ELSEVIER

LETTER TO THE EDITOR

Is A Single Dose of MDMA Harmless?

Drs. Gijsman, Verkes, van Gerven, and Cohen are of the opinion that the risk of long-term MDMA-produced serotonin reductions makes MDMA too dangerous to administer to humans, even when using a single moderate dose in research contexts.

We respect the authors' opinion and agree that the potential risk of administering MDMA to healthy volunteers is an important ethical issue that must be thoroughly evaluated in light of all available evidence. We do, however, not agree with the authors' conclusion that a single oral dose of 1.7 mg/kg MDMA in humans is likely to cause damage to serotonergic neurons. We think the existing evidence does not support such a conclusion.

Firstly, Gijsman et al. argue that repeated administration of MDMA in animals leads to damage of serotonergic axons and terminals and that this neurodegeneration is associated with decreased serotonin (5-HT) levels in the brain. They then conclude, since a single dose of MDMA can also lead to a decrease in serotonin levels, that this would be strong evidence for serotonergic neurodegeneration after a single dose. This conclusion, however, is false, since a MDMA-induced decrease in brain serotonin levels does, by no means, imply that such a decrease is ultimately associated with serotonergic neurodegeneration. Perhaps the best evidence of potential neurodegenerative risks of MDMA comes from studies demonstrating that MDMA decreases not only 5-HT and 5-HIAA, but also [3H]paroxetine binding, a measure of 5-HT uptake sites and more direct indicator of serotonergic neurodegeneration, in a dose- and frequency-dependent manner. In fact, Colado et al. (1995) found that 10 mg/kg, i.p. of MDMA decreased 5-HT and [3H]paraoxetine binding by 30%, while 5 mg/kg i.p. had no effect either on 5-HT levels or [3H]paroxetine binding (Colado et al. 1995 and personal communication). This finding was recently corroborated in a study demonstrating that a single dose (4–15 mg/kg i.p.) of MDMA dose-dependently decreased 5-HT, 5-HIAA and [3H]paroxetine binding in regions of the Dark Agouti rat brain 7 days later, while 4 mg/kg i.p. having no degenerative effects. This dose (4 mg/kg) was also without effects when given once daily for 4 days, but produced a decrease in 5-HT and [3H]paroxetine binding when given twice daily for 4 days (Oshea et al. 1998). Similarly, Battaglia et al. (1988) demonstrated that 10 mg/kg of MDMA given four times every 12 hour s.c. to Sprague-Dawley rats, did not reduce 5-HT uptake sites, although 5-HT and 5-HIAA levels were decreased by about 40%. Even more important for the human case is a study by Insel et al. (1989) performed in monkeys. This group found that administration of 2.5 mg/kg of MDMA twice daily for four consecutive days in rhesus monkey did not reduce the density of 5-HT uptake sites, although 5-HT and 5-HIAA were decreased by 50–70%. However, 10 mg/kg given twice daily for 4 days decreased both the number of 5-HT uptake sites and 5-HT levels. Finally, a linear dose-response relationship between the amount of MDMA used and the average total reduction of 5-HT uptake sites (transporter binding) has recently also been reported in a PET study with MDMA users (McCann et al 1998). In that study, an average reduction in 5-HT uptake sites of about 25% was found in 14 people who had taken MDMA an average of 228 times with an average doses of each time of 386 mgs. None of the subjects showed any evidence of current DSM-IV Axis I psychiatric diagnoses in which 5-HT has been implicated.

In summary, these studies demonstrate that the MDMA-induced decrease in 5-HT and 5-HIAA levels can occur independently of changes in 5-HT uptake sites. Thus reductions in 5-HT and 5-HIAA alone are not reliable indicators of reduced 5-HT uptake sites and neurodegeneration. Given the fact that [3H]paroxetine labelling of the serotonin transporter constitutes a more direct marker for assessing structural changes in 5-HT terminals, and given the supposed dose-response relationship, it seems extremely unlikely that administering MDMA (1.7 mg/kg) only one, two or three times within an experimental context, in a dose of a maximum of

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 21, NO. 4

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(99)00032-9

about 50% of what subjects in the McCann study self-administered (McCann et al. 1998), will produce measurable serotonin reductions or functional or behavioral consequences. Finally, it is noteworthy that changes in the number of 5-HT uptake sites in sensu stricto do not only indicate a loss or overall damage of 5-HT terminals, but also include adaptive modulations of 5-HT reuptake sites. In fact, subchronic (less than a month) administration of 5-HT transporter ligands like antidepressants (SSRIs, TCAs and tianeptine) has also be reported to reduce 5-HT transporter mRNA and radioligand binding to 5-HT transporter (see e.g., Lesch et al. 1993). Hence more research is needed to address the question how to interpret discrete reductions of 5-HT ligand binding in human brain.

Second, Gijsman et al. argue by referring to the review of Steel et al. (1994) that a single dose of MDMA can induce a biphasic decrease in 5-HT and 5-HIAA that may last for years. However, even if we take changes in 5-HT and 5-HIAA levels as markers for serotonergic neurodegeneration in to account, there is no indication in Steel's review that a single dose of MDMA approaching the dose used in our human study (1.7 mg/kg p.o.) leads to a reduction of 5-HT and 5-HIAA levels. The authors may have overlooked that the studies cited in Steel's review did not only use higher doses, but that the study by Schmidt et al. (1986) found that 2.5 mg/kg of MDMA given s.c. to rats produced no acute decrease in 5-HT and 5-HIAA 3 hours post-injection. Since this is the time point where the most dramatic decrease in 5-HT and 5-HIAA levels can be observed after higher doses of MDMA, it seems highly unlikely that there will be a such a decrease with 2.5 mg/kg MDMA at any later time-point. Moreover as outlined above, Colado et al. (1995) and Oshea et al. (1998) found no effects of a single dose of 5 mg/kg and 4 mg/kg (i.p.) respectively, on 5-HT and 5-HTAA content in rats.

Third, we agree that it is generally assumed that primates are more sensitive to MDMA than rats or other non-primates. Although it is difficult to extrapolate from animal to human data, we regard primate studies as more pertinent to the human case. To date, there is no evidence indicating that a single dose of MDMA approaching the dose used in our study (1.7 mg/kg, p.o.) leads to a loss of 5-HT uptake sites in primates. The above-mentioned study by Insel et al. shows that even after repeated administration of MDMA up to a cumulative dose of 20 mg/kg i.m., the number of 5-HT uptake sites was not significantly changed. This is several times the dose used in our study. Moreover, there is evidence that parenteral administration of MDMA increases toxicity 2–3 times over oral intake (Ricaurte et al. 1988), which may again widen the gap between the two dose regimens. In this respect, Ricaurte and colleagues' study (cited by the authors), where a single dose of 5 mg/kg MDMA was given orally to monkeys (Ricaurte et al. 1988), is probably the closest approach to the dose regimen used in our human study. This study found a reduction in 5-HT and 5-HIAA content of about 20% in the thalamus and hypothalamus 2 weeks post-drug. However, as shown above, this does not permit any conclusions as to a possible loss of 5-HT terminals. Finally, 2.5 mg/kg MDMA given p.o. once every 2 weeks for 4 months did not alter 5-HT and 5-HIAA brain content in squirrel monkeys (Ricaurte 1993, pers. comm. to the Swiss Federal Ethical Committee).

As to the benefits from our research, we see three kinds. One, we can generate objective, scientific information about the full range of effects of MDMA that can be used to shed light on the causes and consequences of the non-medical use of MDMA by millions of people around the world. Two, research into the mechanism of action of MDMA in normals should provide insight into pathophysiological processes underlying psychiatric disorders in which the 5-HT system has been implicated. Third, normative data obtained with MDMA in normals should also be useful to interpret psychological and neurophysiological data obtained in MDMA users. Such studies are under way or have been performed using PET, PPI, and EEG/ERP technique (Vollenweider et al. 1998, manuscript in preparation). Fortunately, regulatory authorities in the United States, Germany, Spain, and Switzerland, fully aware of the controversy over the neurotoxicity issue, have all approved human (phase I) studies with MDMA and related drugs such as MDE (Gouzoulis et al. 1992; Hermle et al. 1993; Gouzoulis et al. 1993) and fenfluramine (see e.g., Kapur et al. 1994; Mann et al. 1996; Smith et al. 1997; Meyer et al. 1998). Such studies should allow us not only to investigate the mechanisms of action and potential risks of MDMA, but also to gain insight into pathophysiological mechanism of psychiatric disorders related to the serotonergic system.

Franz X. Vollenweider, M.D.
Alex Gamma, M.S.
Matthias Liechti, M.D.
Theo Huber, M.D.
Psychiatric University Hospital
Zürich, Switzerland

REFERENCES

Battaglia G, Yeh SY, De Souza EB (1988): MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacol Biochem Behav 29:269–274

Colado MI, Williams JL, Green AR (1995): The hyperthermic and neurotoxic effects of "Ecstasy" and 3,4,methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. Br J Pharmacology 115, 1281–1289

Gouzoulis E, Steiger A, Ensslin M, Kovar A, Hermle L (1992) Sleep EEG effects of 3,4-methylenedioxyethamphetamine (MDE; "eve") in healthy volunteers. Biol Psychiatry 32:1108–1117

Gouzoulis E, von Bardeleben U, Rupp A, Kovar KA, Hermle L (1993): Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. Neuropsychopharmacology 8:187–193

Hermle L, Spizer M, Borchardt D, Kovar KA, Gouzoulis E (1993): Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? Neuropsychopharmacology 8:171–176

Insel TR, Battaglia G, Johannesen JN, Marra S, De Souza EB (1989): 3,4-Methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in rhesus monkeys. J Pharmacol Exper Therap 249:713–720

Kapur S, Meyer J, Wilson AA, Houle S, Brown GM (1994): Modulation of cortical neuronal activity by a serotonergic agent: A PET study in humans. Brain Res 646:292–294

Lesch PK, Aulakh CS, Wolozin BL, Tolliver TL, Hill GL, and Murphy DL (1993) Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. Mol Brain Res 1:31–35

Mann JJ, Malone KM, Diehl DJ, Perel J, Nichols ThE, Mintun MA (1996): Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers. J Cereb Blood Flow Metab 16:418–426

McCann UD, Szabo K, Scheffel U, Dannals RF, and Ricaurte GA (1998): Positron emission tomographic evidence of toxic effects of MDMA ("Ecstasy") on brain serotonin neurons in human beings. Lancet 352:1433–1437

Meyer JH, Kennedy S, and Brown GM (1998): No effect of depression on [150]H2O PET response to intravenous d-fenfluramine. Am J Psychiatry 155:1241–1246.

Oshea E, Granados R, Esteban B, Colado MI, and Green AR (1998): The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA (Ecstasy). Neuropharmacology 37:919–926

Ricaurte GA, DeLanney LE, Irwin I, Langston JW (1988): Toxic effects of MDMA on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. Brian Res 446:165–168

Schmidt CJ, Wu L, and Lovenberg W (1998): Methylenedioxymethamphetamine: A potentially neurotoxic amphetamine analogue. Eur J Pharmacol 124:175–178

Smith GS, Dewey SL, Brodie JD, Logan J, Vitkun SA, Simkowitz P, Schloesser R, Alexoff DA, Hurley A, Cooper T, Volkow ND (1997): Serotonergic modulation of dopamine measured with [11C] raclopride and PET in normal human subjects. Am J Psychiatry 154:490–496

Steele TD, McCann UD, Ricaurte GA (1994): 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): Pharmacology and toxicology in animals and humans. Addiction 89:539–551.