

The Properties of 3,4-Methylenedioxyamphetamine (MDA). I. A Review of the Literature*

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The current enthusiasm for the use of drugs for nonmedical purposes has provided much cause for concern, both on the part of the clinician called to treat cases of drug overdose, and on the part of the toxicologist who is frequently asked to provide information concerning the toxicity of drugs of abuse. Recently the situation has become considerably more complex, since, in addition to such well-known agents as marijuana, amphetamines, and LSD, a number of more obscure compounds are appearing on the illicit market. A list of these compounds has been provided by Taylor [1], and although this list may be incomplete (for example, cases of the abuse of diethyltryptamine, DET, have been reported [2]), it is apparent that a major class of these new drugs of abuse consists of various substituted amphetamine derivatives. Among these agents are STP (DOM, 2,5-dimethoxy-4-methylamphetamine [3]), TMA (trimethoxy-amphetamine [4]), MDMA (methoxy-methylenedioxyamphetamine [5]) and the subject of this review, MDA (3,4-methylenedioxyamphetamine).

Although at present the use of MDA cannot be described as widespread, the toxicity of this agent is such that more information is badly needed. In the City of Edmonton a number of deaths have

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been attributed to MDA [6], and at least two more fatalities have recently occurred in California [7]. Despite this, use of the agent continues, and the purpose of this review is to collect together the small quantity of information we have on the subject. Unfortunately Louria [8] is substantially correct when he states that "very little is known" about MDA.

CHEMISTRY AND PHARMACOLOGY

MDA was first prepared by no less a chemist than Mannich, in 1910 [9]. Since that time a number of other syntheses have been reported [10-12] and it is worth pointing out that none of these syntheses are particularly facile. It must thus be supposed that the MDA which appears on the illicit market has been stolen from research laboratories, or that the manufacturers of illicit drugs are capable of greater sophistication than is commonly believed.

The first, and perhaps the most comprehensive study of the pharmacological properties of MDA was carried out by Gunn and co-workers in 1939 [13]. This study, which was concerned with their work on the structure-activity studies of the phenethylamines, involved MDA which had been prepared by an unspecified route. Also, it is not clear whether these workers employed the free base or a salt in their studies, but their findings are consistent with the later work on this agent. These workers reported that MDA had marked sympathomimetic effects in experimental animals; the compound caused a rise in blood pressure, stimulation of the heart, and effects on other smooth muscle similar to amphetamine. They examined the minimum lethal dose of this agent by intraperitoneal injection in mice, and concluded that its toxicity was comparable to that of amphetamine itself, 0.12 gm/kg. Of particular interest was the observation that MDA has central stimulant activities greater than those of amphetamine, and they reported that in high doses the agent caused convulsions and characteristic behavioral changes. This led them to the suggestion that the pronounced central activity could be exploited therapeutically. It is interesting to note in passing that MDA has been patented for therapeutic purposes [14-16] but apparently never for its CNS stimulant activities.

Further studies of the pharmacology of MDA have generally been carried out with a view to determining the mechanism of action of this agent and of the amphetamines in general. Mann

and Quastel [17] reported that MDA could reverse the tyramine-induced depression of brain respiration, and this work was later developed by Fellows and Bernheim [18] who found a good correlation between the inhibition of monoamine oxidase and the central activities of a series of amphetamines including MDA. Ota [19] had previously observed, however, that both the d- and l- forms of MDA were effective inhibitors of amine oxidase while the l-isomer lacked analeptic effects. This was later confirmed by Fujimura and Ohata [20] who suggested that the central activity of MDA was unlikely to be mediated by its effects on respiration or monoamine oxidase. The observation by Goldstein and Contrera [21] that MDA can inhibit dopamine β -oxidase may have some bearing on the activity of this compound, although the very rapid onset of the central stimulation suggests that this property cannot be responsible for the acute effects of this agent.

Ogawa [23] suggested that MDA had a central adrenergic action, and both Daly and co-workers [24] and van der Schoot and co-workers [25], who examined a large number of amphetamine derivatives, concluded that these agents owed their action both to a direct effect and to liberation of catecholamines--a suggestion which is now widely accepted.

The effects on the electrical activity of the brain has been the subject of a single study [26]; it was claimed that "alerting activity" and "hallucinogenic activity" gave rise to different patterns of sub-cortical electrical properties. It was suggested on this basis, that MDA is a hallucinogen of greater potency than mescaline, while, relative to amphetamine it is almost devoid of "alerting activity." Benington and co-workers have also reported the behavioral effects of MDA in cats [27] and found no evidence of aggressive behavior.

To summarize these studies, MDA is a sympathomimetic with properties closely similar to amphetamine. It has pronounced stimulant activity on the central nervous system, but may have hallucinogenic rather than "alerting" properties. MDA has several metabolic effects, but these may be unrelated to the central activity, which has a rapid onset. This limited information would appear to include most of our knowledge of the animal pharmacology and toxicology of this agent.

HUMAN STUDIES

Two studies have reported the effects of low doses of MDA on human perception. Alles [28] in some self-experiments stated

that the drug was not hallucinogenic, but did heighten perception and enabled him to perceive sounds which were usually inaudible. He reported that the threshold dose for the appearance of subjective effects was about 80 mg, and that the drug produced some increase in blood pressure and marked pupillary dilation at this dose. The effects of MDA in preventing sleep were reported as being substantially less than amphetamine. In the discussion of his paper, Alles mentioned that in some toxicity trials, details of which were not provided, MDA was about as toxic as amphetamine.

Naranjo and co-workers [29] tested MDA as a possible adjunct to psychotherapy, using a group of volunteers who had experience of other psychoactive agents such as LSD. Like Alles, they reported that MDA was not hallucinogenic, but apart from this the effects were similar to those of LSD. The suggestion that this agent could prove a useful adjunct to psychotherapy does not appear to have been developed.

Other studies of the effects of MDA in humans are much less detailed; an early report suggested that the use of this drug in Parkinsonism was not indicated, since it appeared to increase rigidity [30]. In addition Naranjo [29] reports a personal communication from one of the workers engaged in the development of the agent for anorexigenic purposes, who stated that in clinical trials high doses were not well tolerated.

MDA AS A DRUG OF ABUSE

It will be apparent that our knowledge of MDA rests heavily on the reports arising from the nonmedical use of this agent. Unfortunately, however this information is subject to considerable criticism. First, the reports arise from self-medication and are thus subject to considerable personal bias; second there is no guarantee that a tablet sold illegally as MDA actually contains this material. Further we have no information as to whether the tablet is adulterated with other materials, and finally such reports are very rare.

With these cautions in mind, however, it is possible to arrive at certain conclusions about the properties of this agent. First, both Louria [8] and Taylor [1] appear to regard MDA as hallucinogenic despite the reports of Alles and Naranjo mentioned above. This has been reinforced by many conversations with those involved in the nonmedical use of drugs, who generally believe the drug to be hallucinogenic. This may well be a dose-related effect, however; it is possible that the use of higher doses than those employed in the human

experimentation discussed earlier would alter the effects of the drug from "heightened perception" to hallucinosis.

The physiological effects of acute dosage with MDA have not been clearly delineated, and we lack information as to the chronic effects or possible teratogenic effects not only in humans but in any animal species. Acute overdose resulting in death has occurred [6, 7] as mentioned earlier, but few clinical details are available. Gunn reported that in mice, death arose from respiratory failure, but it would appear that the cause of death in humans may lie in hypertension-induced hemorrhage or cardiac arrest. Reliable estimates of the dosage responsible for the fatalities are not available.

MDA is administered either orally, as a tablet, or by intravenous injection. The latter route is claimed to give a better "high" using less of the material. Whether tolerance develops to MDA is open to question, and it is not known whether any patterns of addiction occur, although it has been suggested that instances of psychological dependence exist [31].

CONCLUSIONS

Despite the hazards of nonmedical use of MDA, we are in possession of very little information as to its properties. This drug bears a close similarity to amphetamine in many of its effects, but has greater central activity and may be hallucinogenic in high doses. The hazards of its use appear to be similar to those of amphetamine despite the fact that many of those who use the drug appear to regard it as being more closely allied to LSD. This latter observation suggests that some of the problems associated with the use of MDA may arise from confusion on the part of the users as to the nature of the compound they are taking.

While it is profoundly to be hoped that the current wave of drug abuse will decline in the future, there is little doubt that our knowledge of the properties of MDA is inadequate to provide either sound information or effective therapy in the case of overdose. We badly need more information, particularly of a clinical nature.

SUMMARY

A review of the literature of 3,4-methylenedioxyamphetamine (MDA) reveals that this agent is a powerful central stimulant which

may possess hallucinogenic properties when administered in high doses. The pharmacology of this agent appears to be very closely similar to amphetamine itself.

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