

Caffeine and Clozapine

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Fortunately for those of us who love coffee, the good news just keeps on coming: reports suggest that coffee might reduce the risk of Parkinson's disease, gallstones, diabetes, Alzheimer's disease, and cancer. If these benefits turn out to be true, the fact that coffee helps get our synapses firing in the morning will just be icing on the cake.

Another positive aspect of coffee is that caffeine has relatively few drug interactions. A recent case report, however, highlights an interaction that was first described 2 decades ago: caffeine and clozapine. The recent case involved a 19-year-old schizophrenic woman on long-term clozapine therapy who developed unexpected clozapine toxicosis on two occasions.¹ It turned out that she had been drinking 6 caffeine-containing cola drinks per day, a practice she was reluctant to divulge. Stopping the cola intake was followed by a substantial reduction in clozapine concentrations (a positive dechallenge).

It appears that caffeine inhibits the metabolism of clozapine.

Previous Reports

In the mid-1990s, two cases of clozapine toxicosis possibly due to caffeine were reported.^{2,3} In both cases there was a positive dechallenge, suggesting that the caffeine may have caused the increased clozapine plasma concentrations. In a subsequent study of 7 patients on clozapine who drank caffeinated beverages, stopping caffeine for 5 days resulted in a 47% reduction in clozapine plasma concentrations.⁴ After reintroduction of the caffeine for 2 weeks, the clozapine concentrations returned to the original values.

Pharmacokinetic studies have produced similar results. In a randomized crossover study, 12 healthy subjects were given a single oral 12.5-mg dose of clozapine with and without concomitant caffeine (400 to 1000 mg/day). Caffeine modestly increased clozapine plasma concentrations, but the range was from a 14% decrease to a 97% increase.⁵ Similar results were obtained in another randomized crossover study of hospitalized patients on long-term clozapine given caffeinated versus decaffeinated coffee, again with large variability in effect.⁶

Mechanism

It appears that caffeine inhibits the metabolism of clozapine, probably by inhibition of CYP1A2. Given the complex pharmacokinetics of clozapine, however, it is possible that other mechanisms are involved in addition to (or instead of) inhibition of CYP1A2.

Variability

Clozapine plasma concentrations are known to vary dramatically from person to person even in the absence of caffeine, most likely due to the myriad factors that can affect clozapine pharmacokinetics.⁷ Although clozapine is metabolized pri-

marily by CYP1A2, it also appears to undergo metabolism by CYP3A isozymes and possibly other CYP isozymes, such as CYP2C19, and transporters, such as P-glycoprotein (ABCB1).

This opens the possibility for several genetic influences on clozapine disposition, as well as effects by inducers that can increase the activity of these enzymes and transporters. Smoking, for example, has been shown to substantially reduce clozapine concentrations, probably by increasing the activity of CYP1A2. Other inducers, such as carbamazepine, may also reduce clozapine concentrations. In keeping with this high variability, the effects of caffeine on clozapine have been found to vary dramatically from person to person.

Recommendations

It does not appear necessary for patients on clozapine to avoid caffeine, but caffeine intake should be considered as one of the many factors that can influence clozapine plasma concentrations. This interaction may be fairly common because patients on clozapine may be consuming caffeinated coffee, cola drinks, or other caffeinated drinks to offset the sedative effects of clozapine. As much as possible, patients on clozapine should avoid wide fluctuations in their caffeine intake, and one should consider changes in caffeine intake in patients on clozapine who develop unexpected clozapine toxicosis or lack of clozapine response. ■

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