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Assessment of Tolerance to the Hallucinogenic Effects of DOM

Burton Angrist, John Rotrosen, and Samuel Gershon

Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University Medical Center, New York, New York 10016

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Abstract. DOM was administered to five subjects, each of whom received 6 mg of the drug daily for 3 consecutive days. Tolerance was observed. This finding is correlated with prior studies of behavioral biochemical and electrophysiologic aspects of DOM tolerance in cats.

Key words: DOM — Hallucinogens — Tolerance.

Several prior clinical studies have shown that DOM (2,5-dimethoxy-4-methylamphetamine) is hallucinogenic in humans (Faillace, Snyder, and Weingartner, 1970; Hollister, Macnicol, and Gillespie, 1969; Snyder, Faillace, and Hollister, 1967); Shulgin has determined that its potency is on the order of 80 times that of mescaline (Shulgin, Sargent, and Naranjo, 1969). The neuropharmacology of DOM has been studied in our laboratories, where its effects on the behavior, electroencephalogram, and reticular formation multiple unit activity of cats were documented (Wallach, Friedman, and Gershon, 1972). In the course of these studies, it was fortuitously noted at first, and later formally documented, that tachyphylaxis occurred when a second DOM dose was given 24 h after a prior administration of the drug (Wallach *et al.*, 1972).

Since tolerance to the psychedelic effects of other hallucinogens is known to occur in humans (Balestrieri and Fontanari, 1959; Isbell, Wolbach, Wikler, and Miner, 1961), this finding suggested that a human study of tolerance to DOM be undertaken. A prior report by Hollister *et al.* (1969) of marked attenuation of DOM effects in two subjects given large (12 mg) doses of the drug on two successive days suggested that the development of such tolerance was likely.

Methods

Five male subjects, between the ages of 23 and 35 years, participated in this study. All were judged to be non-schizophrenic and free from major emotional instability by two research psychiatrists. Subjects were told that the experiment involved the administration of hallucinogens. Prior experience with this type of

drug was not a cause for exclusion, but subjects who had used such drugs within the past 2 months were excluded. Before DOM was administered, medical histories were taken and physical examinations were performed, to rule out cardiovascular, renal, and hepatic disease. Hematologic and hepatic function tests and urinalyses were done before and after DOM administration.

Six mg of DOM dissolved in tap water was administered in the mornings of 3 successive days. Drug effects were documented 3 h later, by means of:

1. The "significant", "true" items of the Addiction Research Center Inventory (ARCI) (Hill, Haertzen, Wolbach, and Miner, 1963): 59 items which have been shown to discriminate LSD from placebo conditions at less than the 0.05 level of significance.

2. The Perceptual Experience Inventory (PEI) (Tucker, Harrow, Setre, and Hoffman, 1969), a scale designed to explore clinical phenomena such as those seen in early schizophrenia and after psychedelic drug use (Bowers and Freedman, 1965). This scale consists of 22 items which tap such experiences. Of these, 4 are irrelevant to this type of psychiatric phenomenology.

3. Videotaped interview, subjective estimate of intensity of drug experience, and clinical observation by two psychiatrists.

Placebos were not used. Subjects were under constant observation during the 3 days of study, in order to avoid the possibility of other drug use. The only other drug permitted during the course of the study was secobarbital 100 mg, should insomnia prove troublesome. (Only one subject actually requested this, and did so only on the first night after DOM had been given.)

Results

1. Addiction Research Center Inventory. Table 1 gives the number of items scored "true" for each subject before drug and on each study day. The maximum score by this method is 59. This score was assigned to one subject who, on day 1, was too disorganized to attempt to complete the scale. A second subject attempted to do so, but was unable. His unanswered questions were scored positively for a total score of 42. Mean scores for baseline vs. day 1, and for day 1 vs. day 3, differed significantly, corroborating both drug effect and tolerance even in this numerically small group.

2. Perceptual Experience Inventory. Table 2 gives the scores for PEI. Only the 18 relevant questions were scored (Tucker *et al.*, 1969), 9 of these on a scale of 1 ("never") to 5 ("almost all the time"). The remaining 9 were scored "true" or "false" (1 or 0). The maximum possible score therefore is 54. One of the 5 subjects was unable to complete more than 3 items on the first day. Unanswered items were given a maximum score, thus giving him a final calculated score of 51. Mean scores showed the same trend as that on the prior scale, but did not attain statistical significance.

3. Subjective Estimates. All 5 subjects estimated the effects of this dose of DOM as extremely intense on the first day; 4 out of 5 found it unpleasantly so. By the third day, one continued to experience diminished, but moderately strong, effects. Two others rated the effect very much

Table 1. ARCI

Subject No.	Baseline	Day 1	Day 2	Day 3
1	6	24	20	17
2	3	42[a]	22	21
3	1	25	10	6
4	6	32	25	17
5	6	59[b]	27	2
Means:	4.4	36.4*	20.8	12.2**

[a] Unable to complete scale.
[b] Unable to attempt scale.
* Baseline vs. Day 1: $P < 0.005$.
** Day 1 vs. Day 3: $P < 0.05$.

Table 2. PEI

Subject No.	Baseline	Day 1	Day 2	Day 3
1	17	28	24	17
2	25	29	—[b]	19
3	18	23	18	17
4	13	27	26	21
5	20	51[a]	27	17
Means:	18.6	31.6	23.75	18.2

[a] Unable to complete scale.
[b] Answered questions "true" or "false", without quantification. No score assigned.

diminished. A fourth found the last day's drug effects only "barely perceptible", while the fifth felt "absolutely nothing" by day 3. The fourth subject, who had required secobarbital for insomnia on the first night, fell asleep 3 h after ingesting the drug on the third day. The fifth subject also slept soundly, for 45 min until awakened, beginning $1^1/_2$ h after ingesting his third dose of DOM. These subjective estimates were in accordance with the observers' assessments.

Discussion

This study indicates that tolerance develops rapidly to the effects of DOM in humans. This in turn suggests that neurochemical studies of the tolerant state might help elucidate mechanisms of action of DOM and perhaps of other hallucinogenic drugs. Wallach *et al.* (1972) have shown that a single administration of 8 mg/kg DOM induces a significant increase in norepinephrine (NE) in the medulla and a trend toward increased serotonin (5-HT) levels in the hemispheres and diencephalon.

These levels diminished to control values after 24 h. A second dose of DOM produced none of the behavioral or electrophysiologic effects of the first, but again resulted in a significant increase in medullary NE. Diencephalic 5-HT, however, was significantly decreased, as compared with levels found in this area 1 h after single-dose administration. These findings could be interpreted as suggesting that DOM affects both NE and 5-HT levels, but that serotonergic activity may correlated more closely with the drug's hallucinogenic effects.

The fact that 2 subjects slept after the third dose is consistent with the behavior noted by Wallach *et al.* (1972) in cats. While the first 8 mg/kg dose of DOM elicited marked behavioral arousal, aggressivity, EEG hypersynchrony, and elevated reticular formation unit activity, a second such dose 24 h later produced a sleeping animal in which EEG and reticular formation unit activity was also consistent with slow-wave sleep. The unquantified clinical observation that subjects experienced moderate hallucinogenic effects but a diminished sense of stimulation on day 2, taken together with one subject's observation of continued mild hallucinogenic effects while becoming drowsy and actually falling asleep on day 3, suggests the possibility, first suggested by Shulgin (1973), that the stimulant and psychedelic effects of DOM may be mediated by different mechanisms, to which tolerance develops at different rates. Shulgin's observation that the *d*- and *l*-isomers of DOM have differing ratios of hallucinogenic-to-stimulant activity (Shulgin, 1973) also suggests this possibility.

Finally, Kulkarni (1973) has reported that mescaline and several related amphetamine analogues, such as DOM and DOET (2,5-dimethoxy-4-ethylamphetamine), cause a dose-related induction of a scratching response in mice, to which tolerance rapidly develops. He concludes his report by speculating that "It would be interesting to document the data on psychotomimetic effects of DOM in man on repeated exposures, since a rapid tolerance to the induced scratching was seen here in mice." The results of his study correlate well with our observations, suggesting the possibility that this scratching response may, if consistent for other compounds, prove to be useful as a screening procedure for compounds with hallucinogenic activity.

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Dr. Burton Angrist
Neuropsychopharmacology Research Unit
Department of Psychiatry
New York University Medical Center
550 First Avenue
New York, N.Y. 10016
U.S.A.