Short Communications

A REEVALUATION OF PSYCHOTOMIMETIC AMPHETAMINE DERIVATIVES IN HUMANS

Bruce K. Cassels* & Juan S. Gómez-Jeria**

Each time a quantitative correlation is sought between relative potencies of psychotomimetic drugs and physical properties or structural parameters, the same set of human pharmacologic data is used (Shulgin, Sargent & Naranjo 1969). This classic study indicated that a margin of error of ± 25 percent is likely for the activities reported for one-ring psychotomimetics, but it is clear that this degree of precision can only be reached under very stringent experimental conditions, as discussed by Shulgin (1978). When employed as adjuncts in the psychotherapy of neuroses, the effective doses of some of these substances have been seen to vary much more widely from one patient to another. It is not unusual to find that to obtain some *standard* desired effect with a particular drug some subjects may require twice the dosage needed by others, more or less independent of body weight. Such clinical information, which could lead to a more generally meaningful assessment of a drug's activity, is seldom found in the literature.

Over the last decade the authors of this article have received a number of reports from colleagues employing psychotomimetic drugs in clinical practice that 2,5-DMA—(±)-1-(2,5-dimethoxyphenyl)-2-aminopropane—and its 4-bromo derivative DOB almost invariably had to be administered in doses much higher than those expected from their published relative potencies of eight and 400 "mescaline units," respectively (Shulgin, Sargent & Naranjo 1971, 1969). These drugs have been reevaluated using the necessary precautions (Shulgin 1978) and accordingly it was confirmed that their activities must be revised downward. A similar reassessment of the DOB isomer 5-B-2,4-DMA—(±)-1-(5-bromo-2,4-dimethoxyphenyl)-2-aminopropane (Sepúlveda, Valenzuela & Cassels 1972)—has now cast doubt on its psychotomimetic properties.

The threshold oral dose of racemic 2,5-DMA (calculated as the free base) was found to be about 33 mg. A clearly psychedelic (but not psychotomimetic) experience required at least 75 mg, indicating a potency of not more than four or five relative to mescaline. The intoxication with this drug was generally considered pleasant, with an enhanced interest in the subjects' surroundings, but there was no perceptual distortion, no overt stimulation and no gross physiological effects other than slight mydriasis. The drug effect was recognizable about an hour after administration, and at doses in the 75 to 110 mg range gradual recovery was perceived after the sixth or seventh hour, with normal sleeping and eating patterns returning after 12 hours. The low potency of 2,5-DMA explains the apparently large quantity of drug (200 mg of hydrobromide, the equivalent of 140 mg of free base) found in capsules seized by police (Shulgin 1978).

Although as little as 0.5 mg of the very potent DOB produces some recognizable symptoms, in the authors' experience doses of between 1.6 and 2.3 mg (calculated as the free base) were needed to elicit a psychedelic state resembling that brought on by 90 mg of racemic MDA base, taken as a readily available standard. One of the informants reported having to give a patient 3.5 mg to achieve a similar effect. The time of onset was about one hour, as usual with the known one-ring psychotomimetics, but the duration of action was characteristically long: always in excess of 24 hours. A recent profile of DOB (Shulgin 1981) mentions effective doses of this drug in the same range. A calculation of the potency of this drug relative to mescaline results in a value closer to 150 than to the generally cited 400 mescaline units.

Oral administration of 35 mg (calculated as the free base) of racemic 5-B-2,4-DMA resulted, after an induction period of nearly an hour, in vague uneasiness that was interpreted originally as a threshold psychedelic effect. Doses in the 50 to 80 mg range brought on feelings of anxiety and paranoid fantasies as the psychological concomitants of increased malaise with flushing, palpitations and occasionally nausea, vomiting and diarrhea. It now seems that any psychedelic effect that may be present is blurred by the more obviously toxic actions of this substance, which at these doses wear off after five or six hours.

It is interesting to note that the relative potencies found by the authors of this article for 2,5-DMA and DOB are almost exactly those predicted by a linear combination of the ionization potential (IP) and the lipophilicity of the 4-substituent (π) of a set of 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes (Domelsmith et al. 1981). IP

*Lehrstuhl für Pharmazeutische Biologie, Universität München, Karlstrasse 29, 8000 München 2, Federal Republic of Germany.

**Department of Chemistry, Faculty of Sciences, University of Chile, Casilla 653, Santiago, Chile.

measures the overall ability of a molecule to donate electrons; and it is now known that charge transfer from certain atoms, and not from the whole molecule, is important for serotonin receptor affinity (pA_2) associated with psychotomimetic activity (Gómez-Jeria & Morales-Lagos 1984a, 1984b). Also, it is not π but some other property of the 4-substituent (possibly correlated with π for weakly polar groups) that modulates pA_2 (Gómez-Jeria, Cassels & Saavedra-Aguilar 1985). It is significant in this regard that the Domelsmith correlation was not improved by inclusion of log *P* values that are related to the ease with which a molecule would reach its receptor by passive diffusion through biological membranes. The relative potency of DOB as found by the authors of this article comes much closer than the original value to the figure predicted by an equation based only on log *P* (Barfknecht, Nichols & Dunn 1975), but the new relative potency of 2,5-DMA lies far below this correlation line, suggesting again that passive transport does not play an important role in the action of these drugs. Quantitative relationships between structural parameters of psychotomimetic drugs and their potencies in humans will continue to be plagued by the uncertainty of the pharmacological data, which may be considerably greater than the range generally assumed (Shulgin, Sargent & Naranjo 1969).

Additional results with 5-B-2,4-DMA illustrate another aspect that has often been overlooked in studies of this kind: the possibility that a drug's side effects increase the likelihood of error in the estimation of its psychotomimetic potency. The risk of this happening grows with racemic compounds, as both enantiomers can be expected to exert qualitatively different actions and may interact in unexpected ways. The problem is even greater when the psychotomimetic potency is low, where in such cases the necessarily high doses of active isomer are accompanied by equally large amounts of its enantiomer at levels that may well exceed the threshold for some nonpsychotomimetic action.

In conclusion, the relative potencies of psychotomimetic drugs in humans—which span three orders of magnitude—are useful guides in ranking these substances in spite of the large uncertainties involved. It must be kept in mind, however, that they are not represented by precise points on a line going from the very weak, mescaline-like compounds to the extremely potent LSD, but can be better visualized as blurred, irregular, often overlapping segments of a cylinder that is bulging in the different directions that a psychedelic experience can take. Any quantification of these experiences neglects their complexity, which is reflected in the limited success of the various published attempts to derive equations relating psychotomimetic potency and molecular structure.

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