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Is it time to restrict the clinical use of dipyrone?

¿Es tiempo de restringir el uso clínico de la dipirona?

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Dipyrone (or metamizole) is an analgesic and antipyretic for oral or parenteral administration. Its action mechanism is directly related to the inhibition of the signaling of TRPA1 (*Transient Receptor Potential Ankirin* 1). The TRPA1 ion channel, located in the plasma membrane of a subpopulation of nociceptors, plays a major role in pain transmission.[1–3] However, the clinical use of dipyrone is associated with various adverse effects such as agranulocytosis, aplastic anemia, anaphylaxis, toxic epidermal necrolysis, renal failure, upper gastrointestinal tract bleeding, induction of acute attacks of porphyria, among others.[4–7] One study also reported an increased risk of leukemia in children born to mothers who took dipyrone during pregnancy.[8] The most severe adverse effects are undoubtedly aplastic anemia and agranulocytosis, the latter being the most frequent. In a population study in the Netherlands, dipyrone was reported to increase the relative risk of agranulocytosis 23-fold.[9] This increase occurred in patients treated in hospitals throughout that country and was compared with the reference population, which consisted of all persons in the catchment area of the Pharmaco Morbidity Record Linkage System in the Netherlands. Fatal infections subsequent to dipyrone-mediated agranulocytosis have been reported in adults and in children,[10] and mortality associated with agranulocytosis is mostly caused by sepsis.[11–14] Death from anaphylaxis due to allergic reactions type I[15,16] have also been reported.

The incidence of dipyrone agranulocytosis varies in the medical literature. In 1973, Sweden reported an incidence of 1 per 10,000 inhabitants,[17] and in 1981 the incidence of agranulocytosis in Germany was 1 in 20,000. A more recent study in Germany, which analyzed data from 2000 to 2010, reported an incidence of 1 in 1 million.[18] As a consequence of the high number of severe adverse effects and deaths associated with dipyrone, this drug was initially withdrawn from the market in Canada in 1963, and subsequently in the United States in 1973.[19] In addition, a total of 30 countries in the world have withdrawn it from the market, mainly in European countries and Australia.[20] However, despite warnings about the risk of dipyrone causing blood dyscrasias and, at worst, death, many countries in Latin America continue to use it for clinical purposes and its free sale allows an indiscriminate use without control mechanisms. The consumption of dipyrone without medical prescription and its association with agranulocytosis is

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known in the United States among the Latin American immigrant population.[21] In Latin America, the impact of the free sale of dipyrone could be one of the factors for which its mild and moderate adverse effects are neither recognized nor reported and, therefore, its incidence may be underestimated. Reports of adverse effects of dipyrone in these countries are low. Their record would be limited to cases of severe infection, anaphylaxis, and other serious medical conditions, where urgent medical attention is necessary.[22]

The case report of Machado-Alba et al,[23] recently published in our journal, tells the story of a 59-year-old patient with pain due to polytrauma and who developed granulocytopenia associated with dipyrone. Dipyrone was used clinically as an analgesic for a total of 23 days, and once suspended, granulocytopenia was resolved. The report does not mention whether the patient was previously informed about the adverse effects of dipyrone, such as agranulocytosis, aplastic anemia, allergies, nephrotoxicity, among others. Nor does it mention whether alternative analgesics without severe adverse effects were offered to the patient. This case report is not a novel case, a rare adverse effect, or an unknown adverse effect of dipyrone. The relevance of this study is not recognizing the obvious, but perhaps in publicizing that physicians fail to adhere to the ethical principle of *primum non nosere* (do no harm first). Based on randomized, double-blind clinical studies, many drugs with antipyretic, analgesic, and/or anti-inflammatory properties are now available on the market, which have demonstrated clinical safety, tolerability, minimal adverse effects, and no severe adverse effects.[24–26] The new analgesics contrast radically with the severe adverse effects of dipyrone. Currently, there is no clinical evidence justifying the use of dipyrone as an analgesic or first-line antipyretic. More than 30 countries in the world in whose territory the use of dipyrone is banned, including Canada, the United States, and England, demonstrate that this medicine is not only unnecessary, but potentially harmful to health.

The case report of Machado-Alba et al[23] does not refer to the free sale of dipyrone or its indiscriminate use, but could support the thesis that for-profit pharmaceutical companies can greatly benefit from the free and indiscriminate sale of this drug, despite its toxicity and high risk. Access to dipyrone without medical formula significantly increases the risk of adverse effects in consumers. Following the example of the 30 countries in the world that banned its clinical use would eliminate adverse effects, including severe and potentially lethal adverse effects. In fact, the free sale of dipyrone should be eliminated and its indiscriminate use should not be allowed. Physicians who choose to continue using it as an analgesic should inform their patients about its harmful effects, including its complications and risk of death.

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