Does Elevated AP Preclude Hy’s Law

Robert J. Temple, MD
Deputy Center Director for Clinical Science
FDA/Center for Drug Evaluation and Research

Drug Induced Liver Injury
March 24, 2010
What Do We Use Hy’s Law For?

We use it during drug development to determine whether there is evidence that a drug could cause devastating (leading to death or transplant) liver injury.

Premises:
1. We do not expect to see any cases of devastating liver injury in a typical drug development database (n = 1-3000).

2. Hy’s Law serves as a surrogate endpoint indicating the potential to cause such devastating injury because pure hepatocellular injury leading to jaundice (Hy) or “near jaundice” (bilirubin > 2 times ULN, FDA modification) has a substantial probability (> 10%) of causing transplant or death in the individual with that injury.
Premises (cont)

3. The reason Hy’s Law works is that it identifies drugs that cause major hepatocellular injury, perhaps 50% of liver mass, and it is such drugs that can be lethal. This level of damage is needed because the liver has great regenerative capacity and can re-grow after lesser injury, so that finding this extent of injury is the critical observation.

Because of the liver’s excess of bilirubin excretion capacity you need a great deal of damage to decrease excretion capacity by 50% and raise bilirubin to 2X ULN so that such a doubling describes a very worrisome injury. Such a rise in bilirubin from a pure hepatocellular injury therefore:

a. Shows very great hepatocellular damage
b. Identifies drugs that raise major concerns
4. If the increased bilirubin results from some cause other than hepatocellular injury, it does not have the same implications and it cannot be interpreted as a Hy’s Law case because it would not show major hepatocellular injury.

Increased bilirubin could be unrelated to massive liver cell damage. A gallstone or intrahepatic cholestasis could give elevated bilirubin with no little or no liver cell damage.
Hy’s Law and Obstruction

What about a combination of hepatocellular injury (elevated AT) and evidence of obstruction (elevated AP), with elevated bilirubin?

In that case we do not think you can conclude that the elevated bilirubin has resulted from the massive damage that identifies the drug as one with the ability to cause death and need for transplantation.
Uncertainties

Does a small rise in AP along with evidence of substantial hepatocellular damage evidenced by substantial AT rise raise that concern. Probably not, especially if the AP rise occurs well after the initial AT evidence of injury. We know extensive cellular change can sometimes lead to some degree of local obstruction. But more than that makes us uncertain.

Remember, a couple of Hy’s Law cases, perhaps even one is generally a fatal injury for a drug (dilevalol, tasosartan) or perhaps should have been (bromfenac), so you want to be very sure the cases are real. Of course, one would also look at the magnitude of AT elevations, etc.
What We Do Not Mean

Marked AT evidence of injury with elevated AP and bilirubin may not be benign and we don’t propose ignoring it.

BUT it is not Hy’s Law

In addition, examining post-marketing cases may bring different considerations, especially if one already knows that a drug is capable of severe hepatotoxicity.