Piperine Drug Interactions

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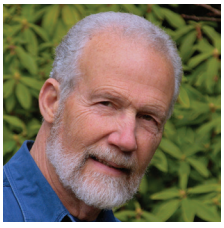

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PIPERINE IS A MAJOR ALKALOID FOUND IN BLACK PEPPER (PIPER NIGRUM), and the alkaloid is used as an herbal product for its purported anti-inflammatory, antioxidant, and antitumor properties. The results of 2 recent reports suggest that piperine may increase plasma concentrations of carbamazepine and diclofenac through inhibition of CYP3A4 and CYP2C9, respectively.

CARBAMAZEPINE

In 12 healthy subjects, a single dose of carbamazepine 200 mg was given before and after administration of piperine 20 mg/d for 10 days.[1] Carbamazepine area under the curve (AUC) increased by 48% after administration of piperine. The study was not double-blind and did not use a randomized, crossover method, but the results are consistent with previous studies suggesting that piperine inhibits CYP3A4. For example, in one study, 10 patients receiving carbamazepine monotherapy for seizures were given a single 20-mg dose of piperine.[2] Even with only 1 dose of piperine, a small increase in carbamazepine AUC was found. In another study, 20 healthy subjects were given oral midazolam 10 mg with and without pretreatment with piperine 15 mg/d for 3 days in a placebo-controlled crossover study.[3] Piperine prolonged midazolam half-life and increased the degree and duration of midazolam-induced sedation.

Although these studies had limitations, taken together they suggest that piperine inhibits CYP3A4 and may increase serum concentrations of CYP3A4 substrates other than carbamazepine or midazolam.

DICLOFENAC

Twelve healthy subjects received a single 100-mg dose of diclofenac before and after administration of piperine 20 mg/d for 10 days.4 With piperine pretreatment, diclofenac AUC increased by 68%, and diclofenac half-life increased by 34%. The study was not double-blind and did not use a randomized, crossover method, but it does suggest that piperine inhibits CYP2C9, the primary isozyme involved in the metabolism of diclofenac. Also, the results are consistent with previous studies looking at the effect of piperine on phenytoin pharmacokinetics. In healthy subjects and in patients with epilepsy, the administration of piperine modestly increased phenytoin plasma concentrations.[5,6] Both of the phenytoin studies had limitations; the healthy-subjects study had only 5 subjects, and the patient study involved only a single dose of piperine. Nonetheless, the data suggest that piperine at 20 mg/d can inhibit CYP2C9.

OTHER DRUGS

In another recent study, 12 healthy subjects took a single 120-mg dose of fexofenadine before and after administration of piperine 20 mg/d for 10 days.[7] With piperine pretreatment, fexofenadine AUC increased by 68%, but the fexofenadine half-life was not significantly affected. As with some of the studies cited above, it was not double-blind and did not use a randomized, crossover method. The authors propose that piperine inhibits P-glycoprotein (PGP), thus increasing fexofenadine bioavailability. Previous evidence from in vitro and animal studies does suggest that piperine inhibits PGP, but more clinical evidence is needed to determine if piperine interacts with other PGP substrates with a greater risk of toxicity, such as digoxin. The possibility of PGP inhibition by piperine also raises the issue of piperine simultaneously inhibiting PGP and CYP3A4. Many drugs are substrates for PGP and CYP3A4, and drugs that inhibit both tend to have a greater effect on such substrates.

Preliminary evidence suggests that piperine also increases serum concentrations of chlorzoxazone, propranolol and theophylline.[8,9]

SUMMARY

The results of clinical studies suggest that piperine (usually in doses of 20 mg/day) can inhibit CYP3A4, CYP2C9, and PGP, resulting in moderate increases in plasma concentrations of CYP3A4 substrates (carbamazepine, midazolam, and possibly others), CYP2C9 substrates (diclofenac, phenytoin, and possibly warfarin and others), and PGP (fexofenadine and possibly digoxin and others). Piperine is found in a number of herbal products, but it is not clear whether dietary use of black pepper would result in clinically significant drug interactions. Individuals who regularly use large amounts black pepper in their diet should at least consider the possibility of such interactions because heavy users may reach a similar amount of piperine as used in the drug interaction studies.[7] ◆

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