Back to basics for idiosyncratic drug-induced liver injury: Dose and metabolism make the poison

F. Ballet

Sanofi-aventis R&D, 91385 Chilly-Mazarin, France

Available online 23 June 2010

Summary  Two studies show that the risk of drug-induced liver injury (DILI) is increased when the daily dose of a drug given by oral route is higher than 10 mg per day and/or when the drug undergoes a significant hepatic metabolism. If confirmed, these data suggest that developing drugs with high potency and low hepatic metabolism will reduce the risk of idiosyncratic DILI in man.

© 2010 Elsevier Masson SAS. All rights reserved.

Résumé  Deux études montrent que le risque d’atteinte hépatique d’origine médicamenteuse est accru quand la dose par voie orale est supérieure à 1 mg/j et/ou quand le métabolisme hépatique du produit est important. Si ces données sont confirmées, elles suggèrent que le développement par l’industrie pharmaceutique de molécules à forte activité pharmacologique et/ou faiblement métabolisées par le foie devrait réduire le risque d’hépatotoxicité idiosyncraticque chez l’homme.

© 2010 Elsevier Masson SAS. Tous droits réservés.

Drug-induced liver injury (DILI) is a major cause of project discontinuation in the pharmaceutical industry and is the first cause of drug withdrawal from market for safety reasons. DILI is responsible for 50% of the cases of acute liver failure in the US, acetaminophen being the most frequent drug involved [1,2]. Recent examples of new drugs discontinued or withdrawn from market due to DILI include ximelagatran, a thrombin inhibitor from [3,4], troglitazone, an antidiabetic PPAR gamma agonist [5] or lumiracoxib, a selective COX-2 inhibitor [6].

In most cases, hepatotoxicity is not detected at the time of the animal toxicology studies systematically conducted before entering into the clinical studies [7]. Nothing is more frustrating than observing unexpected ALT elevations in the course of phase 1 or phase 2 clinical trials indicating that a new compound is associated with a risk of liver injury. Obviously, this does not always mean that the project will be discontinued. Liver injury may be observed in the early clinical trials at doses higher than the targeted therapeutic dose. Also, in some cases, the expected or observed benefit may mitigate the risk e.g. in oncology indications. However, in many cases, this will lead to project discontinuation and...
Dose and metabolism make the poison

will cost to the company hundreds of millions of dollars at best but eventually up to more than one billion dollars if detected at a late (i.e., phase 3) development phase or following launch.

There have been many attempts to detect the hepatotoxic potential of new molecules at an early stage of development. Three main approaches have been developed:

- "In silico" (quantitative) structure activity relationship (QSAR) systems (also called "structure-alert" approaches) correlate structural descriptors of compounds with potential toxicity [8];
- in vitro detection of reactive metabolites which may form protein adducts and can trigger toxicity [9];
- screening for cytotoxicity in human hepatocytes in culture [10].

All have major limitations with a high incidence of false positives and/or false negatives and cannot be used to screen systematically new molecules at an early "lead identification" stage of pharmaceutical development. This is clearly an area where new concepts and new approaches are urgently needed.

DILI is usually a rare event with less than a few percent of patients showing ALT elevations during the course of clinical development. Accordingly, a drug showing remarkable activity may be stopped because of "idiosyncratic" toxicity occurring in a very small number of patients. This is another major frustration for the clinicians developing a new active drug. Identification of susceptibility genes might enable to identify at-risk individuals and therefore should avoid withdrawal of otherwise useful drugs. However, so far for DILI, there have been very few examples where this approach has been successful and in particular has demonstrated "clinical utility" [11].

Lammert and his colleagues should be praised for having revisited some basic underlying assumptions regarding hepatotoxicity with the idea of identifying predictors that could be used in pharmaceutical R&D for lead selection and/or optimization.

In a first study [12], they examined the relationship between the oral daily dose of top 200 brand and 200 generic medications by prescription volume in the US and the risk of idiosyncratic DILI. Compounds were stratified into less or equal to 10 mg per day, 11 to 49 mg per day and greater or equal to 50 mg per day. They were able to show a statistically significant relationship between the oral daily dose and reports of liver failure, liver transplantation and death caused by DILI. Seventeen percent of compounds in the less or equal to 10 mg per day group were reported to cause liver failure versus 32% in the greater or equal to 50 mg per day group. No compound in the less or equal to 10 mg per day group caused liver transplantation in comparison with 14% in the greater or equal to 50 mg per day group. A trend was also observed in the relationship between daily dose and reports of ALT greater than 3XULN (the usual threshold for defining drug-induced hepatocellular injury) and jaundice but they did not reach statistical significance.

They also looked at all reports of suspected DILI received by the Swedish Adverse Drug Advisory Committee since 1970 (n = 598 eligible cases) and were able to show that 77% belonged to the greater or equal to 50 mg per day group whereas only 9% belonged to the less or equal to 10 mg per day group. Only 2% died or underwent liver transplantation in the less or equal to 10 mg per day group as compared to 13.2% in the greater or equal to 50 mg per day group.

Overall, these data show that the oral daily dose is a major determinant of idiosyncratic DILI.

That toxicity is linked to the dose administered is a key toxicology principle known since Paracelsus in the Renaissance: "the dose makes the poison". However, it is traditionally thought that this principle does not apply to idiosyncratic toxicity and particularly to immune-mediated DILI. Uetrecht was the first in 2001 to point out that "it is difficult to think of any clear example of drug given at a daily dose of 10 mg or less that is associated with a high incidence of idiosyncratic drug reaction" [13]. The study by Lammert and his colleagues confirms that the risk of DILI, and particularly severe DILI, is very low when the daily dose of a drug given by oral route is below 10 mg. A practical consequence of this simple rule for drug discovery is that developing highly potent drugs, active at very low concentrations/doses, should be an efficient way to reduce the risk of idiosyncratic DILI in man.

Formation of reactive metabolites in the liver which may potentially bind covalently to cellular proteins is considered to play an important role in the pathogenesis of DILI. If this is true, compounds with significant hepatic metabolism should be associated with a higher risk of DILI than those without it.

This hypothesis was tested by Lammert and his colleagues in another study [14] where they examined the relationship between the rate of hepatic metabolism and the risk of DILI for the 207 most widely prescribed oral medication in the US.

Compared with compounds with lesser hepatic metabolism, compounds belonging to the significant hepatic metabolism group had significantly higher frequency of ALT greater or equal to 3ULN (35% versus 11%), liver failure (28% versus 9%), and fatal DILI (23% versus 4%), but not jaundice (46% versus 35%) or liver transplantation (9% versus 2%).

Twelve compounds with no hepatic metabolism had no reports of liver failure, liver transplantation, or fatal DILI.

When the relationship between hepatic adverse events and combination of hepatic metabolism and daily dose was examined, compounds with both significant hepatic metabolism and daily dose greater than 50 mg (n = 50) were significantly more hepatotoxic than compounds belonging to other groups.

Finally, when compared with medications without biliary excretion, compounds with biliary excretion (n = 50) had significantly higher frequency of jaundice (74% versus 40%).

As underlined by the authors, this study has several methodological drawbacks. In particular, it is based on a selective group of marketed compounds: the 207 most prescribed drugs. It would be interesting to see if these general rules are confirmed in a larger number of marketed compounds and also when including compounds stopped during drug development because of DILI. Indeed, there is a huge amount of unpublished data available in the pharmaceutical industry that could be used to confirm these interesting observations. Also, the cut-off value of 50% which was chosen to define significant hepatic metabolism was selected...
arbitrarily and in several cases was difficult to determine properly-based on available data.

The observation that compounds with biliary excretion were more often associated with jaundice is intriguing and suggest that mechanisms of liver injury may be specifically linked to the excretion of the drug into bile (e.g. transporter inhibition and/or cellular injury due to high concentrations of toxic metabolites in bile).

Finally, if dose and metabolism are important risk factors for drugs administered by oral route, this relationship should be weaker with compounds administered by the IV route because of lack of first-pass effect.

In conclusion, these two studies show that the risk of DILI is increased when the daily dose of a drug given by oral route is higher than 10 mg per day and when the drug undergoes a significant hepatic metabolism. It is therefore tempting to speculate that developing drugs with high potency and low hepatic metabolism would reduce the risk of idiosyncratic DILI in man. Clearly these studies warrant confirmation on a larger number of compounds including those stopped by pharmaceutical industry during drug development and also on hepatotoxic drugs administered by the IV route.

Idiosyncrasy still remains a black box. However, we now know at least that basic toxicology rules applies to this mysterious and very damaging effect: dose and metabolism makes the poison.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

References


