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RESPONSE

Caveat Emptor: Editors Beware☆

We thank Drs. McCann and Ricaurte (2000) for their comments because they give us the opportunity to address some misconceptions about the relevance of interspecies scaling to 3,4-methylenedioxymethamphetamine (MDMA) neurotoxicity and also to make it clear that we have not taken our responsibilities lightly in the design of a clinical study with MDMA.

In their letter, McCann and Ricaurte (2000) misstate both the accuracy and the limitations of allometric interspecies scaling. Allometric interspecies scaling is based on the fact that the regression of the logarithm of a pharmacokinetic parameter and the logarithm of species weight is generally linear. As a result, pharmacokinetic (and therefore pharmacodynamic, including toxicity) parameters for a given drug can be estimated in any species if this linear relationship is determined (Ings 1990). Yates and Kugler (1986) and others have criticized the potential inaccuracy of interspecies scaling, noting the 10-fold range of estimates that may be derived depending on which pharmacokinetic and corrective factors are thought relevant. Accordingly, the accuracy of the technique is dependent on the availability of sufficient data. For example, Mahmood and Balian (1996) have demonstrated that data from three or more nonhuman species are required to predict reliably the clearance of a drug. When sufficient data are collected, it is sometimes found that animals of different sizes have identical susceptibility (on a mg/kg basis) to a drug effect. That is often the case when the relevant drug effect occurs when a particular threshold concentration is reached (Mordenti and Chappell 1989). For example, Gatley et al. (1999) demonstrated that the same mg/kg intravenous doses of cocaine or methylphenidate produce equivalent dopamine transporter occupancy in mice, baboons, and humans. Ultimately, the lack of empirically collected data casts strong doubt on the accuracy of McCann and Ricaurte's (2000) estimates, which are derived from single species. However, McCann and Ricaurte (2000) could potentially confirm the accuracy of their estimates by demonstrating that they can predict the threshold for neurotoxicity in a species of larger size (e.g., a pig).

There is also evidence that allometric interspecies scaling methods may not apply to MDMA neurotoxicity. In the chapter cited by McCann and Ricaurte (2000), Mordenti and Chappell (1989) state that allometric scaling is often not relevant when metabolism produces active metabolites or pharmacokinetics are not first-order in all species. Several researchers have suggested that MDMA neurotoxicity is due to a metabolite. One possibility is that thioether conjugates of alpha-methyldopamine may cause MDMA neurotoxicity (Bai et al. 1999).

Recent pharmacokinetic data from humans suggest that some metabolites, including alpha-methyldopamine, have zero-order kinetics within a range of commonly administered doses (de la Torre et al. 2000). Although the toxicological importance of these thioether conjugates is still in question, it is well established that MDA (3,4-methylenedioxyamphetamine), the desmethyl metabolite of MDMA, is both psychoactive and neurotoxic. While pharmacologically relevant levels of MDA do not appear to form in humans (Mas et al. 1999), the limited available data suggest that MDA formation is more extensive and probably toxicologically relevant in Dark Agouti rats (Colado et al. 1995), the rat strain used in the estimate of McCann and Ricaurte (2000). Finally, we note that nonlinear MDMA pharmacokinetics have been reported in humans (de la Torre et al. 2000) but were not found in Sprague-Dawley rats (Fitzgerald et al. 1990), although this disparity may be due to differences in dose. Therefore, species differences in MDMA pharmacokinetics and the formation of active metabolites would appear to make allometric scaling unreliable.

Estimates of the MDMA dose required to produce serotonergic neurotoxicity in humans are limited by the lack of certainty about the mechanisms of toxicity. Indeed, empirically obtained pharmacokinetic measures of exposure to MDMA are likely to be more accurate than estimates based on allometric interspecies scaling. To our knowledge, pharmacokinetic data for MDMA are only available from two species: humans (Mas et al. 1999; de la Torre 2000; Fallon et al. 1999) and Sprague-Dawley rats (Fitzgerald et al. 1990). Using these data, it is possible to compare the human exposure to MDMA after 125 mg, p.o. (1.78 mg/kg for a 70 kg human) to

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that seen in Sprague-Dawley rats after 20 mg/kg, s.c., the lowest known neurotoxic MDMA dose (Battaglia et al. 1988; Commins et al. 1987). At these doses, human MDMA plasma AUC are approximately 30% of the neurotoxic rat AUC. Similarly, human Cmax are approximately 10% of rat Cmax.

Because MDA likely contributes to neurotoxicity in the rat, estimates based on total exposure MDMA and MDA could provide a larger species difference in drug exposures. It is recognized that these measures suggest a narrow margin of safety, which would likely be undesirable in a commercial product. These comparisons also cannot account for possible differences in the formation of unmeasured metabolites. Nonetheless, there remains no reason to believe that 1.7 mg/kg, p.o. MDMA is neurotoxic when administered in a controlled clinical setting.

In our study, subjects were fully informed about the status of MDMA research and the potential risk of MDMA intake. They were able to understand the given background information relevant to the aim and design of the study and gave their written consent. The dose used was based on a careful review of the literature and was in the lowest range required to produce reliably psychoactive effects (Downing 1986; Greer and Tolbert 1986, Grob et al. 1996; Grob 1998; Vollenweider et al. 1999). This review found no evidence that a single small dose of pure MDMA (e.g., 1.7 mg/kg) produces long-lasting neurological sequelae in humans. Finally, a detailed retrospective analysis of our data obtained in MDMA subjects shows that a single dose of MDMA produces no long-lasting effects on psychological and neuropsychological measures, cerebral blood flow ($H_2{}^{15}O$-PET), and electrophysiological indices of information processing such as prepulse inhibition of the startle reflex (PPI) and brain wave activity (EEG/ERP). Most important, preliminary analysis using positron emission tomography (PET) and the radioligand McN-5256 revealed no significant changes in 5-HT transporter binding after a single dose of MDMA (1.5–1.7 mg/k) in MDMA naive volunteers after four weeks (Vollenweider et al., in preparation), thus confirming our initial conclusion that such doses would not produce neurotoxic effects.

The mechanisms of MDMA neurotoxicity are poorly understood and MDMA pharmacokinetics are complex. Despite these uncertainties, given the possibility of risk, we agree that prospective volunteers, ethics committees, and regulatory agencies should be fully informed about the possibility of MDMA-induced neurotoxicity and the unknown consequences of these potentially permanent changes. We were not cavalier in our experimental design, and considered very carefully whether or not a 1.7 mg/kg dose represented any significant risk to our subjects (Lieberman and Aghajanian 1999; Vollenweider et al. 1999). We have been cognizant of the MDMA toxicology literature in our deliberations, including the work of Ricaurte et al. (1988).

We conclude that our studies did not compromise the safety of our subjects, and our retrospective studies have confirmed the validity of our approach. Clearly, this kind of debate must occur and investigators must be extremely responsible, as we believe we have been, when any clinical study involving a potentially harmful substance is proposed.

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