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LETTER TO THE EDITOR

Caveat Emptor: Editors Beware☆

We were interested to see that the article by Vollenweider and colleagues (1998) stimulated a discussion regarding the safety and ethical issues surrounding the administration of potentially neurotoxic drugs [in this case, the recreational amphetamine analog, (±)3,4-methylenedioxymethamphetamine (MDMA, *"Ecstasy"*)] to human subjects for experimental purposes. Dr. Gijsman and colleagues (1999) objected to the fact that a drug of abuse that has been demonstrated to be neurotoxic toward brain serotonin neurons in animals (including non-human primates) was given to healthy humans without any prior history of MDMA exposure at a dose that animal studies (Ricaurte et al. 1988; O'Shea et al. 1998) predict would produce toxic effects on brain serotonin neurons. Dr. Vollenweider and colleagues (1999) responded by stating that the existing evidence in animals fails to support the view that a single 1.7 mg/kg dose of MDMA is neurotoxic in humans. Finally, Drs. Lieberman and Aghajanian (1999) wrote a scholarly editorial on the use of potentially harmful drugs in pharmacological challenge studies concluding, in agreement with Dr. Vollenweider and colleagues (1999), that the data do not support the view that single oral doses at 1.7 mg/kg of MDMA are likely to produce damage to serotonin terminals in humans.

Unfortunately, when extrapolating the animal data to humans, Dr. Vollenweider et al. (1999) and the Neuropsychopharmacology editorial omitted a critical and fundamental factor in their calculations: the principle of interspecies drug dose scaling (see Mordenti and Chappell 1989). This principle, which is based upon the underlying anatomical, physiological, and biological similarities among mammals, permits researchers to extrapolate animal data to human beings under a variety of experimental conditions. Put simply, smaller animals require higher dosages of drug, on a mg/kg basis, to achieve the same effect. Stated mathematically:

$$D_{\text{human}} = D_{\text{animal}}(W_{\text{human}}/W_{\text{animal}})^{0.7}$$

where D = dose of drug in milligrams (mg) and W = weight in kilograms (Kg).

If the known single oral neurotoxic dose of MDMA in a monkey (5.0 mg/kg in a 1 kg monkey) is substituted into the equation, the equivalent dose in a human being weighing 70 kg is 1.4 mg/kg, slightly lower than the 1.7 mg/kg dose used by Vollenweider and colleagues. When identical calculations are carried out using rodent neurotoxicity data (O'Shea et al. 1998), the equivalent MDMA dose in humans is approximately 1.7 mg/kg, the same as that used by Vollenweider and colleagues. Thus, once principles of interspecies drug dose scaling are considered, data in both rodents and nonhuman primates support the view that a 1.7 mg/kg dose in humans is likely to be associated with a risk of brain serotonin nerve terminal injury.

There are some circumstances under which the principles of interspecies scaling do not apply (e.g., a particular animal species has a unique metabolic pathway involving a neurotoxic metabolite). However, these do not appear to be relevant in the case of MDMA. In particular, MDMA has been found to be neurotoxic in every animal species thus far examined. Further, application of the principles of interspecies scaling is quite accurate in predicting neurotoxic dosages of MDMA across various animal species. Thus, unless humans are somehow uniquely different with regard to the ultimate disposition of MDMA, the dose used in the experiment by Vollenweider and colleagues of 1.7 mg/kg offers little or no margin of safety with regard to brain serotonin neurotoxicity.

All research studies involving the administration of drugs to humans are associated with potential adverse effects. The essential issue is whether the potential risks of a study outweigh its potential benefits (scientific and otherwise). It is of utmost importance that when considering this question, all parties involved (i.e., potential research subjects as well as researchers and reviewers) make their determinations using accurate estimations of risk.

NEUROPSYCHOPHARMACOLOGY 2001–VOL. 24, NO. 3

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/01/$–see front matter
PII S0893-133X(00)00171-8

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☆Refers to PII S0893-133X(99)00071-8