Coadministration of Sertraline with Cisapride or Pimozide: An Open-Label, Nonrandomized Examination of Pharmacokinetics and Corrected QT Intervals in Healthy Adult Volunteers

Jeffrey Alderman, PhD

Pfizer Inc., New York, New York

ABSTRACT

Background: Sertraline hydrochloride is a selective serotonin reuptake inhibitor with demonstrated efficacy and safety for the treatment of the following disorders: major depressive, obsessive-compulsive, panic, premenstrual dysphoric, social anxiety, and posttraumatic stress. Although sertraline is unlikely to cause clinically significant inhibition of cytochrome P450 (CYP) 3A4 substrates, even modest concentration increases for narrow therapeutic index drugs, such as pimozide or cisapride, are potentially important.

Objective: The goal of this study was to determine whether there is a pharmacokinetic interaction, as shown by plasma concentrations and electrocardiographic evidence of QTc intervals, between sertraline 200 mg QD and cisapride 10 mg QID, and between sertraline 200 mg QD and pimozide (single 2-mg dose).

Methods: Patients in group A were administered cisapride on days 1 and 2 (10 mg QID), day 3 (10 mg/d), days 25 through 29 (10 mg QID), and day 30 (10 mg/d). Sertraline was administered on days 4 through 29 at a starting dose of 50 mg/d, which was titrated upward in 50-mg increments every third day to a maximum of 200 mg/d. Patients in group B were treated with 2 mg of pimozide on days 1 and 39. Sertraline was administered on days 18 through 46 at a starting dose of 50 mg/d, which was titrated upward in 50-mg increments every third day to a maximum of 200 mg/d.

Results: There were 9 males and 6 females in group A (sertraline + cisapride) (mean age, 34.4 years for males, 41.7 years for females; mean weight, 78.7 kg for males, 66.6 kg for females; 14 Hispanic, 1 white), and 8 males and 7 females in group B (sertraline + pimozide) (mean age, 26.1 years for males, 33.4 years for females; mean weight, 70.8 kg for males, 61.4 kg for females; 15 Hispanic). Coadministration of sertraline and cisapride resulted in statistically significant reductions of 29% and 36% in cisapride C_{max} and AUC from time 0 to 6 hours, respectively, compared with cisapride alone. Coadministration of sertraline and pimozide resulted in statistically significant increases of 35% and 37% in pimozide C_{max} and $AUC_{0-\infty}$, respectively, compared with pimozide alone. No subject exhibited a prolongation of the QTc interval ≥15% with coadministration of sertraline and cisapride, or sertraline and pimozide.

Conclusions: This study found that coadministration of sertraline with cisapride resulted in decreases in cisapride concentrations, and no significant effects on QTc intervals. Coadministration of sertraline 200 mg/d and a single dose of pimozide 2 mg produced significant increases in pimozide concentrations but no prolongation of the QTc interval ≥15%. This opposite effect for pimozide compared with cisapride, as well as other previously tested CYP3A4 substrates, suggests that there are mechanisms other than CYP3A4 involved in the sertraline–pimozide interaction. (*Clin Ther.* 2005; 27:1050–1063) Copyright © 2005 Excerpta Medica, Inc.

Key words: sertraline, cisapride, pimozide, pharmacokinetics, QTc interval, drug interaction, concomitant use.

INTRODUCTION

Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) that has demonstrated efficacy and safety for the treatment of the following disorders:

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major depressive,[1–3] obsessive-compulsive,[4,5] panic,[6–9] premenstrual dysphoric,[10–13] social anxiety,[14] and posttraumatic stress.[15,16] In addition to these indications that are approved in the United States, sertraline has also recently shown efficacy in the treatment of generalized anxiety disorder,[17] although not currently approved for this use.

After oral administration of sertraline, C_{max} occurs between 4 and 8 hours with a terminal plasma elimination $t_{1/2}$ of ~26 hours.[18] Sertraline is extensively metabolized, primarily by cytochrome P450 (CYP) 3A4.[19] The principal metabolite, *N*-desmethylsertraline (also referred to as desmethylsertraline), is clinically inactive and has a $t_{1/2}$ of ~3 days. Because some psychotropic drugs can prolong the QT interval, evaluation of the impact of such drugs on cardiovascular parameters has assumed increased concern.[20,21] Sertraline, however, does not prolong the QTc interval,[20] and one study has shown its efficacy and safety among subjects with depression recently hospitalized for myocardial infarction or unstable angina.[22]

The indications for which SSRIs such as sertraline are approved often require long-term maintenance therapy.[23–26] Because SSRIs are frequently administered concomitantly with additional medications, possible interactions with these other agents are an important clinical concern. The potential for SSRIs to cause pharmacokinetic drug–drug interactions through inhibition of the CYP system has been extensively investigated; the inhibitory effects among the SSRIs vary substantially.[27] Sertraline generally has only weak (defined as an inhibition constant [K_i] >50 μM) to moderate (K_i between 1 and 50 μM) inhibitory effects on CYP enzymes 2D6 and 3A4.[27,28] When sertraline was coadministered with alprazolam, terfenadine, or carbamazepine—3 drugs that are also principally metabolized by CYP3A4—the metabolism of these drugs was not inhibited.[29]

Cisapride is a serotonin-4 receptor agonist that was indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease. Cisapride is rapidly absorbed after oral administration. C_{max} is reached 1 to 1.5 hours after dosing, and it has an elimination $t_{1/2}$ of 7 to 10 hours.[30] Cisapride is extensively metabolized in the liver, primarily by CYP3A4, to norcisapride.[31] Although cisapride was generally well tolerated, some patients receiving the drug experienced cardiovascular side effects. These included prolongation of QT intervals with associated torsades de pointes when cisapride was administered in conjunction with other drugs that inhibit cisapride's metabolism (particularly drugs that inhibit CYP3A4).[30,32–40] Drugs known to inhibit cisapride's metabolism include clarithromycin, erythromycin, fluoxetine, and cimetidine.[30] Because some of the cardiac events caused by drug interactions with cisapride were serious or fatal, cisapride is no longer marketed in any country, although limited-access programs are available in some countries through the manufacturer (Janssen Pharmaceutica Products, L.P., Titusville, New Jersey) to patients who have not benefited from other treatment approaches.

Pimozide is a diphenylbutylpiperidine neuroleptic that primarily blocks dopamine D_2 receptors. It is approved for use in the United States as a secondary treatment for Gilles de la Tourette's syndrome and is used in other countries (eg, United Kingdom, Egypt, Portugal, The Netherlands) for the treatment of schizophrenia or psychosis. Pimozide is >50% absorbed after oral administration and is extensively metabolized in the liver.[41] Pimozide is also primarily metabolized by CYP3A4.[42,43] C_{max} occurs ~6 to 8 hours after dosing.[44] Pimozide has been found on electrocardiograms (ECGs) to produce prolongation of the QT interval; this prolongation may be responsible for the reported cases of sudden death connected with modest increases above the recommended dosage range.[45]

Because of these safety concerns related to dosage, both pimozide and cisapride are considered narrow therapeutic index drugs. With narrow therapeutic index drugs metabolized by CYP3A4, an important question is whether the risk of QTc prolongation occurring increases when such drugs are coadministered with other agents, even if the coadministered drug has weak inhibitory effects on CYP enzymes. The current study was designed to assess whether there is a pharmacokinetic interaction when sertraline is coadministered with either cisapride or pimozide. Specifically, the effect of coadministering sertraline 200 mg QD with cisapride 10 mg QID on cisapride blood concentrations and concurrent QTc intervals was investigated. The effect of cisapride on sertraline concentrations using this regimen was also estimated. Similarly, the effect of coadministering sertraline 200 mg QD with a single 2-mg dose of pimozide on pimozide blood concentrations and concurrent QTc intervals was investigated.