The Effect of Hepatic Disease on Drug Interactions

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This column has often discussed the role of various modifiers on the magnitude of potential drug interactions. We have reviewed the effects of multiple precipitant drugs on a single object drug, the importance of cytochrome genotypes on the response of object drugs to precipitant drugs, and the impact of some disease states on apparent drug interactions. With many potential drug interactions based on precipitant drug alteration of cytochrome P (CYP) 450 activity, the question of how hepatic disease might influence these interactions would seem to be important.

Hepatic Disease and Interactions with CYP1A2

The effect of fluvoxamine, a CYP1A2 inhibitor, on the metabolism of lidocaine, a CYP1A2 substrate, in healthy subjects and patients with varying grades of cirrhosis has been reported.[1] Each study participant received either placebo or fluvoxamine 50 mg for 2 days and then 100 mg for the next 4 days. On day 6, each received an intravenous 1-mg/kg dose of lidocaine over 1 minute. The lidocaine was given 2 hours after the dose of placebo or fluvoxamine. Fluvoxamine plasma concentrations were increased nearly 3-fold in the patients with severe (Child class C) cirrhosis, compared with the healthy subjects. Among patients administered placebo, lidocaine clearance was reduced by 18% in those patients with mild (Child class A) cirrhosis and by 65% in those with severe cirrhosis, compared with healthy participants. With fluvoxamine coadministration, lidocaine clearance decreased by 60%, 44%, and 9% in the healthy subjects and mild and severe cirrhosis patients, respectively.

Thus, the effect of liver disease on lidocaine metabolism went up with increasing severity of cirrhosis, whereas the effect of the inhibitor, fluvoxamine, was diminished as the cirrhosis worsened. This reduction in response to fluvoxamine occurred in spite of the increased plasma concentration of fluvoxamine.

Hepatic Disease and Interactions with CYP3A4

The metabolism of quinine, a CYP3A4 substrate, was determined in 10 healthy subjects and 20 patients with cirrhosis (Child class A or C) during coadministration with placebo or erythromycin 600 mg 3 times daily for 4 days.[2] A single 500-mg dose of quinine was administered on day 2 of the erythromycin. The clearance of quinine during placebo administration was reduced by 15% and 28% in patients with Child class A and C cirrhosis, respectively, compared with the healthy subjects. The administration of erythromycin reduced the clearance of quinine by 33%, 30%, and increased it by 7% (nonsignificant) in the healthy subjects, Child class A, and Child class C patients, respectively. This is a similar trend as noted with CYP1A2 inhibition, although the true magnitude of the effect of erythromycin on quinine may be larger than that reported, because the duration of erythromycin administration was limited. It is noteworthy that erythromycin-induced protein binding displacement of quinine was increased in patients with more severe cirrhosis, perhaps due to lower protein concentrations associated with hepatic disease.

How Hepatic Disease Affects Metabolic Drug Interactions

The reduced magnitude of effect of CYP450 inhibitors in the presence of hepatic disease appears to mimic the reduced magnitude observed in patients who are genetically poor metabolizers. For example, a genetically poor metabolizer of CYP2D6 will have minimal response to an inhibitor of CYP2D6, because they do not have much CYP2D6 enzyme to inhibit.[3] It is known that the hepatic expression of CYP enzymes can be decreased in patients with liver disease. More recently, CYP450 activity in the small intestine was noted to be reduced in patients with cirrhosis.[4]

Hepatic disease, particularly cirrhosis, results in blood shunting around hepatocytes. This has the effect of reducing the delivery of object and precipitant drugs to metabolizing enzymes. In addition, cirrhosis may alter the ability of hepatocytes to uptake drug, perhaps via active transporters, thus reducing the concentration of an inhibitor in the hepatocyte.

Conclusion

Although preliminary studies suggest a reduced magnitude of enzyme inhibition in patients with liver disease, keep in mind that these patients will have reduced object drug clearance. These patients require careful monitoring when receiving drugs eliminated by hepatic metabolism, regardless of the presence of an interacting drug. ■