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Metoclopramide and Dyskinesia

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

John R. Horn, PharmD, FCCP

Philip D. Hansten, PharmD

Metoclopramide has been used for many years in the treatment of gastroparesis, nausea and vomiting, and gastroesophageal reflux disease (GERD). It acts as an antagonist of the dopamine D_2 receptor and muscarinic receptors and as an agonist of 5-HT_4 receptors.[1,2] These actions increase gastric tone and emptying as well as increase antroduodenal coordination, resulting in some efficacy for gastroparesis and GERD. Metoclopramide's antiemetic effect is thought to be due to its inhibition of D_2 and 5-HT_3 receptors in the chemoreceptor trigger zone.

Metoclopramide-Induced Movement Disorders

Metoclopramide exerts its pharmacologic activity both peripherally and centrally. It is the ability of metoclopramide to affect central dopamine and serotonin receptors that is thought to account for its movement-related side effects. These can include dystonia, akathisia, parkinsonism, and tardive dyskinesia. These usually abate with discontinuation of metoclopramide but tardive dyskinesia may be irreversible. The FDA continues to receive reports of dyskinesia associated with metoclopramide.

Metoclopramide Pharmacokinetics

Metoclopramide is eliminated by several pathways. About 30% is eliminated unchanged in the urine.[3] The rest is metabolized, primarily by cytochrome P450 (CYP) 2D6, with perhaps some contribution from CYP3A4 or CYP1A2.[4,5] Metoclopramide also appears to be a substrate for the P-glycoprotein (P-gp) transporter.

Genetic variations in CYP2D6 or P-gp may alter the risk of movement disorders in patients taking metoclopramide.[6-8] Reduced CYP2D6 activity leads to increased metoclopramide plasma concentrations and risk of toxicity. Reduced P-gp activity increases the brain/plasma concentration ratio of metoclopramide, because P-gp acts as an efflux transporter from brain to blood. For any plasma concentration, a larger percentage of metoclopramide would be expected to collect in the brain in patients with reduced P-gp. Increasing plasma or brain concentrations of metoclopramide would be expected to increase the risk of metoclopramide side effects.

Potential Pharmacokinetic/ Pharmacodynamic Interactions

Little data are available that examine the relationship of metoclopramide concentration to the incidence of side effects, except that several retrospective analyses have found that higher doses are more often associated with tardive dyskinesia. In a study of 24 healthy subjects, pretreatment with fluoxetine (Prozac) 60 mg daily for 8 days resulted in an increase in metoclopramide maximum plasma concentration and area under the concentration time curve of 42% and 89%, respectively. Metoclopramide's half-life increased from 5.5 hours to 8.5 hours.[9]

Metoclopramide may have pharmacodynamic interactions with other drugs, including neuroleptic agents and selective serotonin reuptake inhibitors (SSRIs). Antipsychotic drugs with a high risk of movement disorders include fluphenazine (Prolixin), trifluoperazine (Stelazine), thiothixene (Navane), thioridazine (Mellaril), chlorpromazine (Thorazine), haloperidol (Haldol), perphenazine (Trilafon), risperidone (Risperdal), and loxapine (Loxitane). These drugs will likely potentiate the inhibition of dopamine receptors caused by metoclopramide.

Thioridazine, chlorpromazine, perphenazine, haloperidol, and risperidone have been noted to inhibit CYP2D6 and could increase the plasma concentration of metoclopramide. Theoretically, SSRIs used concomitantly with metoclopramide could increase the risk of serotonin syndrome. Additionally, some SSRIs [eg, duloxetine (Cymbalta), fluoxetine, and paroxetine (Paxil)] are inhibitors of CYP2D6.

Pharmacokinetic interactions with metoclopramide may occur with any inhibitor of CYP2D6 or P-gp. Concurrent administration of metoclopramide with CYP2D6 inhibitors (eg, amiodarone [Cordarone], diphenhydramine [Benadryl], propafenone [Rythmol], quinidine, ritonavir [Norvir], terbinafine [Lamisil], dronedarone [Multaq], bupropion [Wellbutrin]) or P-gp inhibitors (eg, clarithromycin [Biaxin], cyclosporine [Neoral], verapamil [Calan], ketoconazole [Nizoral], tacrolimus [Prograf], itraconazole [Sporanox], nelfinavir [Viracept]) should probably be avoided pending further data. The potential for increased side effects during the concurrent administration of CYP1A2 or CYP3A4 inhibitors with metoclopramide is unknown.

Summary

There is no doubt that metoclopramide can occasionally cause severe side effects. Because it is eliminated by CYP2D6 and appears to be a substrate for P-gp, there are a large number of potential drugs that can interact with metoclopramide to increase its plasma concentration or passage into the brain. Some patients, such as those with renal failure or a genetic deficiency in CYP2D6 or P-gp activity, may be particularly susceptible to metoclopramide movement-related adverse events, including those exacerbated by drug interactions.

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.