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Epidemiology of Agranulocytosis and other Medically Important Adverse Reactions in Mexican Population Associated with Metamizole

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Abstract

Background/Aim: Metamizole, a non-opioid analgesic, has been used for a long time, but studies linking it to potentially life-threatening adverse drug reactions, such as agranulocytosis, have raised safety concerns. However, the reported incidence of these events is widely variable. This study aims to shed light on the pharmacological safety of metamizole in Mexico, with a particular focus on medically important suspected adverse drug reactions, especially agranulocytosis.

Materials and Methods: We extracted data on cases of medically important suspected adverse drug reactions (SADRs) and prescriptions for metamizole and non-steroidal anti-inflammatory drugs (NSAIDs) from the database of medical emergency records within the Mexican Ministry of Health, covering the period from 2014 to 2022. We calculated frequencies, proportions, and reported odds ratios for medically important SADRs and agranulocytosis.

Results: Metamizole ranked as the third most frequently prescribed non-opioid analgesic and accounted for 13.7% of medically important SADRs potentially linked to drugs of its class. Among consultations involving metamizole prescriptions, the most common SADRs included unspecified kidney and ureter disorders, toxic liver disease, other specified forms of angina pectoris, aplastic anemia, and agranulocytosis, the latter being recorded in just 0.002% of these consultations. The reported odds ratio for agranulocytosis associated with metamizole prescription compared to NSAIDs was 0.3 (95% CI 0.20 - 0.45).

Conclusions: The data source we analyzed provides limited evidence regarding the safety profile of metamizole, as it did not allow us to establish a causal relationship between drug prescription and SADRs. Our findings suggest that metamizole is widely used in Mexico and that adverse reactions associated with its prescription may occur less frequently than those linked to NSAIDs. Additionally, metamizole-induced agranulocytosis appears to be rare in the Mexican context.

Keywords: adverse drug reaction; metamizole; dipyrone; non-steroidal anti-inflammatory drugs; agranulocytosis; pharmacovigilance; medical records

1.Introduction

Metamizole is a non-opioid analgesic with antipyretic and antispasmodic effect [1-3]. There is evidence of its effectiveness for treating fever, acute or chronic pain, severe pain, post-traumatic and surgical pain, headache and migraine, tumor pain, and some cases of visceral pain [4,5].

In Mexico, metamizole is available in the basic drug list of the Health Sector with authorization as a monodrug for metamizole sodium tablets of 500 mg, and metamizole sodium solution for injection of 1g/2ml [6]. The 2022 updated list of reference drug products of the Federal Commission for the Protection against Sanitary Risks (COFEPRIS, acronym in Spanish) also

includes metamizole sodium in 2.5 g/5 ml solution for injection, and 250 mg/5 ml syrup [7].

Although metamizole shares similarities with non-steroidal anti-inflammatory drugs (NSAIDs) as a derivative of pyrazolone, some authors posit that it should be classified apart from traditional NSAIDs. Their rationale stems from its relatively minor interference with peripheral prostaglandins, except when administered at concentrations exceeding 4 g per dose, resulting in minimal anti-inflammatory effects [8,9].

Metamizole exhibits comparable analgesic efficacy to NSAIDs, accompanied by a reduced likelihood of inducing adverse effects on the gastrointestinal tract, cardiovascular system, and renal function [9]. For instance, in a pharmacovigilance research based on World Health Organization adverse effect registrations, metamizole didn't show an increased risk of gastric or duodenal ulcers (ROR [95%CI]: 0.9 [0.7 to 1.2]) in contrast to nonselective NSAIDs such as diclofenac (14.3 [13.8 to 14.9]), ibuprofen (8.3 [7.8 to 8.7]), and naproxen (10.7 [10.2 to 11.1]). A marginally increased risk of renal function loss was reported after metamizole use (1.2 [1.0 to 1.3]), but it was higher for diclofenac (2.3 [2.2 to 2.4]) or ibuprofen (2.4 [2.3 to 2.5]). Regarding cardiovascular risk, no increase in the occurrence of ischemic heart disease is reported for metamizole (0.5 [0.4 to 0.5]), in contrast to the selective NSAIDs like celecoxib (8.5 [8.3 to 8.7]) or etoricoxib (1.9 [1.7 to 2.2]) [10]. As a non-opioid analgesic, it seems to be safer than opioids regarding neurological adverse events [4]. Nonetheless, several documented reports of adverse drug reactions (ADRs), including liver injury [11], and agranulocytosis associated with metamizole [1,4,12,13], as well as NSAIDs [14-16], have been published.

In accordance with the Official Mexican Standard on pharmacovigilance, an ADR is an undesired response to a drug, wherein the causal relationship with the drug is, at least, reasonably attributable. Conversely, a suspected adverse drug reaction (SADR) encompasses any unfavorable clinical or laboratory manifestation that arises following the administration of one or more drug products [17].

The safety of metamizole has been questioned for many years due to the possible risk of agranulocytosis, its most serious adverse effect [2,18]. Drug-induced agranulocytosis is a rare yet potentially fatal ADR, characterized by a reduction in peripheral neutrophil count to below 500 cells/µl, thereby heightening the risk of infection [14]. While the precise mechanism underlying metamizole-induced agranulocytosis remains incompletely elucidated, it is likely of immunoallergic origin, since a toxic effect has been ruled out in some studies [1]. Genetic predisposition has also been posited as a contributing factor [19]. Some constitutional chromosomal changes have been found in individuals who develop metamizole-induced agranulocytosis; thus, increased risk may be found in some regions but not in others [18]. Notably, studies have reported widely divergent risk estimates for agranulocytosis, spanning from 1 case per 1500 to fewer than one case per million metamizole administrations [1]. These discrepancies have engendered a spectrum of regulatory approaches. Several countries, such as the USA, Canada, France, Sweden, and Australia, have withdrawn metamizole from the market, citing safety concerns. In contrast, in places like Germany, its use remains widespread, and prescription frequency has increased in recent decades [1].

The reported fatality rates of agranulocytosis also exhibit considerable variability, ranging from 0 to 23%. However, there appears to be a declining trend, potentially attributable to enhanced treatment modalities, the ready availability of broad-spectrum antibiotics, and heightened vigilance regarding drug-induced agranulocytosis [14]. Notably, fatal cases seem to be more prevalent among elderly individuals, those burdened with multiple comorbidities, individuals with a history of prior metamizole use, and those concurrently receiving methotrexate [4].

In Mexico, the reported incidence of metamizole-induced agranulocytosis is low [20]. In a retrospective pharmacovigilance study conducted using data from the National Pharmacovigilance Center in Mexico involving 286 reports of SADRs, it was discerned that antibiotics, antiretrovirals, and analgesics constituted the drug groups most frequently associated with adverse reactions. Among analgesics, diclofenac (24%), ketorolac (17%), and metamizole (12%) held the prominent positions. However, details regarding what reactions were observed were not disclosed; so, the incidence of agranulocytosis or other specific metamizole induced SADRs cannot be estimated [21].

Spontaneous ADRs reports may provide valuable insights about drug-induced agranulocytosis incidence, risk factors and fatality rates. Their role in pharmacoepidemiologic studies and hypothesis generation regarding medically important ADRs and SADRs has gained traction, particularly with the expanded accessibility of population-wide databases [22]. The information obtained in clinical studies up to a drug approval by the health authority often fail to predict the occurrences that may arise during routine clinical practice, especially regarding the detection of rare or late-onset adverse reactions, which are more likely to be identified in post-marketing stages. Hence, it is imperative to continuously monitor the effectiveness and safety of treatments in real-world conditions once they are available on the market [23].

In this study, we aimed to identify agranulocytosis and other suspected medically important adverse reactions associated with metamizole in the Mexican population, as reported in the database of Emergency Services of the Mexican Ministry of Health (MoH) from 2014 to 2022. Additionally, we estimated the probabilities of experiencing medically important SADRs and agranulocytosis associated with the prescription of metamizole and compare them to those associated with the prescription of NSAIDs.

2 Material and Methods

2.1Study design and data sources

Retrospective cross-sectional study with secondary data. Data on suspected adverse drug reactions and prescription of nonsteroidal anti-inflammatory drugs and metamizole were obtained from the database of the Emergency Services of the MoH [24] from 2014 to 2022, the period with comparable and reliable data in the public MoH platform (Table 1). In Mexico, Emergency Services provide immediate medical attention for people who require immediate care to prevent serious adverse outcomes. This mechanism is utilized when the patient cannot wait to be attended at their healthcare center. In this area, triage is conducted to determine which cases represent a true medical emergency.

This database was used because it is the only population-level record of healthcare services in Mexico that includes diagnoses and prescribed medications. MoH serves non-beneficiaries of social security representing about 40% of the Mexican population.

2.2Inclusion criteria and procedures

Within the emergency services database, consultations with metamizole or NSAIDs prescriptions and cases with diagnoses compatible with medically important SADRs were identified. Medically important ADRs are those that, in the physician's judgment, could endanger the patient or require medical intervention to prevent the occurrence of any of the criteria for serious adverse reactions: causing death, endangering life, necessitating hospitalization, or prolonging hospital stay, causing permanent or significant disability, or being the cause of alterations or malformations in the newborn [17].

Medically important SADRs were defined according with the Information for Prescribing Amplified version (IPPA), delivered by the health authority along with the health registration for medications containing metamizole and

published in the Dictionary of Pharmaceutical Specialties (PLM, n.d.) [25]. A list with the names and ICD-10 codes of the conditions considered medically important SADRs is provided in Table 2. In this study, we considered that a consultation had a report of medically important SADR if it had any of the ICD-10 codes listed in Table 2 recorded as the primary condition.

We included all emergency consultation records documenting SADRs as defined above, spanning from 2014 to 2022 in which metamizole or at least one of the main analgesic drugs used in Mexico had been prescribed. Drugs included are listed in Table 3. Metamizole pharmaceutical dosage forms included were metamizole sodium tablet 500 mg, metamizole sodium solution for injection 1g, hyoscine butyl bromide/metamizole sodium tablet 10/250 mg, and hyoscine butyl bromide/metamizole sodium solution for injection 20/250 mg.

It is worth noting that a reasonable attribution of causality cannot be established in our study. Tracking patients would be the ideal approach for identifying causal relationships between a drug and an ADR. However, due to the characteristics of the database and the cross-sectional nature of this study, it was not feasible to gather data such as the time elapsed between the consumption of the suspected drug and the onset of symptoms or diagnosis, the health outcomes following the discontinuation of the drug, or other information that could be used to establish a causal link between medication prescription and the adverse reaction.

To identify the probability of occurrence of a medically important SADR associated with metamizole or NSAIDs, the odds ratio of all the adverse reactions listed in Table 2 in consultations with metamizole or NSAID prescription, compared to those without these prescriptions was estimated according to Equation 1 [34]. The 95% confidence interval was estimated as well (equations 2 and 3) [34].

Equation 1

$$OR\ of SADRs\ associated\ with\ metamizole\ or\ NSAIDs = \frac{odds\ of\ SADR\ in\ consultations\ with\ metamizole\ or\ NSAIDs\ \ prescription}{odds\ of\ SADR\ in\ consultations\ without\ metamizole\ or\ NSAIDs\ prescription} = \frac{\frac{a}{b}}{\frac{c}{d}}$$

Equation 2 $$CI\ 95\%\ upper\ limit = e^{[\ln(SADR\ OR)+1.96\sqrt{\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right)}]}$$

Equation 3 $$CI\ 95\%\ lower\ limit = e^{[\ln(SADR\ OR)-1.96\sqrt{\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right)}]}$$

where:

a = consultations with medically important SADR, with metamizole or NSAID prescription

b = consultations without medically important SADR, with metamizole or NSAID prescription

c = consultations with medically important SADR, without metamizole or NSAID prescription (other drugs prescribed)

d = consultations without medically important SADR, without metamizole or NSAID prescription (other drugs prescribed)

We estimated the Reported Odds Ratio (ROR) of agranulocytosis, defined as the probability of occurrence of agranulocytosis, associated with metamizole use, compared to the odds of the same event occurring with all other NSAIDs prescribed in the 2014-2022 period. A risk of SADR is considered to exist when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one [26-28].

We calculated the ROR and its confidence interval according to Equations 4 to 6 [26,29].

Equation 4

$$ROR\ of\ agranulocytosis\ associated\ with\ metamizole = \frac{odds\ of\ agranulocytosis\ in\ consultations\ with\ prescription\ of\ metamizole}{odds\ of\ agranulocytosis\ in\ consultations\ with\ \ other\ NSAIDs\ prescribed} = \frac{A/B}{C/D}$$

Equation 5 $$CI\ 95\%\ upper\ limit = e^{[\ln(ROR)+1.96\sqrt{\left(\frac{1}{A}\right)+\left(\frac{1}{B}\right)+\left(\frac{1}{C}\right)+\left(\frac{1}{D}\right)}]}$$

Equation 6 $$CI\ 95\%\ lower\ limit = e^{[\ln(ROR)-1.96\sqrt{\left(\frac{1}{A}\right)+\left(\frac{1}{B}\right)+\left(\frac{1}{C}\right)+\left(\frac{1}{D}\right)}]}$$

where:

A = consultations with agranulocytosis, with metamizole prescription

B = consultations with SADRS without agranulocytosis, with metamizole prescription

C = consultations with agranulocytosis, with NSAID prescription, without metamizole prescription

D = consultations with SADRS without agranulocytosis, without metamizole or NSAID prescription

Data management and analysis was performed with R version 4.3.1 for Windows.

3 Results

Between 2014 and 2022, a total of 75,334,660 emergency consultations were recorded, 65.1% in women and 34.7% in men. A similar distribution among gender was maintained throughout the period (Table 1).

As Tables shows during the analyzed period, 8,978,089 consultations with metamizole or NSAIDs prescription were recorded (11.9%) and 66,356,571 without metamizole or NSAIDs, but other drugs prescribed. The most frequently prescribed drugs among the listed analgesics were paracetamol (40.7%), ketorolac (16.3%), metamizole (14.8%), and diclofenac (12.2%) (Table 3).

A total of 28,967 medically important SADRs and 4,664 agranulocytosis cases were identified, accounting for 0.04% and 0.006% of the 75,334,660 emergency consultations respectively. Among all medically important SADRs, 2,169 (7.5%) were associated with the prescription of metamizole or any of the NSAIDs listed in Table 2.

The odds of SADRs in consultations with metamizole or NSAIDs prescription is 0.0002 (2,169/8,975,920), while the odds of SADR in consultations without metamizole or NSAIDs prescription, but with other drugs prescribed is 0.0004 (26,798/66,329,773). The odds ratio of any SADR in emergency consultations with metamizole or NSAID prescription versus consultations with prescription of other drugs is 0.6 (95% CI 0.57-0.62).

Of the 2,169 medically important metamizole or NSAID-associated SADRs, the most frequent events were agranulocytosis (522 [24.1%]), followed by unspecified disorder of the kidney and ureter, (444 [20.5%]) and aplastic anemia (372 [17.2%]) (Table 2). Among all these SADRs, in 297 (13.7%) metamizole was prescribed in at least one of four presentations: metamizole sodium tablet 500 mg (93 consultations), metamizole sodium solution for injection 1g (177 consultations), hyoscine butyl bromide/metamizole sodium tablet 10/250 mg (18 consultations), or hyoscine butyl bromide/metamizole sodium solution for injection 20/250 mg (9 consultations).

Regarding the five main SADRs potentially associated with metamizole prescriptions, the most frequent was kidney and ureter disorder, with 87 consultations (29.3% of the 297 consultations with medically important SADRs and metamizole prescription). The second was toxic liver disease, with 55 consultations associated with metamizole use (18.5%). Other specified forms of angina pectoris were the third most common SARD

associated with metamizole prescription (38 consultations, 12.8%). For unspecified aplastic anemia, 33 consultations were associated with metamizole prescription (11.1%). Agranulocytosis was found in 29 of the consultations with metamizole prescription (9.8% of SADRs potentially associated with metamizole) (Table 2). These 29 cases of agranulocytosis account for 0.002% of the 1,189,818 metamizole prescriptions.

Out of the 522 consultations with agranulocytosis and metamizole or NSAIDs prescription recorded as the primary condition, 287 occurred in men (55%); 395 (75.7%) in population under 15 years. Regarding the consultations associated with metamizole prescription, 15 were recorded in men and 14 in women, without a statistically significant difference (X2 test p-value = 0.72). On the contrary, age distribution showed significant difference (X2 test p-value = 0.002), with people over 15 years showing an OR of 0.32 (0.14-0.74) of agranulocytosis compared with people with 15 years or more (Table 4).

The absolute number of consultations with agranulocytosis associated with prescriptions of metamizole or NSAIDs increased over the period, rising from 26 in 2014 to 170 in 2022. However, the number of consultations specifically related to agranulocytosis and metamizole remained constant, at 4 cases in both 2014 and 2022. Consequently, the proportion of agranulocytosis cases potentially linked to metamizole decreased relative to those potentially linked to other analgesics (Table 4).

The probability (odds) of agranulocytosis in consultations with metamizole prescription was 0.11, compared with those with NSAIDs. The ROR calculated was 0.30 (95% CI 0.20 – 0.45), which represents the ratio of occurrence versus non-occurrence of agranulocytosis in consultations with metamizole prescription and report of medically important SARDs compared to NSAIDs (Table 5).

The supplementary material shows the total SADRs recorded in the database by type of event (Suppl-Table 1), the total SADRs potentially associated with NSAID prescription by drug and pharmacological form (Suppl-Table 2), and the number of cases of medically important suspected adverse reactions potentially associated with metamizole by type of SADR and pharmacological form (Suppl-Table 3).

Year	Women	%	Men	%	Not specified	Total
2014	6,951,010	65.3%	3,694,033	34.7%	582	10,645,625
2015	7,157,950	65.6%	3,760,496	34.4%	414	10,918,860
2016	6,900,253	65.4%	3,654,355	34.6%	300	10,554,908
2017	5,833,692	65.5%	3,066,866	34.5%	807	8,901,365
2018	5,474,125	65.0%	2,943,356	35.0%	873	8,418,354
2019	5,668,588	64.1%	3,174,772	35.9%	1,242	8,844,602
2020	3,442,183	65.1%	1,841,458	34.9%	1,162	5,284,803
2021	3,495,347	65.0%	1,885,136	35.0%	2,822	5,383,305
2022	4,086,136	64.1%	2,293,223	35.9%	3,479	6,382,838
Total	49,009,284	65.1%	26,313,695	34.9%	11,681	75,334,660

Table 1: Consultations registered in the Emergency Medical Services Database of the Ministry of Health, 2014 to 2022.

SADRs	ICD-10 Code	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Aplastic anemia, unspecified	D619	1,186	1,182	1,078	684	602	855	545	466	449	7,047
Disorder of the kidney and ureter, unspecified	N289	581	776	847	673	544	814	488	471	619	5,813
Agranulocytosis	D70X	604	628	588	471	418	661	397	439	458	4,664
Toxic liver disease	K71	1,007	950	852	751	509	100	92	61	56	4,378
Orthostatic hypotension	I951	375	368	391	296	213	333	154	77	98	2,305
Other specified forms of angina pectoris	I208	206	214	265	161	154	191	118	57	71	1,437
Erythema multiforme flictenular	L511	152	187	181	93	50	110	67	26	21	887
Anaphylactic shock due to adverse effect of drug properly administered.	T886	199	158	138	108	52	98	56	16	19	844
Unspecified nephritic syndrome	N05	189	236	214	67	25	26	16	21	9	803
Secondary thrombocytopenia	D695	71	70	89	78	60	73	51	53	61	606
Toxic epidermal necrolysis [LYELL].	L512	13	16	19	29	11	17	18	18	10	151
Aplastic anemia	D611	2	3	8	5	5	1	2	3	3	32
Total		4,585	4,788	4,670	3,416	2,643	3,279	2,004	1,708	1,874	28,967

Supplementary Table 1: Medically important suspected adverse drug reactions (SADRs) in the Medical Emergencies database of the Ministry of Health, by type of event, 2014 to 2022.

SADRs		Cases with metamizole prescription		Cases with NSAIDs prescription		Total
		n	%	n	%	
N289	Disorder of the kidney and ureter, unspecified	87	19.6%	357	80.41%	444
K71	Toxic liver disease	55	25.0%	165	75.00%	220
I208	Other specified forms of angina pectoris	38	16.3%	195	83.69%	233
D619	Aplastic anemia	33	8.9%	339	91.13%	372
D70x	Agranulocytosis	29	5.6%	493	94.44%	522
I951	Orthostatic hypotension	17	10.2%	149	89.76%	166
N05	Nephritic syndrome unspecified	15	19.5%	62	80.52%	77
T886	Anaphylactic shock due to adverse effect of correct drug or drug product properly administered	9	19.6%	37	80.43%	46
D695	Secondary thrombocytopenia	7	15.9%	37	84.09%	44
L512	Toxic epidermal necrolysis [lyell].	5	50.0%	5	50.00%	10
L511	Flictenular erythema multiforme	2	6.5%	29	93.55%	31
D611	Drug-induced aplastic anemia	0	0.0%	4	100.00%	4
	Total	297	13.7%	1,872	86.31%	2,169

Table 2: Cases of suspected medically important reactions associated with metamizole and NSAIDs prescription by type of event, 2014 to 2022.

Drug code	Drug name and presentation	n	%
3422	Ketorolac tromethamine injectable solution or ampoules	359	16.6%
104	Paracetamol tablet	313	14.4%
5721	Paracetamol solution for injection 1 g	271	12.5%
106	Paracetamol oral solution 100 mg	212	9.8%
109	Metamizole sodium solution for injection 1 g	177	8.2%
5720	Paracetamol solution for injection 500 mg	168	7.7%
1206	Hyoscine butylbromide tablet 10 mg	99	4.6%
1207	Hyoscine butylbromide solution for injection 20 mg	94	4.3%
108	Metamizole sodium tablet 500 mg	93	4.3%
103	Acetylsalicylic acid soluble tablet 300 mg	68	3.1%
3417	Diclofenac extended-release capsule or tablet	66	3.0%
4028	Lysine clonixinate solution for injection	50	2.3%
5501	Diclofenac solution for injection	44	2.0%
101	Acetylsalicylic acid tablet 500 mg	41	1.9%
3407	Naproxen tablet	22	1.0%
113	Hyoscine butylbromide/metamizole sodium tablet 10/250mg	21	1.0%
105	Paracetamol suppository 300 mg	10	0.5%
3419	Naproxen suspension	10	0.5%
2146	Hyoscine butylbromide/ metamizol solution for injection 20/250 mg	9	0.4%
3401	Acetylsalicylic acid	9	0.4%

2096	Tramadol-paracetamol tablet	5	0.2%
3413	Indomethacin capsule	5	0.2%
6076	Ibuprofen injectable solution	5	0.2%
2504	Ketoprofen capsule	4	0.2%
514	Paracetamol suppository 100 mg	2	0.1%
3412	Indomethacin suppository	2	0.1%
3415	Piroxicam capsule or Tablet	2	0.1%
3423	Meloxicam tablet	2	0.1%
5943	Ibuprofen oral suspension contains 2 g/100ml	2	0.1%
5944	Ibuprofen drops 40 mg	2	0.1%
5505	Celecoxib capsule 100 mg	1	0.0%
5943	Ibuprofen oral suspension 40 mg/ml	1	0.0%
	Total	2,169	100%

Supplementary Table 2: Cases of medically important suspected adverse reactions associated with metamizole and nonsteroidal anti-inflammatory drug prescription by drug type, 2014 to 2022.

Drug product	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**Total**	**%**
Paracetamol	511,484	480,216	439,800	329,792	450,050	347,140	200,037	233,928	282,822	3,275,269	40.7%
Ketorolac	153,949	151,270	151,897	116,588	205,031	163,163	100,715	132,123	140,146	1,314,882	16.3%
Metamizole	168,948	171,393	160,959	119,238	182,543	140,885	63,491	76,712	105,649	1,189,818	14.8%
Diclofenac	139,065	137,961	135,893	104,012	146,598	106,625	53,954	70,055	90,659	984,822	12.2%
Naproxen	124,750	116,792	115,159	77,909	107,603	73,315	35,666	37,133	61,627	749,954	9.3%
Indomethacin	22,317	20,206	17,409	16,342	23,348	15,826	8,410	6,236	14,445	144,539	1.8%
Acetylsalicylic acid	8,033	8,649	8,632	7,043	12,995	9,523	6,995	43,741	16,878	122,489	1.5%
Lysine clonixinate	6,546	6,357	8,225	8,250	14,041	12,755	5,971	7,771	15,384	85,300	1.1%
Ibuprofen	0	0	0	0	7,384	7,338	3,563	24,732	35,681	78,698	1.0%
Ketoprofen	3,394	3,694	3,961	4,173	6,135	7,026	3,176	2,801	5,137	39,497	0.5%
Meloxicam	2,492	2,481	2,789	2,451	2,886	2,069	955	1,973	2,795	20,891	0.3%
Pyroxicam	2,524	2,956	3,143	2,099	3,249	1,802	629	765	1,228	18,395	0.2%
Celecoxib	1,170	947	634	646	1,860	2,624	1,745	3,784	4,814	18,224	0.2%
Sulindaco	204	294	219	117	146	125	47	122	121	1,395	0.0%
Acemetacin	38	28	27	50	54	57	52	116	125	547	0.0%
Etofenamate	25	30	21	40	30	32	18	21	27	244	0.0%
Etoricoxib	0	6	2	5	20	30	22	89	167	341	0.0%
Total	1,144,939	1,103,280	1,048,770	788,755	1,163,973	890,335	485,446	642,102	777,705	8,045,305	100.0%

Table 3: Main analgesic drugs prescribed in the emergency medical services of the Ministry of Health, 2014 to 2022.

SADR	**108 Metamizole sodium tablet**	**109 Metamizole sodium solution for injection**	**113 Hyoscine butylbromide/**	**2146 Hyoscine butylbromide/**	**Total**	**%**

			metamizole sodium tablet	metamizol solution for injection		
D619 Aplastic anemia, unspecified	3	29	1	0	33	11.11%
D695 Secondary thrombocytopenia	1	5	0	1	7	2.36%
D70X Agranulocytosis	12	16	0	1	29	9.76%
I208 Other specified forms of angina pectoris	9	28	1	0	38	12.79%
I951 Orthostatic hypotension	11	6	0	0	17	5.72%
K71 Toxic liver disease	24	24	6	1	55	18.52%
L511 Erythema multiforme flictenular	0	2	0	0	2	0.67%
L511 Toxic epidermal necrolysis [LYELL].	0	5	0	0	5	1.68%
N05 Nephritic syndrome, unspecified	6	8	1	0	15	5.05%
N289 Disorder of the kidney and ureter, unspecified	24	49	8	6	87	29.29%
T886 Anaphylactic shock due to adverse drug effect	3	5	1	0	9	3.03%
Total	93	177	18	9	297	100%

Supplementary Table 3: Cases of medically important suspected metamizole adverse reactions (SADRs) by type and drug presentation, 2014 to 2022.

	Consultations with agranulocytosis registered					
	Total		**With NSAIDs prescription**		**With Metamizole prescription**	
	n = 522		**n=493**		**n=29**	
.	N	%	n	%	n	%
Gender						
Female	235	45.0	221	44.8	14	48.3
Male	287	55.0	272	55.2	15	51.7
Age group						
<15	395	75.7	380	77.1	15	51.7
15 - 19	62	11.9	59	12.0	3	10.3
20 - 39	13	2.5	11	2.2	2	6.9
40 - 59	37	7.1	33	6.7	4	13.8
>60	15	2.9	10	2.0	5	17.2
Year						
2014	26	5.0	22	4.5	4	13.8
2015	26	5.0	23	4.7	3	10.3
2016	45	8.6	39	7.9	6	20.7
2017	44	8.4	42	8.5	2	6.9
2018	42	8.0	40	8.1	2	6.9
2019	69	13.2	65	13.2	4	13.8
2020	41	7.9	39	7.9	2	6.9
2021	59	11.3	57	11.6	2	6.9

2022	170	32.6	166	33.7	4	13.8

Table 4: Gender, age and year distribution of agranulocytosis cases associated with metamizole and NSAIDs identified in the Emergency Services database, 2014-2022

.	Event of interest (agranulocytosis)	Other events in the database	Total
Metamizole prescription	29	268	297
NSAIDs prescription	493	1,379	1,872
Total	522	1,647	2,169

Table 5: Data recorded for the estimation of the reported odds ratio of agranulocytosis in consultations with metamizole prescription, compared to NSAIDs

4 Discussion

We have conducted a transversal study using emergency medical records to identify medically important suspected adverse reactions associated with metamizole registered in emergency medical consultations of the Ministry of Health of México, with emphasis on cases of agranulocytosis.

The consulted database has more than 75 million medical emergency consultations in population not affiliated to social security in Mexico between 2014 and 2022, and it is the only public population database of medical services with diagnosis and drug prescription information in this country. Among these 75 million records, 31.5 million medical prescriptions were identified in the database. Non-opioid analgesics such as metamizole and NSAIDs were listed in a quarter of the consultations with drugs prescribed. Metamizole accounted for 1,189,818 prescriptions; it is among the three most used, only after paracetamol and ketorolac. According with this data, metamizole is widely used in Mexico [33]. These results are congruent with a previous report in which a group of physicians from different specialties in public and private second- and third-level hospitals in Mexico City were surveyed. In that study, 82% of the physicians interviewed were found to prescribe metamizole in their daily practice [8]. Metamizole is commonly used in other Latin American countries as well. For instance, Sznejder and colleagues' population-based study showed it for Brazil [3].

Between 2014 and 2022, agranulocytosis, kidney and ureter disorders, and aplastic anemia were found to be the three most frequent SADRs potentially associated with NSAIDs; however, considering there is not available personal identifier to track the patients, it was not possible to establish a causal relationship between drug prescriptions and suspected drug reactions [33].

In our study, from 2014 to 2022, 29 cases of agranulocytosis were reported in any emergency consultation in which metamizole was prescribed, representing 0.002% of the total records. Studies performed in other countries where metamizole is not banned have found metamizole to be among the drugs more commonly associated with drug-induced agranulocytosis [14-16]. Moreover, metamizole-induced agranulocytosis incidence has been increasing in countries such as Germany, Spain, and Switzerland in the last 20 years [4], although the reported incidence varies widely between different studies.

The prevalence of agranulocytosis in European patients has been reported to be 0.03% to 0.5%, and in Hispanics about 0.35 cases per million inhabitants [30]. In Germany, for example, an incidence of 1:1602 was estimated using health insurance data [1] and 0.96 cases per million-year in a prospective case-control study [5] In Brazil, a 0.38 per million-year incidence has been estimated [3].

Our findings suggest a higher incidence than the reported for Brazil, but far smaller than that estimated for Germany. Nevertheless, it is worth noting that our results might be overestimating the real incidence, because we were not able to identify the cases that do not meet the minimum imputability criteria to be considered metamizole-induced.

According to our results, metamizole is 70% less likely to be associated with agranulocytosis compared with all NSAIDs together (ROR 0.3 [95% CI 0.20 - 0.45]). In contrast, a systematic review on the safety of metamizole points out that in most studies in which the risk of agranulocytosis was assessed, an increase in relative risk of between 1.5 (95% CI, 0.8-2.7) and 40.2 (95% CI, 14.7-113.3) was found, compared with other analgesics or placebo [31].

Previous studies indicate that the incidence of metamizole-induced agranulocytosis in Mexico is low [20]. Ríos-Quintana and Estrada-Hernández [32] found in a search of adverse drug reactions reported to the National Center for Pharmacovigilance, that in the period from 2011 to 2014, 4,553 reactions related to NSAIDs were recorded, of which 21% were associated with metamizole. However, no cases of agranulocytosis related to this drug were found.

The database of the Emergency Services within the Mexican Ministry of Health exhibits certain limitations. Specifically, the absence of a unique identifier renders it impossible to track patients longitudinally. Consequently, our observations are confined to instances where patients sought treatment for conditions like agranulocytosis or other medically important SADRs and causality with prior metamizole consumption cannot be definitively established.

In future studies using medical services or pharmacovigilance databases to explore drug safety, other clinical and demographic characteristics such as age, sex, and comorbidities of patients with SADRs should be retrieved to identify some potential risk factors.

The identification of SADRs cases associated with metamizole use in the emergency database will be significantly limited due to the absence of a unique patient identifier in the medical services, thereby preventing the determination of how many times a medication was prescribed to the same patient and hindering the accurate identification of duplicate patient records.

This study provides evidence on the safety of metamizole in relation to usage frequency and the probability of occurrence of medically important adverse reactions within a nine-year period.

An important outcome of this work is the reduced probability of developing SADRs associated with metamizole prescriptions compared to NSAIDs in emergency rooms of hospitals managed by the Ministry of Health in Mexico.

Although our findings highlight the high frequency of metamizole prescriptions in our country, additional analysis is required to investigate the characteristics of metamizole users, dosing regimens, outcomes, and the time frames in which suspected medically important reactions, such as agranulocytosis, are identified.

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Conflict of interest

The study was partially funded by Laboratorios Sanofi S.A. de C.V; however, the funding source had no role in the investigation process. Authors declare that they did not receive any type of remuneration for their work on this manuscript.

Presentation

We submit to your consideration the article "Epidemiology of agranulocytosis and other medically important adverse reactions in Mexican population associated with metamizole."

The purpose of this study is to determine the pharmacological safety of these NSAIDs, identifying suspected adverse reactions in the Mexican population reported in the scientific literature and in different databases with health information to identify cases of suspected adverse drug reactions, including fatal cases of blood dyscrasias.

Our results show evidence of high frequency of prescriptions in the Mexican population, but the evidence on metamizole consumption, its doses, and the time windows in which suspected medically important reactions such as agranulocytosis are identified needs to be strengthened to establish direct causality.

We found a lower probability of developing suspected medically important adverse reactions associated with metamizole prescription than with other NSAIDs in emergency departments in the non-eligible population in Mexico, this association was statistically significant, for the period from 2014 to 2021.

Therefore, we consider that our manuscript is of interest to the audience of the ClinicSearch Publishers, concerned about the safety of drugs prescribed in health systems and specifically, in developing countries with similar characteristics.

Contributions

Bistre, Sarah; study conception and design; data interpretation; writing of the work and critical review, final approval of the version to be published.

Palacio-Mejía Lina Sofía; study conception and design; acquisition, analysis and interpretation of data; writing of the work and critical review, final approval of the version to be published.

Castro-del Angel Carlos Arturo; data analysis and interpretation; writing of results, final approval of the version to be published.

González-González Leonel: study conception and design; acquisition, analysis and interpretation of data; writing of the work and critical review, final approval of the version to be published.

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