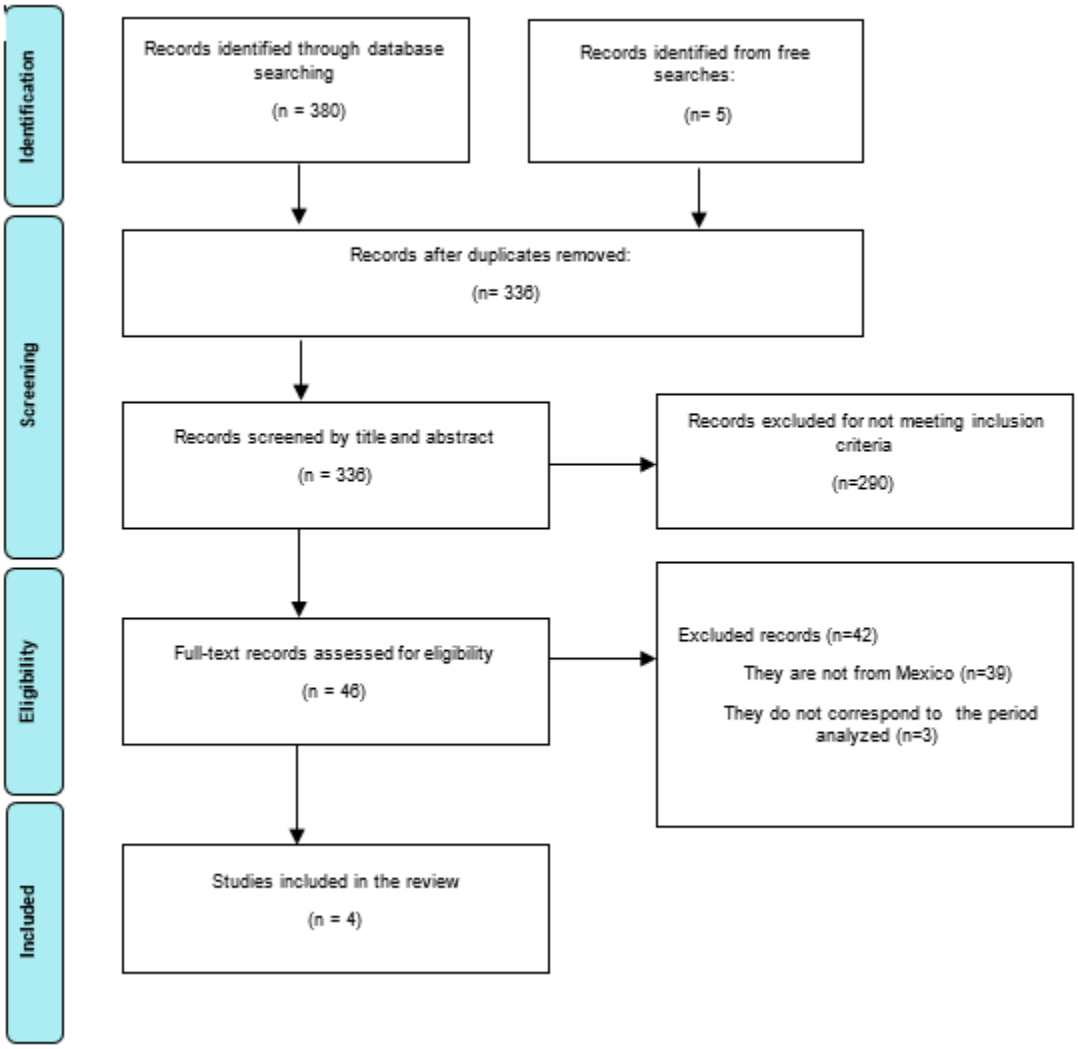

Figure 1: Flowchart of the study selection process for a scoping review.

All included studies were categorized as non-randomized or descriptive quantitative studies. Two were retrospective descriptive studies, two were case reports, and one was a longitudinal study.

Three included studies were conducted in Mexico [12,14,15], while one was conducted in the United States [13]. Three studies provided information on the frequency of ADRs associated with metamizole [12,14,15], and one also addresses the types of reactions observed [15]. One study reported a case of agranulocytosis possibly associated with metamizole use [13]. Detailed characteristics of the selected studies are summarized in Table 1

Reference	Aim of the study	Data source and study period	Study design	Outcomes of interest	Total ADRs/ metamizole-associated ADRs	Reported BD/ metamizole-associated BD	Main results
González-Jiménez, B., Estrada-Hernández, L.O., 2014 [12].	To detect, notify, register, and evaluate ADRs to determine the frequency, some predisposing factors and the most frequent therapeutic groups as causes of adverse reactions.	CNFV database. (Reports from the Adolfo López Mateos Regional Hospital, ISSSTE,	Retrospective, descriptive	ADR frequency, main therapeutic groups associated with ADR	286/5	NA	286 ADR notifications, more frequent in men. The main associated therapeutic groups were antibiotics, antiretrovirals and analgesics.

		Mexico City) January to December 2013.					Sodium metamizole associated with 12% of ADRs for analgesics. Registered ADR types are not identified. The dose, treatment time and pharmaceutical form are unknown.
Ly, N., 2016 [13].	To report the case of a patient with neutropenia and agranulocytosis. Highlight the importance of taking a detailed clinical history and knowing the medications used by patients, including those purchased outside the country.	Clinical record of the emergency room of a hospital in the United States. 2016	Case report	Evolution of a patient with neutropenia and agranulocytosis	1/1	1/1 (Neutropenia and agranulocytosis)	A 73-year-old Mexican woman comes to the emergency room at a North Carolina hospital. Neutropenia and agranulocytosis were diagnosed, presumably associated with the consumption of metamizole, obtained in Mexico. The dose, duration, prescribed treatment, and outcome are unknown.
Rios-Quintana, R., Estrada-Hernandez, L.O., 2018 [14].	To analyze the ADRs associated with non-selective NSAIDs administration reported to the CNFV between 2011 and 2014.	CNFV database, Mexico. 2011-2014	Retrospective, descriptive	ADRs associated with non-selective NSAIDs administration	115,648/ 967	3 (2 neutropenia, 1 agranulocytosis) /NA	4,553 ADRs associated with NSAIDs administration (3.9%, out of 115,684 ADRs registered in that period). Metamizole associated with 21.1% (967) of the total ADR by NSAID. Registered ADR types are not identified. The dose, treatment time and pharmaceutical form are unknown.

Salas Rojas, S.G., Pérez Morales, M.E., Meléndez López, S.G., 2012 [15].	To detect and evaluate ADRs in the internal medicine service of a Mexican Regional Hospital, through an intensive pharmacovigilance method.	Regional General Hospital No. 1 of the IMSS, Tijuana, B.C. Mexico. Jan 2010-Apr 2011.	Longitudinal	Frequency, type, causality, severity, pharmacological groups, drugs, affected organ systems and factors associated with ADRs.	131/5	6 (Hematological reactions)/0	1295 patients were studied, 116 of them presented 131 ADRs. The average age was 53.9 ± 17,750, 56% were women. Among those with ADRs, 50 patients (43%) received metamizole. NSAIDs were associated with 21 ADRs (16%). Among NSAID-related ADRs, five were associated with metamizole (23.8%). Two of these reactions affected the dermatological system, two affected the cardiovascular system, and one to the gastrointestinal system, with the presence of nausea and vomiting. The pharmaceutical form used, dose, or time of use are not reported. According to their causality, 46.6% of the ADRs were classified as probable and regarding severity, 84% were considered moderate.

CNFV: National Center for Pharmacovigilance; ADR: Adverse Drug Reaction; NSAIDs: Non-steroidal anti-inflammatory drugs; BD: blood dyscrasias; NA: not available.

Table 1: Included studies on a scoping review of adverse reactions associated with metamizole prescription in the Mexican population.

The available information on the included subjects' characteristics and the frequency and types of adverse reactions varied across the studies. Two studies focused on ADRs associated with any drug, while another study specifically examined ADRs related to non-steroidal anti-inflammatory drugs (NSAIDs). One study aimed to report a case of agranulocytosis possibly associated with metamizole use. Two studies collected primary data for their research, while the other two retrieved data from pharmacovigilance databases.

Adverse reactions associated with metamizole prescription

Table 1 presents the ADRs and SADRs associated with metamizole prescription identified in the selected studies. It provides information on the number of cases and the types of reactions observed.

In the study by Ríos-Quintana and Estrada-Hernández [14], the authors analyzed ADRs associated with non-selective NSAID administration reported to the National Pharmacovigilance Center (CNFV) during the period 2011-2014. Among the 115,684 ADRs reported during that period, 4,553 (3.9%) were associated with non-selective NSAID administration. Metamizole accounted for the highest number of reported adverse reactions among all NSAIDs, representing 21.1% (967) of the total. However, the total number of prescriptions for each NSAID is unknown, making it impossible to determine the proportion of prescriptions for metamizole and other NSAIDs associated with ADRs. Among the reported ADRs (115,684), those related to metamizole prescription accounted for 0.83%. When stratifying by sex, the authors found that the highest number of NSAID-related ADRs occurred in women, accounting for 66% (3,002) of the cases. The age group with the highest number of ADRs was 45 to 65 years, comprising 19.5% (891) of the cases.

Another study conducted by González-Jiménez and Estrada-Hernández [12] utilized data from the CNFV and focused on the frequency and therapeutic groups of drugs associated with ADRs in patients at the Adolfo López Mateos Regional Hospital of the Institute of Security and Social Services for State Workers (ISSSTE) in Mexico City. The study period spanned from January to December 2013, during which 286 ADR notifications were identified. Antibiotics were the primary therapeutic group responsible for adverse reactions, followed by antiretrovirals and analgesics. Among analgesics, diclofenac accounted for 24% of the adverse reactions, followed by ketorolac (17%) and metamizole sodium (12%). Based on the information provided, it can be estimated that five ADRs associated with metamizole were reported in the hospital during the study period, representing 1.8% of the total 286 ADRs identified.

Unlike Ríos-Quintana and Estrada-Hernández [14], González-Jiménez and Estrada-Hernández [12] found that the highest number of reported ADRs occurred in men, although the exact amount was not specified. The age group with the highest proportion of ADRs was 30 to 59 years, followed by individuals 60 years and older, although precise figures were not provided.

None of the studies specified the pharmaceutical forms, doses, or time of use of the drugs associated with ADRs, nor is it possible to identify the type of adverse reaction related to metamizole prescription.

In the study by González-Jiménez and Estrada-Hernández [12], a partial analysis of the information quality was performed, revealing that out of the 286 notifications, 205 had grade three information, 73 had grade two information, and eight had grade one information, based on a scale ranging from zero to three, with three indicating the highest data availability. Neither of the two studies utilizing CNFV data established a causal relationship between ADRs and the administered drugs.

Salas-Rojas et al. [15], conducted a longitudinal study using an intensive pharmacovigilance method. They included adult patients hospitalized in the Internal Medicine service of the Regional General Hospital No. 1 of the Mexican Institute of Social Security (IMSS) in Tijuana City, over a 15-month period from January 2010 to April 2011. The study recorded patient information such as age, sex, weight, cause of hospitalization, and duration of hospital stay. It identified the frequency of ADRs, the drugs used, and the pharmacological groups associated with ADR reports. The ADRs were classified according to the Rawlins and Thompson criteria (A and B), and the Naranjo algorithm was utilized to determine causality. The severity of ADRs was categorized as mild, moderate, severe, or fatal.

In the study by Salas Rojas et al. [15], 1,295 patients met the inclusion criteria, out of which 116 patients presented 131 ADRs. The average age of the patients was 53.9 ± 17.7 years, with 56% being women. On average, patients had 2.8±1.4 diagnoses, were hospitalized for 12.7±13.9 days, and were prescribed 17.3±8.4 drugs. The most administered drugs were omeprazole, prescribed to 90 out of 116 patients (77.6%); ranitidine, given to 75 patients (64.7%); ketorolac, administered to 69 patients (59.5%); furosemide, prescribed to 61 patients (52.6%); and metamizole, used by 50 patients (43.1%).

Out of the 131 ADRs observed, 22 (16.8%) were identified upon admission, while 109 (83.2%) occurred during the hospital stay. The pharmacological groups most frequently associated with ADRs were anti-infectives (including antibiotics, antifungals, antivirals, and antimycobacterials) and drugs for the musculoskeletal system (such as NSAIDs, antirheumatics, calcium regulators, and corticosteroids). NSAIDs were linked to 21 ADRs (16%), with six occurring upon admission and 15 observed during hospitalization.

Five NSAID-related ADRs were associated with metamizole (23.8%), representing 3.8% of the total ADRs. Two of these reactions affected the dermatological system, resulting in skin rash, pruritus, and urticaria. Two affected the cardiovascular system, causing hypotension and agitation, while one affected the gastrointestinal system, leading to the presence of nausea and vomiting. However, no information was provided regarding the specific pharmaceutical form, dosage, or duration of use. Additionally, the researchers identified that factors such as age, duration of hospitalization, number of medications used, and comorbidities like diabetes mellitus and arterial hypertension, including both conditions simultaneously, were influencing factors in the occurrence of ADRs.

Salas Rojas et al. [15] reported that 67.2% of the registered ADRs were classified as type A; that is, predictable and therefore avoidable. Most ADRs were classified as probable in terms of causality (46.6%), and 84% were considered to have moderate severity.

Agranulocytosis and other blood dyscrasias associated with metamizole prescription

In the study conducted by Ríos-Quintana and Estrada-Hernández [14], one case of agranulocytosis was reported among 4,553 ADRs associated with non-selective NSAIDs. The authors do not mention the drug-associated; however, in the discussion of their results, they state that metamizole was not involved. In the same study, two cases of neutropenia associated with NSAID prescription were identified, but the drugs related to these cases were not reported.

Salas-Rojas et al. [15] found six ADRs affecting the hematological system out of the 131 total ADRs identified in their study, accounting for 4.6%. The reported hematological manifestations included decreased hemoglobin and platelets levels, anemia, and swollen and bleeding gums. Two hematological ADRs were associated with methotrexate, two with acenocoumarol, one with acetylsalicylic acid, and one with amlodipine. No cases of agranulocytosis or any other blood dyscrasia associated with metamizole were reported.

In the case report by Ly [13], a 73-year-old Hispanic woman, likely of Mexican origin, presented to the emergency room of a hospital in North Carolina, USA, with mild headache, breathing difficulty, and throat swelling. Laboratory studies revealed a white cell count of 2,100/mcL, a platelet count of 73,000/mcL, and an absolute neutrophil count of 1,000/mm3. B-type

natriuretic peptide, cardiac markers, and thyroid-stimulating hormone levels were within normal limits. The diagnosis of neutropenia and agranulocytosis was established. Upon further investigation of the patient's medical history, it was learned that she had lived in the United States for several years but occasionally travelled to Mexico, where she obtained metamizole that she was taking for her headaches. The physician concluded that it was highly probable that metamizole had caused the patient's symptoms and abnormal laboratory results and advised her to stop taking it. However, the case report does not provide information about the pharmaceutical form, dose, or duration of metamizole use, nor does it mention whether the patient consumed it with other medications. The outcome after the discontinuation of the drug is unknown, and likewise, if there was any corrective treatment.

Discussion

A scoping review of the available literature was conducted to explore the frequency of agranulocytosis, blood dyscrasias in general, and other adverse drug reactions associated with metamizole prescription in the Mexican population. The results strongly indicate that studies are scarce on this topic in the Mexican population, and the existing studies have significant methodological limitations. However, our findings suggest that metamizole is frequently prescribed in Mexico, and the incidence of agranulocytosis and other blood dyscrasias associated with its use is very low.

The proportion of ADRs associated with metamizole among the total ADRs recorded ranges from 0.8% to 3.8% in the studies where it was possible to calculate it. The highest proportion (3.8%) was reported in the survey by Salas-Rojas et al. [15], which only included patients admitted to the Internal Medicine service of an IMSS hospital. In contrast, the study by Ríos-Quintana and Estrada-Hernández [14], which analyzed a heterogeneous set of ADRs from any hospital and service reported to the CNFV between 2011 and 2014, reported the lowest proportion (0.8%). The study by González-Jiménez and Estrada-Hernández [12], with a proportion of 1.8%, included ADRs reports from the same database, but from a single hospital. Therefore, although precise data are not available, it can be assumed that there are diverse patient characteristics among the studies, making valid comparisons between these proportions challenging.

Analgesics, NSAIDs and anti-infectives, are among the pharmacological groups with the highest reports of associated ADRs. The two studies that calculated the proportion of adverse drug reactions due to NSAIDs associated with metamizole yielded similar results: 23.8% in the survey by Salas-Rojas et al. [15] and 21% in the study by Ríos-Quintana and Estrada-Hernández [14]. However, it is unknown how frequently metamizole was prescribed compared to other NSAIDs, and it is not possible to estimate the proportion of patients receiving this drug who developed an adverse drug reaction.

Based on the available data from the included studies, it is not feasible to calculate the proportional reporting ratio (RRR) or the reported hazard ratio (ROR) of agranulocytosis or blood dyscrasias associated with metamizole prescription. Among the four studies included in this review, a single case of agranulocytosis, likely associated with metamizole, was identified in the case report by Ly [13]. Unfortunately, like the other studies, essential data such as the dose, duration of use, pharmaceutical form, or the case outcomes are not reported.

In the study by Ríos-Quintana and Estrada-Hernández [14] two cases of neutropenia and one of agranulocytosis were identified; however, the drugs associated with these cases were not reported. Additionally, in the study by Salas-Rojas et al. [15], six ADRs involving the haematological system were identified, but none of them was associated with metamizole.

The withdrawal of metamizole from the markets of North American and other countries due to its potential association with agranulocytosis and aplastic anemia, has prompted several studies to investigate the incidence of this conditions. One such study was conducted by Hamerschlak et al. [9] in a Latin American population between January 2002 and December 2005. The study involved seven hospitals in Brazil (Campinas, Curitiba, Goiânia, Juiz de Fora, Manaus, Ribeirão Preto, and São Paulo), two centers in Argentina (both in Buenos Aires), and one center in Mexico (Monterrey). With a sample size of 548 million people, only 52 cases of agranulocytosis were recorded, concluding that the incidence rate is 0.38 cases per million inhabitants/year. The incidence in Brazil was 0.35 cases per million inhabitants per year, while in Argentina, it was 2.09 cases per year. No instances of agranulocytosis were identified in the investigated area of Mexico. The researchers stated that although the average number of instances of fatal agranulocytosis is 11.5%, the incidence is relatively low, and therefore, it was not considered a significant public health problem in the regions investigated, and no measures were taken to restrict the marketing of the drug.

The risk of medically significant ADRs such as agranulocytosis is likely influenced, at least in part, by genetic predisposition. A study conducted by Radulovic [16] describes three patients with metamizole-associated agranulocytosis who underwent pharmacogenetic testing. The study concluded that metamizole-induced agranulocytosis was probably a consequence of the underlying genetic predisposition, with hemolysis potentially increasing the toxicity of metamizole metabolites.

Based on the data from our scoping review, it is impossible to determine the incidence rates or rule out cases of agranulocytosis. However, the data strongly indicate a very low incidence of metamizole-associated agranulocytosis in Mexico.

We acknowledge some limitations in our study. It is important to note that the survey by Ríos-Quintana and Estrada-Hernández [14] analyzed records from the CNFV database from 2011 to 2014. The study by González-Jiménez and Estrada-Hernández [12] used the same data source. Still, it included reports only from one hospital (Adolfo López Mateos Regional Hospital, ISSSTE, Mexico City) from January to December 2013. In the study by Salas-Rojas et al. [15], ADRs identified at the IMSS Regional General Hospital No. 1 in Tijuana from January 2010 to April 2011 should have been registered in the CNFV. Therefore, it is highly likely that some reports will be duplicated, particularly from January to April 2011 and January to December 2013. However, with the available information, it is not possible to determine the exact number of duplicate reports.

Conclusions

This review suggests that adverse reactions associated with metamizole are relatively common, but severe conditions like agranulocytosis are rare in the Mexican population. Metamizole is considered a safe and widely used analgesic, even showing a lower risk of gastrointestinal damage compared to other pain relievers. However, it is crucial to promote research and reporting of adverse drug reactions (ADRs) as severe and potentially fatal reactions pose a latent risk to patient's health and can also become an economic burden for both patients and healthcare institutions.

Health institutions should implement intensive pharmacovigilance methods to identify and evaluate ADRs in clinical practice. These methods are accessible, cost-effective, and easy to implement and can be adapted to any hospital service.

In Mexico, ADR reports are submitted to the National Pharmacovigilance Center's database through the Permanent Pharmacovigilance Program.

However, under-reporting remains a significant challenge that hinders the assurance of drug safety and monitoring. Efforts should be made to encourage healthcare professionals to actively report ADRs and enhance the country's overall pharmacovigilance system. This would contribute to a more comprehensive understanding of the risks and benefits associated with medication use, ultimately improving patient care and medication safety.

List of abbreviations

ADRs: Adverse drug reactions

CNFV: Mexico´s National Pharmacovigilance Centre

ISSSTE: Mexico´s Institute of Social Security and Services for State Workers

Lilacs: Latin American and Caribbean Literature in Health Sciences

Medline: Medical Literature Analysis and Retrieval System Online

MeSH: Medical Subject Headings

NSAIDs: non-steroidal anti-inflammatory drugs

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PubMed: is the Internet search platform which enables searching Medical Literature Analysis and Retrieval System Online

Redalyc: Network of Scientific Journals of Latin America and the Caribbean, Spain, and Portugal

SADRs: Suspected Adverse Drug Reactions

Declarations

Ethics approval and consent to participate:

'Not applicable'

Consent for publication:

'Not applicable'

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no relevant conflicts of interest in this study. Likewise, they declare that they have not received any type of remuneration for their work on this manuscript, that they maintained complete control of the content and made the final decisions for each aspect of the development of this article.

Funding

The study was partially funded by Laboratorios Sanofi S.A. de C.V. The funding was used to buy access to bibliography sources and language translation services. The funder had no role in the study design, collection, data analysis, nor writing of this article and the decision to submit it for publication.

Authors' contributions

ER: Conceptualization, formal analysis, methodology, investigation, methodology, writing review & editing.

LGG: Conceptualization, formal analysis, supervision, validation, writing original draft, writing review & editing.

MAA: Formal analysis, methodology, investigation, visualization, writing original draft, writing review & editing.

LSPM: Data curation, formal analysis, software, visualization, writing original draft.

MPP: Conceptualization, methodology, project administration, writing original draft, writing review & editing.

Acknowledgements:'Not applicable'

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Supplementary Material

1 Potentially eligible studies reviewed in full text

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