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Paroxetine Binding to the Rat Norepinephrine Transporter In Vivo

To the Editor:

Owens et al (2000) reported that paroxetine binds to the rat norepinephrine transporter at concentrations of >100 ng/mL. 21% and 34% inhibition of the transporter occurring at mean paroxetine concentrations of 210 ng/mL and 677 ng/mL, respectively. The authors stated in their abstract that this finding “may underlie the broad therapeutic utility of paroxetine in mood and anxiety disorders.”

There are published clinical data that contradict this speculation. With reference to healthy subjects, Kaye et al (1989) reported mean maximum steady-state plasma paroxetine concentrations of 47 (range, 14–90) ng/mL and 62 (range, 8.6–105) ng/mL in subjects receiving paroxetine 20 mg/day and 30 mg/day, respectively. Özdemir et al (1999) reported mean steady-state plasma paroxetine concentrations of 32 ng/mL and 16 ng/mL in young adults with wild-type heterozygous and homozygous CYP2D6 genotypes, respectively, receiving paroxetine 20 mg/day. The maximum plasma concentration in both groups was 62 ng/mL. With reference to depressed patients, Kaye et al (1989) reported mean minimum steady-state plasma paroxetine concentrations of 49 (range, 9.4–96) ng/mL, 86 (range, 7.5–255) ng/mL, and 129 (range, 39–575) ng/mL in nonelderly patients receiving paroxetine 20 mg/day, 30 mg/day, and 40 mg/day, respectively. Tasker et al (1989) reported that, in 94 patients treated with paroxetine 30 mg/day, only 14% had steady-state plasma concentrations of >100 ng/mL, and of the 68 patients showing improvement, only 13% had concentrations of >100 ng/mL. The maximum plasma concentration in any patient was 190 ng/mL.

These clinical data indicate that patients receiving standard therapeutic doses of paroxetine should have little or no inhibition of their norepinephrine transporter. Allowing for some nonlinearity of dose versus serum concentration, due to saturability of metabolizing enzymes (Gunasekara et al 1998; Kaye et al 1989), even at the highest recommended therapeutic doses of 50–60 mg/day (Drug Facts and Comparisons 2000, 927; Physicians’ Desk Reference 2000, 3027–3033), the majority of nonelderly patients should have serum paroxetine concentrations less than those required to achieve even minimal inhibition of their norepinephrine transporter. Had Owens et al (2000) considered these clinical data, they likely would have come to just the opposite of their stated conclusion—namely, that inhibition of norepinephrine uptake by paroxetine is of little or no consequence for its therapeutic efficacy in mood and anxiety disorders. Given paroxetine’s 395- to 1308-fold greater affinity for the serotonin transporter than for the norepinephrine transporter, as indicated by Owens et al themselves, it also is highly likely that a dose–response study of norepinephrine transporter inhibition by paroxetine in humans, such as that reported by Harvey et al (2000) for venlafaxine, would be negative. Indeed, Hassan et al (1985) reported that paroxetine 30 mg/day for 10 days given to young adult male volunteers did not alter norepinephrine uptake, as determined by the tyramine pressor test.

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Reply

To the Editor:

Dr. Rubin contends that clinical pharmacokinetic data from select studies show that paroxetine concentrations are too low to significantly affect norepinephrine transporter (NET) function. Moreover, he states that the cited data should lead to the conclusion that paroxetine has no effects on NET function in a clinical setting. We were quite clear in our report that “the clinical importance of our findings is currently obscure,” “we are unaware of any reports of indirect evidence suggesting NET antagonism by paroxetine,” and “it is not known... whether these are of any measurable therapeutic benefit.” Nevertheless, the data are the data. Thus, we and others have shown that paroxetine is moderately potent at binding to the NET in vitro.
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(Béique et al 1998; Owens and Knight 2000; Owens et al 1997; Tatsumi et al 1997). Moreover, both in vitro and in vivo binding to the NET are concentration dependent. Therefore, at certain concentrations of paroxetine NET inhibition will occur. We have shown that, using all data points between 101 and 500 ng/mL, a mean inhibition of 21% was produced by paroxetine on NET binding (Figure 2). The mean concentration in this range of values was 210 ng/mL, somewhat higher than that routinely observed in patients receiving standard paroxetine therapy. Being concentration dependent, smaller, but real, inhibition of NET binding will surely occur at lower concentrations.

Dr. Rubin cites several articles indicating that paroxetine concentrations rarely, if ever, reach those needed for NET inhibition, though ironically he has never conducted research in this particular area himself. There are considerable data available that support our contention that paroxetine concentrations are attained to produce some degree of NET inhibition in a clinical setting. It is well established that there are great interindividual differences in serum paroxetine concentrations after treatment with the same dose of paroxetine. Moreover, kinetics are non-linear in some individuals. Kaye et al (1989) report that, in a long-term study of over 200 patients receiving paroxetine (10–50 mg/day), observed plasma concentrations ranged between 0.9 and 573 ng/mL. In nonelderly depressed patients receiving 60 mg/day, minimum steady-state serum concentrations were 124 and 166 ng/mL at 8 weeks and >5 months of treatment, respectively (Kaye et al 1989). Sindrup et al (1992) reported that steady-state concentrations of paroxetine varied from 8 to 221 ng/mL in patients receiving 30 mg/day. Obviously serum paroxetine concentrations would be even higher in patients receiving 40 or 50 mg/day. In a large study (Duboff 1993), mean steady-state paroxetine concentrations were approximately 85 and 110 ng/mL in patients receiving 40 and 50 mg/day, respectively. Moreover, many subjects (see Figure 5 scatterplot from Duboff 1993) were near or well above 100 ng/mL.

Concentrations above 100 ng/mL are common in elderly subjects. Lundmark et al (2000) reported mean paroxetine concentrations of >100 ng/mL in elderly patients receiving 30 or 40 mg/day. Similarly, Pollock et al (2000) observed mean serum paroxetine concentrations ranging between 100 and 150 ng/mL during weeks 5–12 of a long-term study in which elderly patients received 20–30 mg/day. Kaye et al (1989) reported minimum steady-state concentrations of paroxetine of 146 and 227 ng/mL in elderly patients receiving 30 and 40 mg/day, respectively. Concentrations in younger patients at the same doses were 86 and 129 ng/mL, respectively. All of the above data are all minimum concentrations at steady state. With paroxetine’s pharmacokinetics, maximum daily concentrations (~3–8 hours after dose) will be 1.5- to threefold higher.

The overall clinical response to paroxetine is not overtly dose dependent, though higher doses are associated with higher response rates in severe and refractory patients (Tignol et al 1992). The current laboratory and clinical data suggest that paroxetine does partially inhibit the NET in some patients. What is unclear is whether this contributes to its therapeutic actions. All experienced clinicians have noted on many occasions that patients who fail to respond to one selective serotonin reuptake inhibitor (SSRI) go on to respond to another. One explanation for this not uncommon phenomenon is that the SSRIs share the property of serotonin uptake blockade but have other distinct properties that are responsible for the therapeutic differences observed. Thus, NET inhibition is one potential mechanism that may account for the clinical observations that paroxetine may possess therapeutic properties that are not shared by other SSRIs (e.g., broad efficacy in social anxiety disorders, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, and depression) and why higher doses of paroxetine are often more effective in a given patient than lower doses. Other effects of paroxetine such as its inhibition of corticotropin-releasing factor (CRF) messenger RNA expression and, therefore, CRF secretion may mediate some of its effects (Nemeroff 1999).

We look forward to advances that will allow for direct measurement of NET function in individual patients (e.g., positron emission tomography imaging with a selective NET ligand). At present, we believe that the pressor response to tyramine challenge is woefully inadequate as a measure of in vivo NET inhibition. For example, in a recent study by Harvey et al (2000), although a trend appeared clear, the effects of 375 mg/day of venlafaxine, the prototype dual NE/5-HT uptake inhibitor, were not statistically different from those of 75 mg/day of venlafaxine or 50 mg/day of sertraline. We are currently conducting a clinical study that should shed light on this important area. It should reveal information regarding the question of paramount importance—how much NET inhibition occurs at different doses of paroxetine and what magnitude of NET inhibition is necessary to produce clinically meaningful effects?

We are grateful to Dr. Rubin for allowing our group the opportunity to clarify our position on this issue.

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