Notice of correction 1/8/2013: In Table 1, point 2 now correctly cites reference 22.

Drugs That Escape Hepatic Metabolism

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In this column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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- In certain patients, hepatic metabolism of drugs is slower or more rapid than usual; consequences include an increased risk of adverse effects or diminished treatment efficacy.
- There are at least 5 important situations in which the hepatic metabolism of drugs is altered. These situations are briefly explained. If clinicians encounter such situations, they will need to make appropriate dose adjustments, or they can prescribe drugs that are not metabolized in the liver.
- Important neuropsychopharmacologic agents that are not metabolized in the liver are presented and briefly discussed.

In a recent case report,[1] Paulzen and colleagues discussed the challenges they faced in treating a woman with psychotic depression who was found to be a cytochrome P450 (CYP) 2D6 ultrarapid metabolizer. She underwent many medication trials and eventually improved only after receiving sulpiride (300 mg/d), the action of which is terminated by renal excretion.

Patients who are abnormal metabolizers, who have liver disease, or who are taking drugs that induce or inhibit CYP enzymes necessitate an awareness of the few drugs in neuropsychopharmacology that are not metabolized by the CYP enzymes in the liver. Knowledge of possible treatment strategies, which may include dose adjustment or selection of drugs not metabolized by CYP enzymes in the liver, can be important in 5 situations in which hepatic metabolism of drugs differs from that expected (Table 1).

Adjusting the Dose

A knowledge of pharmacokinetics and drug interactions may guide dose adjustments in some situations; for example, low rather than standard doses of clomipramine are advisable if augmentation is desired in a patient who is already receiving fluoxetine (a CYP enzyme inhibitor).[6]

Selecting a Drug Not Metabolized by CYP Enzymes

As an alternative to dose adjustment, clinicians can prescribe drugs that are not metabolized or are only minimally metabolized by the CYP enzymes. A list of such drugs is presented in Table 2.

How *Much* Is the Drug Metabolized by the Liver?

It helps to know how much a drug is metabolized, if it is metabolized by the liver. For example, only about 20% of topiramate is metabolized in the liver; the remaining 80% is excreted unchanged. However, when enzyme-inducing drugs such as phenytoin or carbamazepine are administered, up to 50% of topiramate may be metabolized.[20] Thus, topiramate may be a useful drug in certain, but not all, of the situations in Table 1.

Metabolism via Glucuronidation

Lorazepam and lamotrigine are possible candidates in many of the situations listed in Table 1. Lorazepam is metabolized by glucuronidation, but, because this pathway is relatively spared in liver disease,[9] lorazepam is safer than diazepam or chlordiazepoxide in alcoholic patients with hepatic impairment.[21] Lamotrigine is also metabolized predominantly by glucuronidation. Like lorazepam, it is vulnerable to factors that induce or impair glucuronidation.[18]

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Table 1. Five Clinical Situations in Which It Is Useful to Know Which Drugs Are Not Metabolized by CYP Enzymes in the Liver

1. **The patient is an ultrarapid metabolizer.** (Represents 0%–30% of the population, depending on geographical origin, in the case of CYP2D6.[2]) Such patients will not respond to standard doses of drugs metabolized by the enzyme in question
2. **The patient is a poor metabolizer.** (Represents 0%–14% of the population, depending on geographical origin, in the case of CYP2D6.[22]) Such patients are at increased risk of adverse effects with standard doses of drugs metabolized by the enzyme in question
3. **The patient is taking CYP enzyme inducers.** These medications (eg, rifampin, carbamazepine[3,4]) can lower drug levels and hence compromise the efficacy of drugs metabolized by the induced enzymes
4. **The patient is taking CYP enzyme inhibitors.** These medications (eg, fluoxetine, paroxetine[2]) can raise drug levels and hence increase the adverse effects of drugs metabolized by the inhibited enzymes
5. **The patient has liver disease.** Diminished CYP metabolism can result in higher drug levels and greater adverse effects of drugs metabolized by the liver

Table 2. Some Neuropsychopharmacologic Agents That Are Not Metabolized or Are Minimally Metabolized by CYP Enzymes in the Liver

Anxiolytics
Pregabalin[8]
Lorazepam[9]
Antidepressants
Milnacipran[10]
Desvenlafaxine[11]
Low doses of amisulpride,[12,13] sulpiride,[14] and levosulpiride[15]
Antipsychotics
Paliperidone[13]
High doses of amisulpride,[12,13] sulpiride,[14] and levosulpiride[15]
Anticonvulsants and mood stabilizers
Gabapentin[8]
Levetiracetam[16]
Lithium[17]
Lamotrigine[18]
Dementia treatment
Memantine[19]

Selecting a Drug With an Active Metabolite Not Further Metabolized by the Liver

Finally, drugs that have active metabolites that are not further metabolized by the liver can be appropriate in patients who are rapid metabolizers and in those who are receiving CYP enzyme inducers. For example, risperidone (which is metabolized to 9-hydroxyrisperidone, or paliperidone)[13] can be considered rather than olanzapine in a schizophrenia patient who is a heavy smoker.[7] (For more on how smoking affects metabolism of antipsychotics, see my June column on the topic.) Another example (which could have benefited the patient described by Paulzen et al[1]) is venlafaxine; this antidepressant is metabolized to desvenlafaxine.[11] The actions of paliperidone and desvenlafaxine are terminated principally by renal excretion.[11,13]

Conclusion

The hepatic metabolism of most neuropsychopharmacologic agents may be altered in various situations, such as when patients also receive drugs that influence the CYP enzymes responsible for drug metabolism or when they smoke or have liver disease. Consequences of altered drug metabolism include compromised medication efficacy or increased medication adverse effects. Corrective measures include appropriate dose adjustments or the use of medications that are not metabolized or are minimally metabolized by the CYP enzymes in the liver.

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