Adaptation: A Clinical Conundrum

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Drug-Induced Liver Injury, Are We Ready to Look?
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The Dilemma

A major quandary for a consultant asked to assess newly recognized elevated liver-related serum enzyme values in a person taking a drug is not only whether the drug is responsible for the abnormalities but also whether the raised enzymes are signals for incipient serious liver disease or whether there will be adaptation to the drug
Definition: Adaptation

Adaptation to a drug refers to resolution of increased serum aminotransferase levels attributed to a drug while continuing its use at the same dose. It has been recognized most commonly when the abnormality consists of raised serum enzymes only, but has also rarely been noted among those who develop raised serum enzymes as well as jaundice.
Evidence of Adaptation Among Cases of DILI with Raised Serum Enzymes and Bilirubin*

201 tuberculin-positive men begun on INH prophylaxis

Blood samples drawn prior to, monthly for 1 year during, and following treatment, and stored frozen

At end of treatment, AST levels were measured

3 men developed AST levels >15 x ULN and bilirubin >3 mg/dL.

Despite continued INH treatment, abnormalities resolved

One Year on INH: 3 "Hy's Cases"

Mitchell, et al., 1975

- AST, TBL: log10 x UN
- red = AST; green = TBL

Graph showing the progression of AST and TBL levels over weeks with peak values at 22.1x, 14.6x, 4.3x, 2.8x, and 3.3x.
Another concept is that of drug tolerance which refers to resistance to liver injury induced by administering repeated, incrementally increasing doses of the drug, as has been shown for acetaminophen*

Drugs Found to be Associated With Adaptation

Drugs that have been shown to demonstrate adaptation include isoniazid, tacrine, troglitazone, the statins, ximelagatran, and heparin. It is probable, however, that adaptation occurs with many other, if not most, drugs that are capable of injuring the liver.
Adaptation Among Cases of Liver Dysfunction Not Associated with Jaundice

Tacrine

49% of patients in clinical trials for tacrine developed at least 1 abnormal ALT value, 25% of whom developed values >3 times ULN, and 2% developed values >20 x ULN

145 patients with values >3 x ULN who discontinued tacrine, following which the values returned to normal, were later re-challenged with the drug. In 88%, treatment resumption did not lead to re-development of liver injury

Adaptation Among Cases of Liver Dysfunction Not Associated with Jaundice

Ximelagatran

In a clinical trial involving 6931 subjects treated with Ximelagatrin, 7.9% developed ALT values >3 x ULN and 0.5% developed ALT values >3 x ULN, bilirubin >3 mg/dL.

Treatment was discontinued in approximately ½ who developed increase enzyme levels, but was continued in the other ½.

ALT values normalized in 87% of those discontinued but also in 89% whose treatment continued.

Liver-Related Responses To Administered Drugs

Three liver responses to drug administration have been suggested:* 

Most people exposed to a new drug show no injury - Tolerators

Some people show transient injury but adapt - Adaptors

A few fail to adapt and show serious toxicity - Susceptibles

*Senior J: FDA/CDE-AASLD-PhRMA presentation, 2005
Dili, a rare event, can present as:

- Raised serum enzymes only
- Raised serum enzymes and bilirubin (Hy’s cases)
- Fulminant hepatic failure

The former presentation predominates and is the category within which adaptation occurs most often.
Potential Manifestations of Drug-Induced Liver Injury

- Fulminant hepatitis
- Increased enzymes and bilirubin, “Hy’s law” cases
- Increased serum enzymes only (frequency of adaptation unknown)
A true frequency of adaptation is unknown, in part because it may occur silently or may not be considered because the entity is unfamiliar to most clinicians. More commonly it is because in both pre-marketing controlled clinical trials and general practice, the drug is discontinued when aminotransferase levels exceed 5-8 x ULN, fearing evolution to serious liver injury. While not inappropriate, adaptation has occurred even when enzymes have exceeded 1,000 IU/L.
Growing Recognition of Adaptation

Knowledge that adaptation can occur is increasing, examples being the statins and isoniazid. In both instances, upward of 90% of those who develop raised serum enzymes will adapt, only a small fraction developing overt serious liver disease.

Accordingly, an acceptable strategy if ALT/AST levels are not markedly elevated (eg. >10 x ULN) is to continue treatment but with frequent enzyme monitoring, discontinuing the drug if the enzymes continue to rise or jaundice develops.
Concluding Thoughts Regarding Adaptation

The frequency of adaptation among persons who develop dili, whether as raised serum enzymes only or together with jaundice, is not fully known. An accurate frequency of adaptation will not be realized until a diagnostic test for drug-induced liver injury is found and appropriate surveillance conducted.

It is highly likely that, like the fact that there are differences in the frequency of overt liver injury among different drugs, the frequency of adaptation, too, will differ among the drugs.
Available data suggest that not all drugs need to be discontinued when abnormal enzymes attributed to dili are found. However, there is as yet no agreed-upon clinical scenario and enzyme level at which drug continuation is considered acceptable nor what limits should be set with regard to discontinuing the drug so as to reduce or prevent the likelihood of potentially progressive dili.
Concluding Thoughts Regarding Adaptation (contd)

Greater insight is needed in regard to what the reasons are for drug susceptibility to liver injury and specifically why exposed persons differ in their liver injury response, some developing serum enzyme elevations only, some developing jaundice in addition, and some proceeding to fulminant liver disease.
Determining the true frequency of adaptation rests ultimately with increasing awareness of its existence so as to more widely alert clinicians to the phenomenon, and to undertake appropriate surveillance studies designed specifically to seek its frequency and define how best to respond and deal with it. An improved knowledge of adaptation should help to curtail unnecessary drug withdrawal.