

Triptans

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Triptans are potent serotonin (5-HT) 1B/1D receptor agonists used to abort and treat migraine headaches. Although the triptans share pharmacodynamic characteristics at 5-HT_{1B/1D} receptors, they differ pharmacokinetically. This column reviews how the triptans are metabolized. Generally, the triptans are metabolized by phase I monoamine oxidases (MAOs) and by various cytochrome P450 enzymes. However, each triptan has a unique metabolic profile, leading to significant differences in each triptan's potential for drug-drug interactions. These differences are detailed in this review. (Psychosomatics 2002; 43:502–504)

The triptans are felt to induce vasoconstriction of cranial blood vessels at arteriovenous anastomoses (site of many 5-HT_{1B/1D} receptors, whereas 5-HT₂ receptors are found in peripheral arteries) and reduce inflammation. Sumatriptan, the first-generation triptan, has many limitations, including poor oral bioavailability, a short half-life, and that it may not cross the blood-brain barrier. Newer and more tolerable triptans have been developed and are presented in Table 1. All triptans share very similar pharmacodynamic (receptor) characteristics, but they differ pharmacokinetically. For a review of the differences in oral bioavailability, absorption, protein binding, and recommended doses, please see the comprehensive table in the article by Jhee et al.¹ This table even includes hours to pain relief. However, their table does not include how and where the drugs are metabolized. That information has been col-

lected and presented in a review by Deleu and Hanssens² and updated in Table 1.

Metabolism

All of the triptans go through “Phase I” metabolism. Phase I metabolism includes oxidative reactions that prepare the parent drug to become a more soluble or polar compound. Phase I reactions generally add or remove a “functional” group via *N*-dealkylation, *O*-dealkylation, hydroxylation, *S*-oxidation, or deamination, oftentimes making the compound sufficiently polar to be excreted. Phase I metabolism includes reactions that occur through the cy-

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TABLE 1. Triptan Drug Metabolism

Drug	Metabolism ^a
Almotriptan (Axert®)	MAO-A, 3A4, 2D6
Eletriptan	3A4 ^b
Frovatriptan	1A2
Naratriptan (Amerge®)	P450 ^c , renal, MAO-A
Rizatriptan (Maxalt®)	MAO-A
Sumatriptan (Imitrex®)	MAO-A
Zolmitriptan (Zomig®)	1A2, MAO-A

^aPrimary mode of metabolism listed first.

^bEletriptan is a substrate of P-gp, and may be inhibited or induced by P-gp inhibitors/inducers, which may cause changes in its efficacy for migraine headaches.

^cSpecific enzymes not yet reported.

tochrome P450 system (also known as the microsomal mixed oxygenase system) or the monoamine oxidase (MAO) system. We have discussed the cytochrome P450 system at length in this column. The MAO system has a critical role in the metabolism of endogenous biogenic amines by inactivating catecholamines and their metabolites. There are two enzymes in this system, MAO-A and MAO-B. The triptans may be metabolized by the cytochrome P450 system, the MAO system, or both. None of the triptans appear to actively inhibit or induce P450 metabolism themselves.

Drug-Drug Interactions

Triptan metabolism may be affected by competing drugs that utilize, inhibit, or induce metabolic enzymes, particularly if the triptan in question is dependent upon a specific cytochrome P450 or MAO enzyme for its metabolism. Triptan toxicity/side effects include dizziness, chest or neck tightness, palpitations, shortness of breath, and acute anxiety. Myocardial ischemia has been reported, especially with patients who have coronary artery disease.¹ Monoamine oxidase inhibitors (MAOIs)—particularly MAO-A inhibitors like moclobemide—are contraindicated with triptans whose metabolism is solely dependent upon MAO (rizatriptan, sumatriptan). Gardner and Lynd³ found no reports of adverse events with sumatriptan and MAOIs administered simultaneously, but the manufacturer lists this combination as absolutely contraindicated (*Physician's Desk Reference*, 2002). Propranolol may be an inhibitor of MAO-A and has been found to increase plasma concentrations of rizatriptan, so dose reduction of triptans dependent upon MAO-A is recommended with concomitant use of propranolol. The other β blockers do not seem to have the same interaction.⁴

Cytochrome P450 interactions with the triptans are predictable based upon the cytochrome P450 enzymes the triptans are dependent upon. Eletriptan and almotriptan are primarily metabolized at cytochrome P450 3A4. One would predict that potent inhibitors of 3A4 [nefazodone (Serzone[®]), clarithromycin (Biaxin[®]), erythromycin, ke-

toconazole, itraconazole (Sporanox[®]), ritonavir (Norvir[®]), ciprofloxacin (Cipro[®]), and grapefruit juice] would potentially increase plasma levels of the triptans and may worsen side effects/toxicity. Verapamil, a moderate inhibitor of 3A4, and fluoxetine, a moderate inhibitor of both 3A4 and 2D6, both caused a moderate increase in C_{max} and AUC of almotriptan in healthy volunteers, which is metabolized by MAO, 3A4, and 2D6.^{5,6} In the 2001 report of Fleishaker et al., no significant clinical events occurred, and the authors suggested that no dose adjustment was necessary. These modest findings reflect almotriptan's multiple avenues of metabolism, which allow the drug to be biotransformed despite "roadblocks" at some of its metabolic sites. We could not find case reports or studies concerning triptan use with potent 3A4 inhibitors. We suspect that more potent inhibitors would cause more robust side effects, particularly with eletriptan. Eletriptan is predominantly metabolized at 3A4, but is relatively new and not yet available in the United States. Eletriptan also requires higher dosing than other second-generation triptans because of an active P-glycoprotein (P-gp) efflux system at the blood-brain barrier.⁷ Triptans dependent upon cytochrome P450 1A2 (frovatriptan and zolmitriptan) may become toxic with co-administration with potent 1A2 inhibitors like oral contraceptives, fluvoxamine, the quinolone antibiotic ciprofloxacin (Cipro[®]), and the antiarrhythmic mexiletine.^{7,8} Buchan et al.⁹ reviewed results of in vitro studies, healthy volunteer studies, and a retrospective analysis of phase I clinical data concerning triptans and commonly co-administered drugs with frovatriptan. In addition to being inhibited by the potent 1A2 inhibitors listed above, they found lower C_{max} and AUCs of frovatriptan in tobacco smokers (tobacco smoke is a potent *inducer* of 1A2).

Summary

The triptans are all effective in aborting migraine headaches, having similar pharmacodynamic effects. The pharmacokinetics of these drugs vary widely, due to P-gp efflux pump differences, P450 and MAO interactions, and differing bioavailability.

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Med-Psych Drug-Drug Interactions

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