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Current controversies on the clinical use of dipyrone: safe alternative?

Controversias actuales sobre el uso clínico de la dipirona: ¿alternativa segura?

Upon carefully reading Gómez-Duarte's[1] editorial on the need to restrict the use of dipyrone due to its adverse and potentially lethal effects, we thought that some of the expressed ideas must be reviewed in detail in the light of current controversies and methodological limitations of the available evidence, for the purpose of making better decisions regarding its clinical use.

The editorial does not cover dipyrone's analgesic effectiveness. The lack of studies directly comparing dipyrone to other analgesic drugs limits the assessment of its effectiveness. However, the number needed to treat (NNT) to reduce pain by 50% has been used as an indirect measurement, which allows to objectively approach to the comparative differences among different analgesic drugs. Cochrane's meta-analysis estimated that low dipyrone doses (500 mg) are associated with a NNT of 2.4 (95% confidence interval [CI] 1.9–3.2), with an effect magnitude comparable to that of drugs such as diclofenac 50 mg, ibuprofen 400 mg, and naproxen 550 mg, and higher than that of celecoxib 200 mg, oxycodone 15 mg, and paracetamol 1000 mg (Table 1). It is difficult to draw a definitive conclusion with respect to the effectiveness of these drugs, due to the quality of the basic studies, the heterogeneity of the population and the surgical model. Notwithstanding the foregoing, the best available evidence suggests that dipyrone is an effective drug to treat acute[2] and chronic[3] pain.

The frequency of severe adverse side-reactions to the use of dipyrone, specifically the agranulocytosis incidence, varies. A frequency of 1:10,000 to 1:1 million[1] is reported. This variability is explained, to a small extent, by the genotypical differences of surveyed populations and mainly by the methodological limitations of studies, which have been criticized. Some of them based their estimations on the frequency of patients with agranulocytosis and the previous use of dipyrone, while other studies compared the number of agranulocytosis cases to the amount of dipyrone prescribed. Considering that this information is incomplete and selective, such records cannot be used to generate reliable incidence rates, and even less so to suggest a causal relation between exposure and outcome.[4] There are case–control studies with proper bias and sample size control, which estimate an agranulocytosis frequency between 1:1.1 million[5] and 1:1.8 million.[6] In conclusion, the agranulocytosis incidence is variable, undetermined, but probably infrequent.

Mortality related to agranulocytosis is also variable. However, the trend suggests a significant reduction over time.[7,8] The international study on agranulocytosis and aplastic anemia reports a mortality rate of 9% for patients diagnosed with agranulocytosis and an overall agranulocytosis-related mortality of 0.5 per million per year. The World Health Organization (WHO) reported that the mortality risk caused by adverse effects related to different

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Table 1. Number needed to treat of different analgesic drugs used to reduce pain by at least 50%.

Drug	Dose (mg)	NNT	95% CI
Dipyrone	500	2.4	1.9–3.2
Diclofenac	50	2.7	2.4–3.0
Ibuprofen	400	2.5	2.4–2.6
Paracetamol	1000	3.6	3.4–4.0
Etoricoxib	120	1.9	1.7–2.1
Oxycodone	15	4.6	2.9–11
Celecoxib	200	4.6	3.4–5.6
Naproxen	500/550	2.7	2.3–3.3

CI = confidence interval, NNT = number needed to treat.
Source: Adapted from.[2]

analgesic drugs is of 5.92, 2.03, 0.25, and 0.2 per million of inhabitants per year for diclofenac, aspirin, paracetamol, and dipyrone, respectively. This suggests that the death risk derived from adverse effects related to dipyrone is similar to the risk derived from paracetamol and is even lower than other analgesic drugs.[9,10]

The editorial highlights the availability of drugs with analgesic, antipyretic, and/or anti-inflammatory properties that have proven to be clinical safe and tolerable and to have minimum adverse effects, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The frequency of dangerous adverse effects is not insignificant. According to the WHO pharmacovigilance program, the exposure to dipyrone is associated with a relative indirect risk (Reporting odds ratio) of gastric or duodenal ulcers, gastrointestinal hemorrhage, and kidney failure of 0.9 (95% CI 0.7–1.2), 1.5 (95% CI 1.3–1.7), and 1.2 (95% CI 1.0–1.3), respectively. This effect magnitude is lower than the risk after administering other selective and non-selective NSAIDs (Table 2).[6]

Opioids are related to respiratory depression and low blood pressure, which are caused to 1% and 5%, respectively.[11] In addition, for the past 3 decades, the prescription of opioids has significantly increased in high-income countries, particularly in North America. This significant and disproportionate increase has been related to the unproper use, abuse, use disorder, and addiction to opioids, in addition to overdose and death by overdose. This is the main public health issue in the United States, where 62 people die every day as a result of opioid overdose.[12] According to WHO data, an estimate of 69,000 people die around the world and 25 million people are addicted to them, mainly heroine, although the abuse and addiction to opioids with medical prescription has been growing.

In conclusion, we consider that this is not the time to restrict the clinical use of dipyrone, but we should consider it a therapeutic alternative in selected cases and encourage high-quality clinical research with low bias probability within the context of multimodal analgesic schemes, for the purpose of optimizing clinical outcomes and diminishing the use of opioids.

Table 2. Reporting odds ratio of gastric or duodenal ulcers and upper gastrointestinal hemorrhages of different non-steroidal anti-inflammatory drug.

Adverse effects	Gastric or duodenal ulcer		Upper gastrointestinal hemorrhages		Kidney insufficiency	
Drug	ROR	95% CI	ROR	95% CI	ROR	95% CI
Dipyrone	0.9	0.7–1.2	1.5	1.3–1.7	1.2	1.0–1.3
Diclofenac	14.3	13.8–14.9	9.1	8.8–9.3	2.3	2.2–2.4
Ibuprofen	8.3	7.8–8.7	8.2	8.0–8.5	2.4	2.3–2.5
Naproxen	10.7	10.2–11.1	7.9	7.7–8.1	1.2	1.1–1.3
Meloxicam	18.9	17.4–20.5	13.1	12.4–14	1.9	1.7–2.2
Celecoxib	6.9	6.5–7.3	5.9	5.7–6.1	2.1	2.0–2.2
Etoricoxib	7.2	6.4–8.2	5.8	5.2–6.4	1.9	1.7–2.2

CI = confidence interval, ROR = reporting odds ratio.
Source: Adapted from.[4]

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