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Cardiovascular toxicities associated with loperamide use

Loperamide-associated cardiovascular toxicities: a pharmacovigilance approach

We read with great interest the case report entitled 'Loperamide-induced cardiogenic syncope: a case report of a life-threatening presentation of an over-the-counter drug', recently published in the *European Heart Journal—Case Reports*.[1]

Loperamide is an opiate medication used worldwide for its antidiarrheal properties. However, as it is sold over-the-counter at low price and crosses the blood–brain barrier at high dose, it is also used for recreational purposes. In North America, it is referenced as the 'poor man's methadone' because the ingestion of hundreds of tablets of 2 mg loperamide can lead to significant neuropsychological effects. The US Food and Drug Administration released in 2016 a safety notice regarding a potential risk of loperamide-associated cardiovascular adverse drug reactions (CV-ADRs),[2] based on several case reports such as the one from Hegde *et al.*. On a mechanistical level, loperamide is a synthetic opioid structurally similar to methadone, which is known to prolong ventricular repolarization and induce ventricular arrhythmias. *In vitro* studies found that supratherapeutic circulating concentration of loperamide is an effective inhibitor of both NaV1.5 and potassium human ether-a-go-go related gene (hERG) cardiac ion channels,[3,4] with consequences on ventricular arrhythmogenesis and function.

We recently performed an analysis of the World Health Organization pharmacovigilance database (VigiBase), encompassing more than 22 million reports from more than 130 countries.[5] Association between loperamide and CV-ADRs was assessed using the information component (IC), an indicator value for disproportionate Bayesian reporting that compares observed and expected values to find associations between drugs and ADRs. From a total of 12 845 reports on loperamide-associated ADRs, we found that only 6.2% were CV-ADRs, but that half of those were life-threatening or fatal. Eighty percent of the reports originated from North America, and drug overdose or misuse was reported in 82% of the cases. Ventricular arrhythmia was the most frequently reported loperamide-associated CV-ADR ($n = 302$; IC = 4.1), followed by QT interval prolongation ($n = 277$; IC = 4.4). Although rare, the strongest association was found between loperamide and Brugada electrocardiogram (ECG) pattern ($n = 23$; IC = 5.1), as seen in the case report by Hegde *et al.*[1] Heart failure ($n = 25$; IC = 2.8) and cardiorespiratory arrest ($n = 192$; IC = 2) were also significantly over-reported. Importantly, as in the case report, ventricular arrhythmia was associated with previous QRS complex or QT interval prolongation in almost half of the reports.

Conclusion

The case report by Hegde *et al.* is an exhaustive illustration of every loperamide-associated CV-ADRs, as reported earlier in our pharmacovigilance analysis. Altogether, those data might increase awareness on a major public health issue, in order to encourage stronger loperamide regulations. Unexplained acute heart failure, ECG modifications, and ventricular arrhythmias, alone or in combination, must alert about a potential loperamide misuse.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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