

Short Communications

A REEVALUATION OF PSYCHOTOMIMETIC AMPHETAMINE DERIVATIVES IN HUMANS

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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—(\pm)-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—(\pm)-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

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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 an-

other 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.

REFERENCES

- Barfknecht, C.F.; Nichols, D.E. & Dunn, W.J., III. 1975. Correlation of psychotomimetic activity of phenethylamines and amphetamines with 1-octanol-water partition coefficients. *Journal of Medicinal Chemistry* Vol. 18: 208–210.
- Domelsmith, L.N.; Eaton, T.A.; Houk, K.N.; Anderson, G.M., III; Glennon, R.A.; Shulgin, A.T.; Castagnoli, N., Jr. & Kollman, P.A. 1981. Photoelectron spectra of psychotropic drugs. 6. Relationships between physical properties and pharmacological actions of amphetamine analogues. *Journal of Medicinal Chemistry* Vol. 24: 1414–1421.
- Gómez-Jeria, J.S.; Cassels, B.K. & Saavedra-Aguilar, J.C. 1985. Unpublished manuscript.
- Gómez-Jeria, J.S. & Morales-Lagos, D. 1984a. The mode of binding of phenylalkylamines to the serotonin receptor. In: Kuchar, M. (Ed.). *QSAR in Design of Bioactive Compounds*. Barcelona: J.R. Prous.
- Gómez-Jeria, J.S. & Morales-Lagos, D. 1984b. Quantum chemical approach to the relation between molecular structure and serotonin receptor binding affinity. *Journal of Pharmaceutical Sciences* Vol. 73: 1725–1728.
- Sepúlveda, S.; Valenzuela, R. & Cassels, B.K. 1972. Potential psychotomimetics. New bromoalkoxyamphetamines. *Journal of Medicinal Chemistry* Vol. 15: 413–415.
- Shulgin, A.T. 1981. Profiles of psychedelic drugs. 10. DOB. *Journal of Psychoactive Drugs* Vol. 13: 99.
- Shulgin, A.T. 1978. Psychotomimetic drugs: Structure-activity relationships. In: Iversen, L.L.; Iversen, S. & Snyder, S.H. (Eds.). *Handbook of Psychopharmacology*. New York: Plenum.
- Shulgin, A.T.; Sargent, T., III & Naranjo, C. 1971. 4-Bromo-2,5-dimethoxyphenylisopropylamine, a new centrally active amphetamine analog. *Pharmacology* Vol. 5: 103–107.
- Shulgin, A.T.; Sargent, T., III & Naranjo, C. 1969. Structure-activity relationships of one-ring psychotomimetics. *Nature* Vol. 221: 537–541.

PHARMACOSEXOLOGY UPDATE:
YOHIMBINE AND SEXUAL FUNCTION

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Yohimbine is a drug that has a reputation as an aphrodisiac. Historically, an aphrodisiac has been considered to be a substance that either (1) produces penile erections or (2) increases sexual desire, without the presence of any other sexual stimulation. Yohimbine is reputed to fall into the former category: It causes erectile stimulation without increasing sexual desire. Popular subjective accounts of the use of yohimbine for sexual enhancement describe not only erectile stimulation in males, but "pelvic tingles," "warm spinal shivers" and increased pleasure from coitus and orgasm in both sexes (Young et al. 1977; Gottlieb 1974).

Yohimbine is primarily an α -2-adrenergic antagonist: It stimulates the presynaptic release of norepinephrine (Goldberg & Robertson 1983). Stimulation of the α -2-adrenergic receptor is thought to inhibit norepinephrine release, decreasing sympathetic outflow from the central nervous system. The α -2 antagonist activity of yohimbine is 20 to 500 times more potent than its α -1 activity, depending on which tissue is examined (Steers, McConnell & Benson 1984).

The exact mechanism by which yohimbine exerts its sexual effects is unknown. It is thought that yohimbine acts to either increase blood flow to the corpora, decrease venous outflow from the corpora or both.

There are not many studies of the sexual uses of yohimbine. One early study looked at the effects of yohimbine in 15 schizophrenics, 20 mental hospital patients with mixed diagnoses and nine normal volunteers who were given an intravenous dose of 0.5 mg/kg over a five-minute period (Holmberg & Gershon 1961). Erection was observed to occur in 10 to 20 percent of the subjects. Additionally, the subjects exhibited facial flushing, increased heart rate, perspiration, salivation, lacrimation and pupillary dilation. In those subjects most affected, nausea, urgency of micturition and defecation also occurred along with the rise in blood pressure. No mention was made of how long the erection lasted.

A more recent study examined the effects of yohimbine administration in 23 patients in a sexual dysfunction clinic, all of whom gave a history of three months of continuous failure to obtain a full erection (Morales et al. 1982). All patients met the criteria for organic erectile

impairment. Those with psychogenic causes were excluded as well as those patients with hypothalamic-pituitary-gonadal dysfunction. In the majority of patients the erectile dysfunction was due to diabetes, vascular disease or antihypertensive therapy. The dose of yohimbine used was six milligrams orally three times a day. Six of the 23 subjects (26 percent) reported full and sustained erections with resumption of satisfactory sexual performance. Four of the 23 subjects (17 percent) reported some improvement, but also that the quality of erections was unsatisfactory. Thirteen of the 23 subjects (56 percent) reported no improvement in erectile function. Reported side effects at this dose were minimal and consisted of dizziness in two patients and nervousness in one patient. These two studies constitute the only literature on the human use of yohimbine as an aphrodisiac.

There are several other studies using a combination of yohimbine, methyltestosterone and nux vomica (strychnine) that describe the use of those drugs in a combination product called Afrodex®. The *Medical Letter on Drugs and Therapeutics* reviewed these studies and found them to be severely lacking (Unsigned 1968). The conclusion was that "despite the favorable reports, there is still no good evidence that Afrodex and similar drugs have more than placebo effects."

In a recent study, nine rabbits were injected with yohimbine (1.0 mg/kg or 2.0 mg/kg) and then sacrificed so their penile tissue could be studied (Steers, McConnell & Benson 1984). Erections were noted in two of the rabbits given the higher dose.

A study done on male rats showed increased mounting behavior when given yohimbine (2.0 mg/kg) intraperitoneally (Clark, Smith & Davidson 1984). This occurred in spite of the fact that their genital areas had been previously anesthetized. This finding was interpreted to mean that yohimbine enhanced sexual motivation.

Currently, injectable yohimbine is classified as an investigational drug in the United States and as such would require special protocols and permission for human testing by the Food and Drug Administration. However, yohimbine hydrochloride (5 mg tablets) are available under the brand name Yohimex® and are manufactured by Kramer Pharmacal of Miami, Florida. The 1984 *Physicians' Desk Reference* (Medical Economics 1984: 1047) lists the following indications for its use: "Yohimex is indicated as a sympatholytic and mydriatic [sic]. It may have activity as an aphrodisiac." There is a further caution that "yohimbine HCl may injure kidneys, cause hypertensive reactions, as well as cause an allergic reaction in individuals prone to be sensitive to its use." Moreover, there is also a warning against its use in preg-

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nant or lactating women. The recommended adult dose is five milligrams three to four times a day.

The more common source of yohimbine is a tea made from the bark of the yohimbe tree (*Corynanthe yohimbe* or *Pausinystalia yohimbe*). The bark is available in some herb shops or health food stores. The tea is made by simmering five to 10 teaspoons of the shaved bark in one pint of water. It has been suggested that 0.5–1.0 g of vitamin C be added to the tea. This converts the yohimbine alkaloid to the more water soluble yohimbine ascor-

bate. It should be noted that the bark contains other alkaloids similar to yohimbine (e.g., yohimbiline, ajmaline and corynanthine), some of which have significant autonomic activity of their own.

In conclusion, it would appear that about 20 percent of males given yohimbine responded with an erection. It is unclear why these men responded and the others did not. A 20 percent response is not sufficient for yohimbine to be considered an aphrodisiac, but it would seem to be reason enough to justify further study.

REFERENCES

- Clark, J.T.; Smith, E.R. & Davidson, J.M. 1984. Enhancement of sexual motivation in male rats by yohimbine. *Science* Vol. 225: 847–849.
- Goldberg, M.R. & Robertson, D. 1983. Yohimbine: A pharmacological probe for study of alpha-2-adrenoreceptor. *Pharmacological Reviews* Vol. 35: 143–179.
- Gottlieb, A. 1974. *Sex Drugs and Aphrodisiacs*. New York: High Times/Level Press.
- Holmberg, G. & Gershon, S. 1961. Autonomic and psychic effects of yohimbine hydrochloride. *Psychopharmacologia* Vol. 2: 93–106.
- Medical Economics Company. 1984. *Physicians' Desk Reference*. 38th ed. Oradell, New Jersey: Medical Economics.
- Morales, A.; Surrege, D.H.; Marshall, P.G. & Fenemore, J. 1982. Nonhormonal pharmacological treatment of organic impotence. *Journal of Urology* Vol. 128: 45–47.
- Steers, W.D.; McConnell, J. & Benson, G.S. 1984. Some pharmacologic effects of yohimbine on human and rabbit penis. *Journal of Urology* Vol. 131: 799–802.
- Unsigned. 1968. Afrodex and impotence. *Medical Letter on Drugs and Therapeutics* Vol. 10: 97–98.
- Young, L.A.; Young, L.G.; Klein, M.M.; Klein, D.M. & Beyer, D. 1977. *Recreational Drugs*. New York: Macmillan.