Effect of Sertraline on Plasma Nortriptyline Levels in Depressed Elderly

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Background: Several serotonin selective reuptake inhibitors have been reported to be inhibitors of the cytochrome P450 2D6 (CYP2D6). Thus, they may increase the plasma level of secondary amine tricyclic antidepressants, which are predominantly metabolized through this enzyme. Except for a few case reports, no clinical data document the degree of this drug-drug interaction in elderly depressed patients.

Method: We systematically examined this interaction by determining the change in plasma nortriptyline levels in 14 elderly depressed patients in whom sertraline was added to nortriptyline.

Results: After addition of 50 mg/day of sertraline, the median increase in plasma nortriptyline level over baseline was 2% (range, –26% to 117%; p = .30). In 2 patients (14%), there was an increase of 50% or more. For patients taking higher sertraline doses (N = 7; 100 or 150 mg/day), the median increase in plasma nortriptyline level over baseline was 40% (range, –12% to 239%; p = .08).

Conclusion: Overall, a modest effect of sertraline was observed on nortriptyline metabolism in these elderly depressed patients. This is consistent with prior reports of a weak inhibition of CYP2D6 by sertraline in vitro and in young healthy volunteers. However, some patients showed a change in plasma nortriptyline level that would be considered clinically significant. Thus, careful monitoring of plasma nortriptyline levels is recommended in all patients treated with a combination of nortriptyline and sertraline.

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Several studies have suggested that a combination of a tricyclic antidepressant (TCA) and a serotonin selective reuptake inhibitor (SSRI) may be more efficacious in treating treatment-resistant depression than either agent taken alone.[1–3] The clinical use of these combinations has led to the identification of a drug-drug interaction between antidepressants of these two classes, attributed to the effect of SSRIs on cytochrome P450 2D6 (CYP2D6).[4] CYP2D6 is one of the hepatic enzymes that are involved in the oxidative metabolism of various substrates including many psychotropics.[5–7] In particular, CYP2D6 is the main enzyme responsible for the hydroxylation of the secondary TCAs, nortriptyline and desipramine.[8,9] It is inhibited by several neuroleptics[10,11] and SSRIs,[12–15] explaining the metabolic interaction between these drugs and secondary amine TCAs.

While these interactions have been systematically studied in vitro[16,17] and in healthy young volunteers,[18,19] few studies have assessed them in depressed patients. In particular, except for case reports, we are not aware of any study of TCA-SSRI interaction in elderly depressed patients. Elderly persons may be the most at risk for drug-drug interactions and are the most likely to suffer from serious adverse reactions from them.[20,21] Thus, we conducted a retrospective study in a series of elderly depressed patients who had failed to fully respond to nortriptyline and in whom sertraline had been added by their treating physicians. The aim of this study was to determine the extent to which the SSRI sertraline interferes with the metabolism of the secondary amine TCA nortriptyline in these patients.

METHOD

Using two computerized databases, we identified all patients aged 60 years and over who were concurrently prescribed nortriptyline and sertraline by their attending psychiatrist between January 1992 and December 1996 on an inpatient unit at Western Psychiatric Institute and Clinic and at the outpatient multidisciplinary geriatric clinic (Benedum Geriatric Center) of the University of Pittsburgh Medical Center. We focused our analysis on 14

Table 1. Demographic and Clinical Characteristics of Individual Patients

Patient	Age (y)	Sex	Race	Nortriptyline Dose (mg/d)	Duration (d)	Plasma Nortriptyline Level Before Sertraline (ng/mL)	Sertraline Dose (mg/d)	Plasma Nortriptyline Level After Addition of Sertraline (ng/mL)
1	83	F	White	30	30	102	50	142
2	86	M	White	25	12	73	50	66
3	77	M	White	50	6	112	50	102
4	82	F	White	60	10	118	100	109
5	64	F	White	50	30	96	50	74
6	60	F	White	75	9	144	50	106
7	70	M	White	75	24	122	50	121
8	78	F	White	75	5	107	50	138
9	78	M	White	75	5	100	50	78
10	81	M	White	75	7	97	50	120
11	70	F	White	60	10	67	50	101
12	68	F	White	75	13	76	50	79
13	62	M	White	100	21	88	50	121
14	63	F	Black	100	63	59	50	128

patients (9 inpatients; 5 outpatients) who fulfilled the following conditions: (1) sertraline was added to nortriptyline; (2) plasma nortriptyline levels had been obtained before and after this addition; (3) these plasma levels were drawn after a minimum of 5 days during which all medications (including nortriptyline and sertraline) were held constant. Typically, these patients had not or had only partially responded to nortriptyline given for at least 4 weeks as a single dose at bedtime to maintain a plasma level between 50 and 150 ng/mL. In all patients, nortriptyline dosages were kept constant after addition of sertraline. Sertraline was started at a dose of 25 or 50 mg, given as a single dose in the morning or at bedtime, and initially titrated to 50 mg/day in 13 patients and 100 mg/day in 1 patient. In 7 patients, sertraline was subsequently increased from 50 mg/day to 100 mg/day (N = 5) or 150 mg/day (N = 2).

In inpatients (N = 9), plasma samples were obtained in the morning (about 12 hours after the evening dose of nortriptyline); in outpatients (N = 5), plasma samples were obtained early in the afternoon (about 18 hours after the evening dose of nortriptyline). All plasma nortriptyline levels were determined by the University of Pittsburgh Medical Center Central Clinical Laboratory by high-performance liquid chromatography (HPLC) with control parameters (a coefficient of variance of 3.1% for a plasma nortriptyline level of 100 ng/mL). In 5 patients, several nortriptyline levels were available after addition of sertraline. In these patients, the nortriptyline level obtained after the longest concomitant treatment with nortriptyline and sertraline was used for the analysis.

First, we determined the percentage change in plasma nortriptyline levels in the 14 patients relative to baseline before addition of sertraline. We assessed whether this change was statistically significant using the Wilcoxon signed-rank test, a nonparametric equivalent of the paired t test. To test whether the change in plasma nortriptyline levels was more pronounced in the more extensive CYP2D6 metabolizers,[10] Spearman's nonparametric coefficient of correlation was used to assess the association between percentage change in plasma nortriptyline level and the initial quotient of plasma nortriptyline level to daily nortriptyline dose (L/D). L/D corresponds to the inverse clearance of nortriptyline and thus reflects the subjects' CYP2D6 metabolizer status (i.e., patients who have lower L/D are more extensive CYP2D6 metabolizers).[22,23] Finally, to test whether a higher dosage of sertraline would produce a greater change in plasma nortriptyline level, we compared in the 7 patients who had a further titration of sertraline the percentage change in nortriptyline level induced by 50 mg/day versus 100 or 150 mg/day of sertraline by using the Wilcoxon signed-rank test. All comparisons were two-tailed.

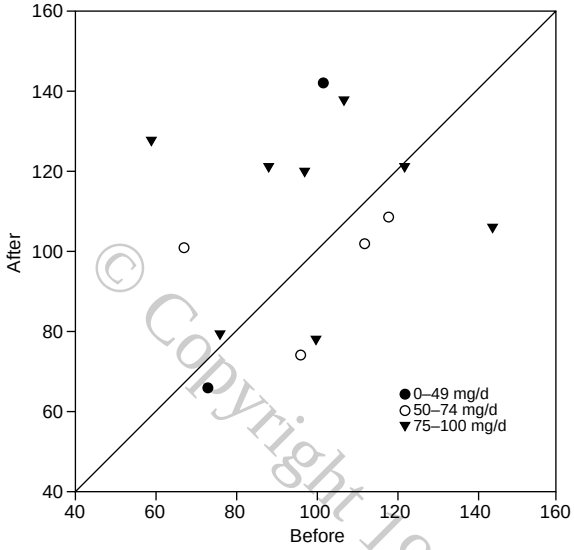
RESULTS

The patients consisted of 8 women and 6 men; 13 were white and 1 was black. Their mean ± SD age was 72 ± 9 years. In addition to nortriptyline and sertraline, patients were taking a mean ± SD of 2.6 ± 1.8 prescription medications. These patients were taking a mean ± SD nortriptyline dose of 66 ± 22 mg/day and, before addition of sertraline, they had a mean ± SD plasma nortriptyline level to dose quotient (L/D) of 1.7 ± 0.8. For individual patient demographic and clinical characteristics, refer to Table 1.

Figure 1 presents plasma nortriptyline levels before and after addition of sertraline, while Figure 2 presents percentage change in plasma nortriptyline levels. The change in nortriptyline level after addition of sertraline was not statistically significant (median 2%; range, –26% to 117%; p = .30), but there was a trend for this change to be inversely correlated with the initial nortriptyline level to dose quotient (Spearman r = –0.49; p = .07).

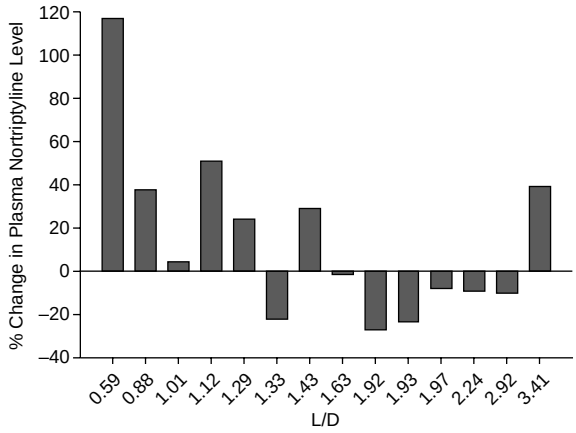
In 7 patients, plasma nortriptyline level was also obtained before and after sertraline was increased from 50 mg/day to 100 mg/day (N = 5) or 150 mg/day (N = 2). While taking 50 mg/day of sertraline, these 7 patients had experienced a median increase in plasma nortriptyline

Figure 1. Plasma Nortriptyline Levels (ng/mL) Before and After Addition of Sertraline*†



*Plasma nortriptyline levels before addition of sertraline are plotted along the x-axis; plasma nortriptyline levels after addition of sertraline are plotted along the y-axis. The diagonal line corresponds to unchanged plasma nortriptyline levels. Thus, patients below this diagonal line experienced a decrease in their plasma nortriptyline level after addition of sertraline; patients above this diagonal line experienced an increase in their plasma nortriptyline level after addition of sertraline.
†All patients in this figure received 50 mg/d of sertraline except for one (100 mg/d).

Figure 2. Percentage Change in Plasma Nortriptyline Levels After Addition of Sertraline*



*Abbreviation: L/D = Plasma nortriptyline level (ng/mL) to daily dose (mg/d) quotient. L/D values are plotted along the x-axis; lower values correspond to more extensive metabolizers and higher values correspond to less extensive metabolizers. Percent changes in plasma nortriptyline level after addition of sertraline are plotted along the y-axis.

level over baseline of 29% (range, –23% to 117%; p = .22); with 100 or 150 mg/day of sertraline, they experienced a median increase over baseline of 40% (range –12% to 239%; p = .08). The median increases in plasma nortriptyline level associated with the lower and the higher doses of sertraline were not significantly different (29% vs. 40%; p = .22).

DISCUSSION

In 14 elderly patients, typically in their 70s, we found that the addition of 50 mg/day of sertraline to nortriptyline had only a minimal overall effect on nortriptyline metabolism: it resulted in a median increase in plasma nortriptyline level of only 2%. However, this lack of group effect needs to be interpreted cautiously given that 2 (14%) of these 14 patients experienced an increase in their plasma nortriptyline levels of 51% and 117%, respectively, changes that would be considered clinically meaningful.

Of note, there was a trend suggesting that a higher degree of inhibition was observed in more extensive CYP2D6 metabolizers. This is consistent with two recent reports showing that extensive metabolizers are more likely to experience drug-drug interactions.[10,24] Furthermore, escalation in the dose of sertraline from 50 mg/day to 100 or 150 mg/day in a subgroup of 7 patients was associated with a greater increase in plasma nortriptyline level. This apparent dose-dependent difference in metabolic interaction failed to reach statistical significance, probably due to the small number of patients in whom it was studied. A power analysis revealed that an effect of similar magnitude would have been statistically significant if the number of patients had been 10 or higher.

Our results are consistent with several published studies conducted in vitro or in healthy young volunteers that have shown the major SSRIs to inhibit CYP2D6, the main enzyme involved in the hydroxylation of the secondary amine TCAs nortriptyline and desipramine. When compared with fluoxetine, norfluoxetine, or paroxetine, sertraline has the smallest K_i for CYP2D6,[16] leading to the expectation that, of these drugs, sertraline would have the smallest inhibition of the metabolism of secondary amine TCAs. However, extrapolation of in vitro to in vivo data cannot be assumed[14,15] since metabolism is determined not only by the affinity of the inhibitor to the metabolizing enzyme (i.e., K_i), but also by the concentration of the inhibitor, particularly the unbound fraction,[6,7] by the concentration of the metabolite and its affinity to the enzyme, and by other factors such as genotype and phenotype. In two studies conducted in young healthy volunteers who were free of other drugs, sertraline in a dosage range of 50 to 150 mg/day had an overall modest effect on the metabolism of desipramine,[18,19] comparable to the overall effect on the metabolism of nortriptyline we found in our elderly patients. Several case reports have described more substantial interactions between desipramine and sertraline in some individuals.[25–27] However, the accuracy of these re-

ports has been questioned,[28] and since the secondary amine TCAs desipramine and nortriptyline differ in their pharmacokinetics,[29] it is inaccurate to assume these drugs to have the same drug interaction profile with sertraline.

In summary, this report confirms that, in most older patients, sertraline seems to have a modest but variable effect on the metabolism of the secondary amine TCA nortriptyline, making the use of this combination relatively easy and safe, as long as plasma nortriptyline levels are closely monitored. This effect may be dose-dependent and more pronounced in extensive metabolizers than in poor metabolizers. These results need to be confirmed by studies involving a larger number of patients, ideally with prospective determination of patients' genotype or phenotype and measurement of plasma sertraline level. In the meantime, careful monitoring of plasma nortriptyline levels is recommended in all patients treated with a combination of nortriptyline and sertraline.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

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