



Overview on drug-induced liver injury in Brazil

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Abstract

Drug-induced liver injury (DILI) is an uncommon event in clinical practice, which makes knowing its true incidence difficult. Prospective, retrospective and registry-based studies are the most important methods to obtain epidemiological data on DILI. Latin America (LA) has a historical lack of prospective studies on this topic. New definitions and the creation of hepatotoxicity registries have significantly improved the epidemiological understanding of hepatic drug reactions in several regions of the world. The Latin American DILI network, referred to as LATINDILI, has been created in 2011, and recently published its own DILI recommendations describing the most relevant issues on the management of hepatotoxicity in general, and those based on findings from our own LA experience in particular. Although most of the registries do not carry out population-based studies, they may provide important data related to the prevalence of DILI. The joint work among researchers and the corresponding health and regulatory authorities should be stimulated due to the high impact that hepatotoxicity represents for public health.

Key Words: Hepatotoxicity; Drug-induced liver injury; Drug-induced liver injury registries; Herbs; Hepatitis

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Core Tip: Liver damage induced by drugs and herbs was historically underreported in Latin America until the advent of a Latin American Registry of Hepatotoxicity (LATINDILI), which progressively improved knowledge about the most frequently involved drugs inducing liver injury in this region. This article letter emphasizes on the value of being able to centralize cases linked to hepatotoxicity in a Latin American drug-induced liver injury network, and discuss the present and future advantages of this

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valuable tool, which should work along with regulatory entities to achieve a high impact on public health policy.

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TO THE EDITOR

I have read with great interest the systematic review by Becker *et al*[1], analyzing Drug-induced liver injury (DILI) publications in Brazil. The authors carried out a thorough search on the main bibliographic sources over a long period of time, including several decades.

Our group published more than a decade ago a review on DILI articles reported from Latin America (LA) up to 2010[2]. Only well documented case reports and series with a small number of patients could be identified. We found the same difficulties to Becker *et al*[1], since the definitions used for DILI were heterogeneous at that moment, and we did not find any prospective or retrospective studies carried out with a careful and detailed design that would have involved a large number of patients[2].

Many papers published before 2011 do not meet the criteria for DILI proposed by an expert meeting led by Aithal *et al*[3], which defined hepatotoxicity as (1) An ALT elevation ≥ 5 upper limit of normal (ULN), (2) An ALP elevation ≥ 2 ULN, or (3) An ALT elevation ≥ 3 ULN with a simultaneous elevation of total bilirubin concentration ≥ 2 ULN[3].

Of note, liver enzymes elevation below this cutoff are nowadays interpreted as adaptive phenomena. This is a very frequent asymptomatic biochemical issue observed at the beginning of drug intake, and it should not be initially interpreted as hepatotoxicity, because these biochemical parameters usually return to normal values despite continued drug consumption[4].

All DILI articles coming from LA should mention our LATINDILI registry, because, for the first time, we have a very well-structured hepatotoxicity network capable of recruiting patients associated with liver damage induced by drugs, thus being able to study the epidemiological behavior of medicaments and herbs used more often in our region[2]. This ambitious research project became a registry in 2011, and has already recruited more than 400 patients, with 8% of them corresponding to herbal-induced liver toxicity (HILI). Unfortunately, our registry was not mentioned by Becker *et al*[1]. However, its recognition would have helped them to establish better reference points for comparisons within the region and guidance on DILI distinction based on our operational criterion[2].

LATINDILI is a collaborative and interdisciplinary network aimed to (1) Establish the characteristics of DILI expression, search for risk factors, and evaluate the outcome; (2) Improve the instruments for causality assessment; (3) Increase knowledge on etiopathogenic mechanisms and identification of susceptible subjects; and (4) Help to develop diagnostic and predictive biomarkers in DILI[2].

Interestingly, the authors also stated that their research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and its integration with other DILI networks[1]. This is a very important point linked to one of the main objectives of DILI registries, which highlight the importance of working in close connection with regulatory and health authorities to strengthen both pharmacovigilance and the reporting cases of drug-induced liver reactions[5].

In addition, one of the most relevant objectives from our registry is to make physicians fully aware that hepatotoxicity is a distinct disease in which we have to improve its early diagnosis and management, and to be able to report these cases to the LATINDILI registry. If this feedback works in a regular and organized manner, it will allow clinicians to design and facilitate the carry out of multicenter clinical trials to assess the effect of new therapeutic agents with potential to induce idiosyncratic DILI [6].

Finally, LA already has its recommendation position paper for DILI management, which include our own data, and reinforces points exclusively inherent to LA, such as the differential diagnoses that should be made regarding the presence of tropical diseases, which can be mistakenly interpreted as DILI.

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