Interactive Properties of Tizanidine (Zanaflex)

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Tizanidine (Zanaflex; Novartis) has several pharmacokinetic and pharmacodynamic properties that predispose it to adverse drug interactions, including the following:

- Tizanidine is metabolized mainly by cytochrome P-450 1A2 (CYP1A2), a cytochrome P-450 isozyme that is susceptible to inhibition by several other medications
- Tizanidine undergoes considerable first-pass metabolism, so drugs that inhibit tizanidine metabolism may produce large increases in tizanidine plasma concentrations
- Tizanidine regularly produces sedation, so concurrent use with other central nervous system (CNS) depressants is likely to produce additive effects
- Tizanidine tends to lower blood pressure and may exhibit additive effects with antihypertensive agents

Pharmacokinetic Interactions

Fluvoxamine

In a randomized controlled study of healthy subjects, pretreatment with fluvoxamine (100 mg/day for 4 days) resulted in a dramatic 33-fold increase in tizanidine area under the plasma concentration–time curve (AUC).[1] The marked increases in tizanidine plasma concentrations were accompanied by pharmacodynamic changes, such as marked reduction in systolic blood pressure and increased sedation. These findings suggest a potentially dangerous drug interaction, and concurrent use of tizanidine and fluvoxamine is contraindicated. Fluvoxamine is a potent CYP1A2 inhibitor, which is probably the primary mechanism for this interaction.

Oral Contraceptives

Retrospective analysis of tizanidine pharmacokinetics in women taking oral contraceptives found that they had about a 50% lower clearance of tizanidine, compared with women not taking oral contraceptives. This finding is consistent with other evidence showing that estrogens are modest inhibitors of CYP1A2. In women taking oral contraceptives, tizanidine should be initiated with conservative doses and gradually increased based on response.

Other CYP1A2 Inhibitors

Since tizanidine appears to be very susceptible to interactions with inhibitors of CYP1A2, one should monitor for increased tizanidine response if any CYP1A2 inhibitor is used. Drugs known to inhibit CYP1A2 include atazanavir (Reyataz), ciprofloxacin (Cipro), enoxacin (Penetrex), mexiletine (Mexitil), tacrine (Cognex), and zileuton (Zyflo). Monitor particularly for excessive sedation and hypotension.

Pharmacodynamic Interactions

CNS Depressants

Sedation is a prominent side effect of tizanidine, and this is likely to be additive with any other CNS depressant. Tizanidine-induced sedation appears to be dose-related, so patients on larger tizanidine doses, and/or reduced CYP1A2 activity due to drugs or other reasons, would be at greater risk. Alcohol may increase tizanidine plasma concentrations somewhat and produce additive CNS depression, so patients should be warned to limit alcohol intake.

Antihypertensive Agents

Tizanidine, like clonidine, is an alpha$_2$-adrenoreceptor agonist and thus can produce hypotension when given alone or can enhance the hypotensive effects of other drugs. Two cases of acute hypotension have been reported (in a 10-year-old boy and a 48-year-old woman) when tizanidine was added to lisinopril therapy.[2,3] Monitor blood pressure and patient response when tizanidine is initiated in patients receiving angiotensin-converting enzyme inhibitors or any other antihypertensive drugs. Since tizanidine is an alpha-adrenergic agonist, it generally should not be used with other alpha-adrenergic agonists such as clonidine, guanabenz, or guanfacine.

Summary

- Fluvoxamine produces dramatic increases in tizanidine plasma concentrations, and the combination should be absolutely avoided
- Other CYP1A2 inhibitors should be used with tizanidine only if the patient can be observed carefully for adverse effects such as excessive sedation and hypotension
- Tizanidine is a CNS depressant and produces additive sedation with other CNS depressants; monitor for excessive sedation and adjust doses as needed
- Tizanidine tends to lower blood pressure and produces additive effects with antihypertensive drugs. Monitor blood pressure closely. PT

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: astahl@ascendmedia.com.