Safely Using Quetiapine

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Quetiapine is an atypical antipsychotic drug and has become one of the most commonly used psychiatric medications in the United States. It tends to be better tolerated than older antipsychotic drugs and is less likely to cause extrapyramidal symptoms. It is used not only for psychoses, but also for bipolar disorder and other psychiatric diseases. To maximize the safety of quetiapine therapy, it is important to realize that it is metabolized by cytochrome P450 3A4 (CYP3A4), and its serum concentrations can be affected by CYP3A4 inhibitors or inducers.

CYP3A4 Inhibitors

Quetiapine is a CYP3A4 substrate, and CYP3A4 inhibitors increase quetiapine plasma concentrations. In one study, healthy subjects received quetiapine before and after ketoconazole 200 mg/day for 4 days. Ketoconazole increased quetiapine area under the plasma concentration-time curve by over 522%.[1] Because quetiapine was given as a single dose, adverse effects were not expected, but multiple doses of both drugs are likely to increase the risk of quetiapine toxicity.

A 32-year-old man stabilized on quetiapine had a marked increase in quetiapine plasma concentrations (about 7 times the recommended levels) soon after starting clarithromycin.[2] He developed reduced consciousness and respiratory depression requiring intensive surveillance.

The CYP3A4 inhibitors in the Table are expected to increase quetiapine plasma concentrations. Keep in mind that the magnitude of interaction with quetiapine will vary depending on the potency and dose of the CYP3A4 inhibitor, as well as the inherent susceptibility of the patient. Quetiapine toxicity can result in symptoms such as sedation, mental confusion, acute hypotension, syncope, dizziness, and respiratory depression.

Enzyme Inducers

Enzyme inducers can produce marked reductions in quetiapine plasma concentrations that may result in loss of quetiapine efficacy. For example, both carbamazepine and phenytoin have been shown to markedly reduce quetiapine plasma concentrations.[3-5] Enzyme inducers that are likely to reduce quetiapine plasma concentrations include barbiturates, efavirenz, nafcillin, nevirapine, oxcarbazepine, primidone, rifabutin, rifampin, rifapentine, and St. John's wort.

As with the CYP3A4 inhibitors, the magnitude of the interaction of quetiapine with enzyme inducers varies depending on the situation. Nonetheless, the effect is often large and may result in undetectable plasma concentrations of quetiapine. Thus, in some cases, it may be necessary to use an alternative to either the enzyme inducer or the quetiapine.

Other Quetiapine Interactions

Clozapine

Clozapine was associated with substantial increases in quetiapine plasma concentrations in one study, but the mechanism for this effect and the clinical importance is not clear. Be alert for quetiapine toxicity.

Valproate

Several studies have addressed a possible interaction between quetiapine and valproate, and it appears that valproate may somewhat increase quetiapine plasma concentrations.[6] Other evidence suggests that the combined use of quetiapine and valproate may increase the risk of bone marrow suppression.[7]

Table

CYP3A4 Inhibitors

• Amiodarone	• Imatinib
• Amprenavir	• Indinavir
• Aprepitant	• Itraconazole
• Atazanavir	• Ketoconazole
• Clarithromycin	• Nelfinavir
• Conivaptan	• Posaconazole
• Cyclosporine	• Quinupristin-dalfopristin
• Darunavir	• Ritonavir
• Delavirdine	• Saquinavir
• Diltiazem	• Tamoxifen
• Erythromycin	• Telithromycin
• Fluconazole	• Verapamil
• Fluvoxamine	• Voriconazole

Methadone

In a study of patients stabilized on methadone, the addition of quetiapine produced a modest increase in the active (R)-methadone plasma concentrations.[8] Although the effect was not large, there was considerable variability among the patients; it is possible that some patients would be adversely affected.

Recommendations

- In patients on quetiapine, monitor for quetiapine toxicity if CYP3A4 inhibitors are started and for lack of quetiapine efficacy if enzyme inducers are started.
- If a patient has been stabilized on therapy with quetiapine plus a CYP3A4 inhibitor or inducer, monitor for altered quetiapine effect if the inhibitor or inducer is stopped or reduced in dosage. ■