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.

Robert T. Rubin

Center for Neurosciences Research
Allegheny General Hospital
320 East North Avenue
Pittsburgh PA 15212-4772

References


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...