Loperamide

Danger of Elevated Plasma Concentrations

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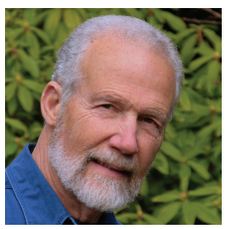

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LOPERAMIDE (IMODIUM A-D) HAS BEEN AVAILABLE OVER THE COUNTER FOR TREATING DIARRHEA FOR MANY YEARS. It has several pharmacologic effects, including binding to mu-opioid receptors. The opioid-receptor agonist activity is responsible for its motility-slowing, constipating response.

Loperamide has proved to be remarkably safe when used at recommended doses.[1] Recently, perhaps as a result of efforts to reduce access to opiates, loperamide has been abused by opiate addicts to ward off the symptoms of withdrawal. This has prompted warnings from the FDA regarding the safety of loperamide, particularly at high plasma concentrations.

Loperamide is a unique opioid in that it usually only demonstrates peripheral activity, slowing gastrointestinal motility without the central nervous system (CNS) effects seen with other opiates. This selective response is due to 2 properties of loperamide. First, it has a very low bioavailability: reportedly 0.3%. Therefore, when a patient takes a 2-mg dose, only 0.006 mg of loperamide reaches systemic circulation. As is true of many drugs with very low bioavailability, loperamide is metabolized primarily by CYP3A4, with some contribution from CYP2C8. The reported plasma concentrations following usual doses of loperamide range from 0.2 to 1.2 ng/mL. CNS exposure to loperamide is further limited by P-glycoprotein (P-gp) efflux at the blood-brain barrier.

RISK OF LOPERAMIDE ABUSE

Patients self-treating diarrhea and loperamide abusers report taking daily doses of 25 to more than 200 mg. At these doses, the plasma loperamide concentration can exceed 100 ng/mL.[2] In addition to decreasing gut motility, these large doses can cause sedation, urinary retention, respiratory depression, cardiac arrhythmias, and death.[3,4] At supratherapeutic plasma concentrations, loperamide prolongs the QRS complex and slows repolarization of the ventricle. This can lead to ventricular arrhythmias, which can be fatal. The mechanism for these cardiac effects is thought to be a combination of sodium, potassium, and calcium channel blockade in the myocaradium.[2]

DRUG INTERACTION POTENTIAL

Drug interaction data on loperamide are rather limited. CYP3A4 and CYP2C8 inhibitors have been reported to increase the plasma concentration of loperamide by about 2- and 4-fold, respectively, and by over 12-fold when both enzymes are inhibited concurrently.[5] Inhibitors of P-gp also increase the plasma concentration of loperamide (2- to 3-fold) and may increase the loperamide CNS concentration by reducing the effectiveness of the blood-brain barrier (P-gp mediated) efflux.[6-8] Although patients taking approved doses of loperamide for a short episode of diarrhea are unlikely to suffer adverse reactions from these interactions, patients taking excess doses are at much greater risk for adverse events.

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Consider that the plasma concentration resulting from even a modest supratherapeutic dose will be magnified by coadministration of CYP3A4 inhibitors (eg, aprepitant, atazanavir, boceprevir, cobicistat, clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole, voriconazole, posaconazole, nefazodone, nelfinavir, verapamil, cimetidine) and CYP2C8 inhibitors (eg, gemfibrozil, clopidogrel, grapefruit juice, amitriptyline, trimethoprim). Adding a P-gp inhibitor (eg, clarithromycin, erythromycin, ketoconazole, verapamil, quinidine, ritonavir, ranolazine, posaconazole, cyclosporine) can further increase the bioavailability of loperamide and enhance its CNS penetration. Amiodarone and lapatinib have been reported to inhibit the activity of CYP2C8, CYP3A4, and P-gp. Due to the potential for serious adverse outcomes, it would be prudent to avoid the use of loperamide in patients taking amiodarone or lapatinib, or combinations of drugs that inhibit multiple loperamide elimination pathways.

SUMMARY

Patients taking loperamide should be counseled to avoid taking more than the labeled dose. If usual doses of loperamide are not effective in relieving diarrhea, patients should be advised to see their health care provider. When counseling patients about the appropriate use of loperamide, pharmacists should ask patients about other drugs they are taking. ◆