

The Livertox® Categorization of Drug Hepatotoxic Potential. a Critical Appraisal

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Abstract Text

Background: A recent publication ranked hepatotoxic potential of drugs in LiverTox® website into 5 categories based on numbers of published drug-induced liver injury (DILI) case reports (A: ≥50 reports; B: 12-49; C: 4-11; D: 1-3; E: 0) (Björnsson & Hoofnagle, 2016). We aimed to validate this categorization using the Spanish DILI Registry database and published cohorts of DILI and drug-induced acute liver failure (ALF).

Methods: We classified 187 causative drugs from 829 cases enrolled in the Spanish DILI Registry into the 5 categories. We also collected information on causative drugs in adjudicated DILI cases from other established DILI registries and drug-induced ALF cases from previous publications (Suzuki et al 2010, Devarbhavi et al 2017, Reuben et al 2014, Russo et al 2004) and drugs that led to regulatory actions due to hepatotoxicity regardless of countries.

Results: Thirty-six drugs (19%) in the Spanish DILI Registry were classified as category A, 42 (22%) as B, 39 (21%) as C, 17 (9.1%) as D and 14 (7.5%) as E. Other 39 drugs (21%) (e.g. clomethiazole) were unclassified. The severity (defined by frequency of ALF and liver-related death/transplant) of DILI cases was compared between the A/B and C/D drugs (high vs low hepatotoxic potential). Cases caused by the C/D drugs presented higher severity with more ALF cases compared to cases caused by the A/B drugs (7% vs 3%, $p=0.02$). Orlistat (C) and sibutramine (D) were associated with ALF in the Spanish DILI Registry. Drugs that have been withdrawn from the market or led to hepatotoxicity safety warnings (e.g. nefazodone and dronedarone) were found in category C. On the contrary, amoxicillin-clavulanate (A) was not associated with ALF cases in the Spanish database although it was associated with the largest number of DILI cases. Some drugs included in categories A (e.g. thioguanine) and B (e.g. heparin) were not present in any published DILI cohorts.

Conclusion: Classification of drugs' hepatotoxic potential based on numbers of published case reports can be misleading as the numbers may not accurately capture all the elements of DILI risks (e.g. frequency, severity, and causality). DILI risk categorization utilizing more comprehensive information on liver safety regulatory measures, DILI frequencies and the presence/absence of drug-induced ALF cases could be developed by international collaborative efforts, providing a more inclusive, global drug list.

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Disclosures

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