

Preventing Rasagiline Drug Interactions

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Rasagiline (Azilect) is a new selective, irreversible inhibitor of monoamine oxidase type B (MAO-B) that shows promise as an advance in the treatment of Parkinson's disease. Rasagiline is in the same category as selegiline but has some properties that differ from selegiline, and thus the drug interactions are not exactly the same.

Interactions with Other Drugs

Inhibition of MAO-B. Rasagiline inhibition of MAO-B is not an important source of drug interactions per se, but since it has not been ruled out that rasagiline may inhibit MAO-A under some circumstances, a number of contraindications and warnings appear in the product information as described later on.

Rasagiline metabolized by CYP1A2. Because CYP1A2 is susceptible to both inhibition and induction by other drugs, such drugs may increase or decrease rasagiline plasma concentrations.

Differences Between Rasagiline and Selegiline

Because rasagiline, like selegiline, is a selective MAO-B inhibitor that might also inhibit MAO-A, its interactions based on MAO inhibition are assumed to be essentially the same as for selegiline. The primary difference in drug interactions is that rasagiline is metabolized primarily by CYP1A2, while selegiline is metabolized by more complex pathways involving CYP2B6 and CYP2C19.¹

Potential Adverse Outcomes

Serotonin syndrome. Several drugs are listed in the product information as contraindicated with rasagiline due to the risk of serotonin syndrome. Meperidine is contraindicated primarily because it has resulted in severe and fatal interactions with MAO-A inhibitors and in at least 1 case with selegiline. Other drugs listed as contraindicated with rasagiline based on similar theoretical considerations include tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, mirzapine, and cyclobenzaprine. Although there is little evidence to suggest these combinations are actually dangerous, the potential adverse outcomes are so severe that the "contraindication" designation is probably appropriate.

Serotonergic antidepressants such as selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants (TCAs) are *not* listed in the rasagiline product information as "contraindicated," but concomitant use of rasagiline with these agents "is not recommended." Hundreds of patients in rasagiline clinical trials received concomitant SSRIs or TCAs, apparently without adverse interactions, but the regulators correctly mention that this does not rule out the possibility of a rare, serious adverse outcome from these combinations.

Hypertensive crisis. Since nonselective MAO inhibitors can cause acute hypertensive reactions if the patient ingests high-tyramine foods, and since one cannot rule out that rasagiline will be a nonselective MAO inhibitor in some patients, patients should be warned to avoid foods rich in tyramine. For the same reasons, patients should avoid OTC sympathomimetics such as pseudoephedrine, phenylpropanolamine, ephedrine, and phenylephrine.

Altered rasagiline response. Rasagiline

is metabolized primarily by CYP1A2, so inhibitors of this isozyme would be expected to increase rasagiline plasma concentrations. Ciprofloxacin purportedly can double rasagiline plasma concentrations,² and one would expect other CYP1A2 inhibitors such as atazanavir, cimetidine, enoxacin, mexiletine, tacrine, and zileuton to increase rasagiline levels as well. Of these drugs, fluvoxamine and enoxacin markedly inhibit CYP1A2 and their use with rasagiline should probably be contraindicated.

One should also expect reduced rasagiline effect in patients receiving CYP1A2 inducers such as barbiturates, carbamazepine, and rifampin. Smoking is a particularly potent stimulant to CYP1A2 activity, so one would expect smokers to have substantial reductions in rasagiline plasma concentrations. One should be alert for the need to increase rasagiline dosage in patients on CYP1A2 inducers.

Conclusion

Although most rasagiline drug interactions are based on theoretical considerations rather than actual clinical data, the potential severity of many of the adverse outcomes dictates a conservative approach when giving rasagiline concomitantly with these drugs. Many of the potentially interacting drugs are not life-saving and have alternatives (eg, OTC nasal decongestants, dextromethorphan, meperidine). For other drugs such as antidepressants that may be important for the patient, one should weigh the benefits versus the (usually small) risk of using them with rasagiline. **R**

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Rybovic, Pharmacy Times, Ascend Media Healthcare, 103 College Road East, Princeton, NJ 08540; or send an e-mail request to: arybovic@ascendmedia.com.