Capter 96

A bibliographic analysis on the use of dipyrone and agranulocytosis

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ABSTRACT
Introduction: The association of dipyrone with agranulocytosis has a variable incidence in different studies. The geographic variety, with risk proportions between 0.8 and 23.7, it can be explained by differences in patterns of use, doses, and concomitant use of other drugs. Methodology: Based on this variation of protocols on the use and release of dipyrone, this paper is a study carried out through a literature review, adding data, studies and research related to dipyrone and the association with cases of agranulocytosis, guiding the reasons why is prohibited, or released only by medical prescription in some countries, and unrestricted in others. Results and discussion: Considering the over-used of metamizole by the brazilian, a higher frequency of cases of agranulocytosis was expected, but this has not been the case. due to the undeniable effectiveness of dipyrone as analgesic and antipyretic, its adverse effects are lower compared to other drugs of the same class, such as paracetamol; In 2010, the Federal Public Ministry requested that dipyrone-based drugs be dispensed with a medical prescription, because their adverse effects, however the request was rejected by ANVISA, who claimed that: the incidence of side effects are low and the benefits of the drug outweigh the risks. Considerations: Based on the studies is noticeable the need for more research, with different populations, ethnicities and ages, aiming at reliable and decisive results for the continuity and/or return of the commercialization and safe supply of metamizole.

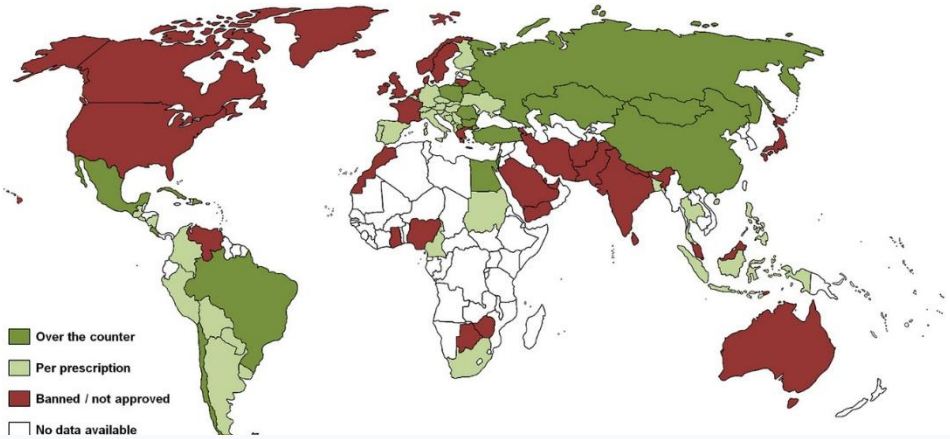
Keywords: Drug-Related Side Effects, Adverse Reactions, Safety-Based Drug Withdrawal, dipyrone, metamizole, Agranulocytosis.

1 INTRODUCTION

In traditional use, Dipyrone was first produced by the German company Hoechst AG 100 years ago (Arellano and Sacristan, 1990; Maluf, Hamerschlak et al, 2009). With analgesic, antipyretic and antispasmodic properties, dipyrone is widely used in countries like Turkey, Israel, India, Argentina, Mexico, Spain and in Brazil since it is an over the counter medicine (OTC) in virtually all Latin America.

However, after agranulocytosis's reports related with dipyrone use, some countries such as Scandinavia, United States of America (USA), Canada, United Kingdom (UK), banned the dipyrone's marketing (Sebode et al., 2020). In other countries, the dispensing of dipyrone has been restricted to prescription only, for example, Germany, and Spain (Hearn. L et al. 2016).

Figure 1. Green: Released; Light Green: Under Medical Prescription; Red: Banned / Not Approved; White: No data available.



Source: Lutz, M. (2019)

Image 1 presents an overview of the legal status of dipyrone worldwide. It can be seen that in Asia and South America for the most part, dipyrone is either prescription-only or restricted to sale and in almost all of North America the marketing of dipyrone is prohibited.

Agranulocytosis is the term used to define a total reduction in the number of circulating granulocytes in the peripheral blood (Mendes, M. et al., 2020) technically, this reduction includes neutrophils, eosinophils, basophils and monocytes, elements that are extremely important against infectious agents. It is an acute dyscrasia of the blood which subjects the individual to the high risk of acquiring infections, against which the weakened organism is not prepared to defend itself (Souza et al., 2013). The association of dipyrone with agranulocytosis shows variable incidence in different studies. The geographic variability, with risk proportions ranging from 0.8 to 23.7, it may be partially explained by differences in patterns of use, doses, duration of treatment, and concomitant use of other medications (Wannmacher L., 2012).

In 2001, the National Health Surveillance Agency (ANVISA) held an International Panel on the Safety Evaluation of Dipyrone, with national and international scientist's participation. The objective of this panel was to promote broad clarification on the safety aspects of dipyrone, often questioned by various medical-scientific segments and representatives of sectors involved in consumer protection.

Therefore this paper aims to add information, studies, and research related to dipyrone, also known as metamizole, and its connection with cases of agranulocytosis, thus explaining the reasons why it is forbidden, or only allowed with a prescription in some countries, and totally allowed in others.

2 METHODOLOGY

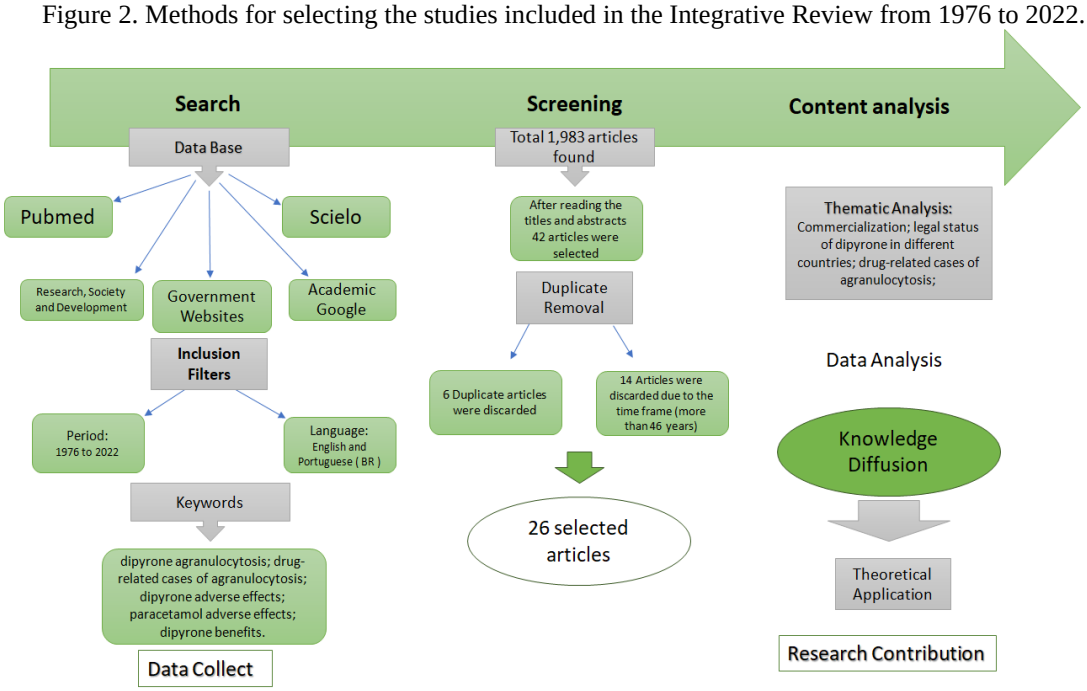
For a more complete approach, the integrative review method was applied, which aims to synthesize results obtained in research on a topic, in a systematic, ordered and comprehensive manner, thus constituting a body of knowledge (Ercole. Et al., 2014).

The literature review was conducted between March and August 2022, through research of scientific articles by the qualitative method, materials that were collected from online databases in the following platforms: Scientific Electronic Libraryonline (SciELO), Google Scholar, Research, Society and Development, PubMed and governmental sites (FDA and ANVISA). The parameters used for selection were as follows: 1 - Portuguese (BR) and English language articles; 2- materials that discussed dipyrone, as well as its safety, sale exempt from medical prescription, restriction, prohibition of commercialization, and legal status in several countries.

Articles that contained the following terms: dipyrone agranulocytosis, drug-related cases of agranulocytosis, dipyrone adverse effects, paracetamol adverse effects, dipyrone benefits; were also analyzed, if they contained the terms, but the publication date was outside the given time window or did not aggregate this review in the proposed context, were discarded.

In image 2 below, it is possible to observe the research methods, screening and data analysis performed. Described in Table 1 are the main documents used to construct the Discussion and Results regarding Dipyrone Use and Agranulocytosis.

Figure 2. Methods for selecting the studies included in the Integrative Review from 1976 to 2022.



Source: Authors

Table 1. Main documents used for the construction of the Discussion and Results separated by authors, year, title and place of publication.

Authors	Year	Title	Place of Publication
ANVISA	2001	Painel Internacional de Avaliação da Segurança da Dipirona	
Knappmann, A.L.; Melo, E.B	2010	Qualidade de Medicamentos Isentos de Prescrição: Um Estudo com marcas de Dipirona Comercializadas em uma Drogaria de Cascavel (PR, Brasil)	Ciênc. Saúde Coletiva
Sznejder, H., Amand, C., Stewart, A., Salazar, R., & Scala, W.	2022	Real world Evidence of the use of metamizole (dipyrone) by the Brazilian population. A retrospective cohort with over 380,000 Patients	Einstein (Sao Paulo, Brazil)
Sollero, L.	1976	Incidence of Agranulocytosis and the Use of Dipyrone in Brazil. Results of an Inquiry Carried out by F. A. P. B., Reviewing the Incidence of this Blood Dyscrasia and its Medico-Social Relevance in Brazil.	Rev Pesquisas Med Biol
Basak, G. W., Drozd-Sokołowska, J., & Wiktor-Jedrzejczak, W.	2010	Update on the incidence of metamizole sodium-induced blood dyscrasias in Poland	The Journal of International Medical Research
Cismaru, A. L., Rudin, D., Ibañez, L., Liakoni, E., Bonadies, N., Kreutz, R., Carvajal, A., Lucena, M. I., Martin, J., Sancho Ponce, E., Molokhia, M., Eriksson, N., EuDAC Collaborators, Krähenbühl, S., Largiadèr, C. R., Haschke, M., Hallberg, P., Wadelius, M., & Amstutz, U.	2020	Genome-Wide Association Study of Metamizole-Induced Agranulocytosis in European Populations	Genes
Stammschulte, T., Ludwig, W. D., Mühlbauer, B., Bronder, E., & Gundert-Remy, U.	2015	Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990-2012.	European Journal of Clinical Pharmacology
Ghanem, C. I., Pérez, M. J., Manautou, J. E., & Mottino, A. D.	2016	Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity.	Pharmacological Research
Goodman, L. S. G., Hardman J.G., Limbird L.E.	2010	As bases Farmacológicas da Terapêutica. 11 ed. Rio de Janeiro	McGraw-Hill
U.S. Food & Drog Administration.	2014	All Manufactures of Prescription Combination Drug Products with more than 325mg of Acetominophen have Discontinued Marketing.	
Hedenmalm, K., & Spigset, O.	2002	Agranulocytosis and other Blood Dyscrasias Associated with Dipyrone (metamizole).	European Journal of Clinical Pharmacology
Newburger, P. E., & Dale, D. C.	2013	Evaluation and Management of Patients with Isolated Neutropenia.	Seminars in Hematology
Wannmacher L.	2005	Paracetamol versus Dipirona: Como Mensurar o Risco? . Uso Racional de Medicamentos.	Unidade Técnica de Medicamentos e Tecnologias da Organização Pan-Americana da Saúde/Organização Mundial da Saúde – Representação do Brasil e do Departamento de Assistência Farmacêutica e Insumos Estratégicos da Secretaria de Ciência, Tecnologia e Insumos Estratégicos do Ministério da Saúde

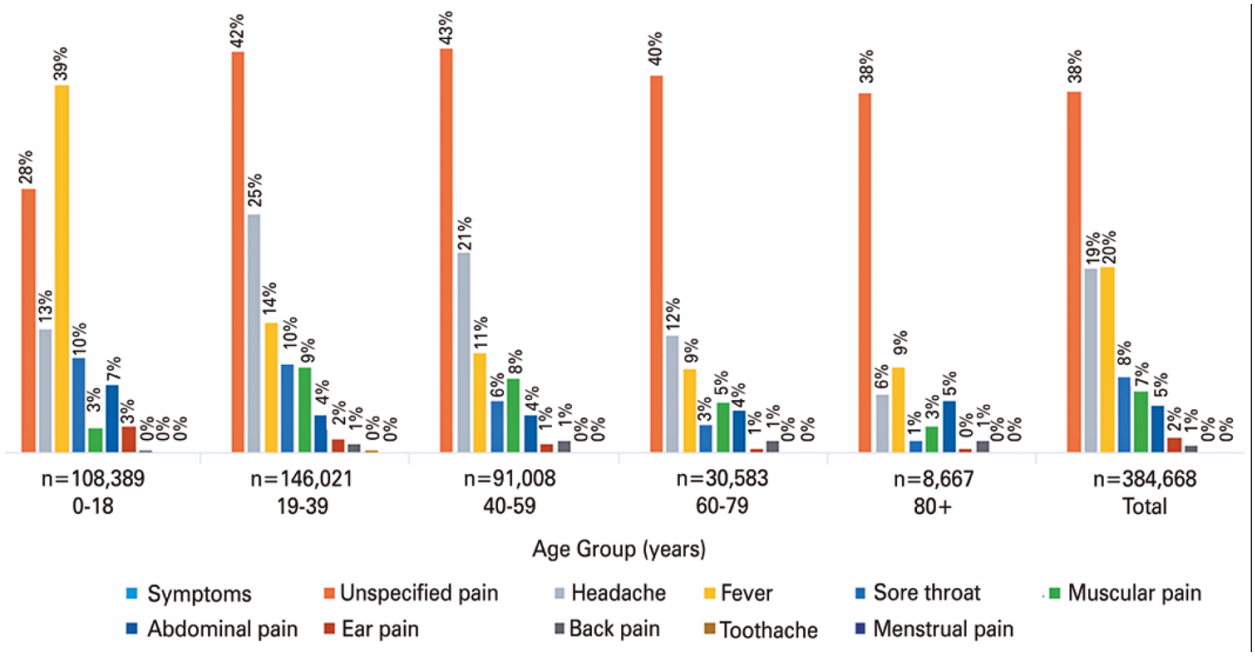
Conselho Regional de Farmácia do Estado de São Paulo – CRFSP.	2010	Notícias: Justiça Mantém Venda de Dipirona em Farmácias e Drogarias.	
Jage, J., Laufenberg-Feldmann, R., & Heid, F.	2008	Medikamente zur postoperativen Schmerztherapie: Bewährtes und Neues. Teil 1: Nichtopioide [Drugs for postoperative analgesia: routine and new aspects. Part 1: non-opioids].	Der Anaesthesist
Derry, S., Faura, C.C., Edwards, J.E., McQuay, H., & Moore, R.A.	2013	WITHDRAWN: Single dose Dipyrone for Acute Postoperative Pain.	The Cochrane Database of Systematic Reviews
Casagrande, E. P. ., & Sabec Pereira, D. K.	2022	Analysis of handbooks of patients affected with chronic residual pain after hip surgery with drug therapy.	Research, Society and Development
Brasil.	2020	Agência Nacional de Vigilância Sanitária.	9º Boletim, Brasília

Source: Authors

3 RESULTS AND DISCUSSION

In Brazil, dipyrone is included in the framework of Medicines Exempt from Prescription (MIPS), and is therefore freely available and widely accessible to the population due to its low cost and effectiveness. In 1999, the brazilian consumption was 190.54 tons of dipyrone (ANVISA, 2001); And in 2020, ANVISA, through its 9th Pharmacovigilance Bulletin, points to dipyrone as the most consumed drug in the country. Dipyrone is in Brazil one of the drugs who are recommended for dengue symptoms and it is part of the list of medicines of the popular pharmacy program of the Ministry of Health. Dipyrone is also used in associations for the production of low-cost MIPs, in addition the great demand by the population for the treatment of fevers and analgesia (Knappmam; Melo, 2010).

Figure 3. Use of dipyrone in Brazil by age group and the most incident symptoms and conditions.



Source: Sznejder. H. et al., 2022.

The figure above (3) presents the use of dipyrone in Brazil by age group, as well as the most incident symptoms and conditions. It can be observed the evaluation done by age group, adult patients most often use metamizole to treat symptoms of headache, fever, and sore throat, followed by myalgia and abdominal pain. In the case of children, the main reason for using the drug was pointed out as fever and general pain.

Considering the high consumption of metamizole by brazilian population, a higher frequency of agranulocytosis's cases was to be expected, but it has not been a reality. In such a way that by means of the unquestionable efficacy of dipyrone as an analgesic and antipyretic, and the adverse effects, such as agranulocytosis, are of lower threat if compared to the adverse effects of other drugs of the same class, such as paracetamol. In Brazil, ANVISA did not withdraw the product from the market, claiming that: "*The change in the current regulation of DIPYRONE would incur in negative aspects for the population, increasing the risks of using other drugs indicated for the same therapeutic purpose*"(2001).

The non-prohibition of dipyrone in Brazil is also due to the insufficient number of studies performed in the country with the objective of evaluating if there is a reason for withdrawing it from the market. The largest and most notorious study was carried out in the 1970s, evaluating 531,261 patients, of which 15 had been diagnosed with agranulocytosis. Among these, 8 cases were related to prior use of pyrazolone derivatives and only one was directly associated with the use of dipyrone (Sollero, 1976). It demonstrates a low rate of metamizole-related agranulocytosis. In addition to Brazil, Mexico, Spain, Bulgaria, Africa, Russia and India also have cleared sales for dipyrone (Basak et al., 2010; Cismaru et al., 2020).

Switzerland and Germany are two of almost 30 countries that have restricted dipyrone to prescription-only sales. In Germany in 1986, regulatory measures were employed after reports of agranulocytosis and pseudo-allergic shock, restricting it to sale by prescription and only for severe and acute post-traumatic and post-surgical pain, colic pain, cancer pain, treatment of other severe pain if other measures are not indicated, and treatment for high fever if other measures fail (Stammschulte et al., 2015). However, the United States, Denmark, Canada, Norway, and Sweden among others went beyond the restriction, and discontinued the production and marketing of dipyrone. Upon the discontinuation of the drug, it was claimed that its adverse effects were similar to acetaminophen and less than acetylsalicylic acid adverse effects, in addition to the possibility of non-pharmacological antipyretic methods, such as bathing and warm compresses.

This allegation can be reviewed and analyzed, because the adverse effects of acetaminophen are considerably more serious than dipyrone's; being the leading cause of acute liver failure in the United States, Great Britain, and other European countries (Ghanem et al., 2016). As well as dipyrone, is a low-cost drug, easy access to the population, which, where there is no access to metamizole, resorts to acetaminophen more continuously, overloading the body as well as the liver. Unintentional overdoses among adults and children, represent >50% of cases that present themselves during a short period of time, usually more than three days of use by self-medication. The conventional therapeutic dose ranges from

325 to 1000 mg in adults, not to exceed 4000 mg per day. In children, the therapeutic dose is 10mg/kg, using no more than 5 doses in 24 hours (Goodman et al., 2010).

Over 100,000 calls to the Poison Control Centers, 56,000 emergency room visits, 2,600 hospitalizations, and nearly 500 deaths are attributed to acetaminophen use in the United States each year (Ghanem et al. 2016). By the seriousness and number of cases, in 2014 in the USA, it became a public health problem, and all manufacturers of prescription combination drugs with more than 325mg of paracetamol, per tablet, capsule, by determination of Federal Drug Administration (FDA), discontinued the marketing of them.

Drug-induced agranulocytosis is rare and unpredictable, some underlying individual genetic or other risk factors are probably mandatory for these reactions to occur (Hedenmalm, Karin. 2002). Agranulocytosis can be triggered by several factors, such as nutritional deficiency of vitamin B12, folic acid, protein-calorie malnutrition, AIDS, genetic factors, radiation exposure, ethnicities (individuals of African, Middle Eastern and West Indian descent) and medications (Newburguer et al. 2013).

Another retrospective study evaluated acute exposure to dipyrone over a three-year period. In 243 medical records reviewed, 49 adverse events were recorded in 39 (16%) patients. And in 57% of these patients mild gastrointestinal manifestations occurred, even in those who ingested high doses with suicidal intent. Agranulocytosis did not occur in any patient, proving that it is a rare idiosyncratic effect, not dose dependent (Wannmacher. 2005).

In 2010 in Brazil, the Federal Public Ministry requested that drugs based on dipyrone be dispensed by prescription, due to its adverse effects, but the request was denied by ANVISA, on the grounds that the incidence of side effects is low and the benefits of the drug outweigh the risks (CRF-SP, 2010). Among the benefits presented by the use of metamizole are: the use through the intravenous route, decreased blood pressure (practice adopted in hospital emergency area), antipyretic, analgesic, anti-inflammatory effects, remarkable spasmolytic effect and is rarely associated with agranulocytosis and other hematopoiesis disorders (Jage et al. 2008).

In postoperative cases, a study review conducted in 2013, spelled out studies in which dipyrone was administered for acute postoperative pain, and one of these, validated that "a single 2.5g dose of intravenous dipyrone was equivalent to 100mg of intravenous tramadol for at least 50% pain relief" (Derry et al. 2013). And in an observational study, it was found that the use of dipyrone sodium was fundamental for the analgesia of hospitalized patients after surgical procedures, considering that there were no reports of side effects and its pain control was very effective (Casagrande, Pereira. 2022).

Thus, a pharmacotherapeutic measure of great value, demonstrating that before resorting to opioids, metamizole can be the first option, since it is as effective as opioids, avoiding addiction and giving the possibility that if necessary, another drug with another mechanism of action can be administered for pain relief.

4 FINAL CONSIDERATIONS

From the studies used in this paper, it is possible to see the need for research of a larger proportion, with populations from different countries, ethnicities, and ages, making possible evaluations in the picture of patients with agranulocytosis and the association of this condition with ethnicity and geographical location; Aiming at reliable and decisive results for the continuity and/or return of the commercialization and safe administration of metamizole.

Being a drug with so many beneficial effects, as mentioned above, it can be administered to patients of all age groups, because of its variety of presentation (drops, suppository, tablets, effervescent tablets, syrup), children with high fever for example, who cannot take the medicine orally, have the alternative of the suppository, which is painless and effective.

An alternative for the monitored use of dipyrone in places where it is forbidden is the sale under pharmaceutical prescription, where there is a greater possibility of patient follow-up, enabling non-steroidal anti-inflammatory, analgesic, and antipyretic treatments, in an effective and less aggressive way to the organism.

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