CLINICAL TOXICOLOGY, 6(2), pp. 193-199 (1973)

The Properties of 3,4-Methylenedioxyamphetamine (MDA). II. Studies of Acute Toxicity in the Mouse and Protection by Various Agents*

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The emergence of MDA as a drug of abuse, and the paucity of information concerning its effects, have prompted us to carry out some experiments on the toxicity of this agent in experimental animals, with a view to providing some estimates of the hazards associated with its use. Further, we have investigated a possible therapy for massive MDA overdose, a syndrome which has been reported both in Canada and the U.S. [1, 2].

The only detailed data previously available concerning the toxicity of MDA were obtained by Gunn and co-workers in 1939 [3], who estimated the minimum lethal dose by intraperitoneal injection in mice to be 0.12 g/kg, similar to that of amphetamine itself. Since nonmedical use of MDA occurs via oral or intravenous administration, it is desirable to investigate the toxicity of the agent via these routes. The experiments have been carried out

*This work was supported in part by a grant from the Canadian Department of National Health and Welfare.

using the mouse, both for convenience and to obtain a direct comparison with the toxicity of amphetamine.

METHODS

White mice of the ALAS strain weighing about 25 gm were employed in these studies. The toxicity of MDA was determined using groups of 6-12 animals at each dose, each group comprising half males and half females. MDA, obtained from the Canadian Food and Drug Directorate, was administered as a hydrochloride solution in normal saline, and doses were recorded as milligrams free base per kilogram test animal. Other drugs employed in this study were phentolamine (Regitine, Ciba Pharmaceuticals) and phenobarbital (BDH). Intraperitoneal injections were made into the lower left abdominal quadrant, intravenous injections were made into the lateral tail vein, and oral administration was accomplished by gavage using a blunt-ended 24 gauge needle. In cases where there was some doubt as to whether the animal had received a full dose of drug by the required route, the animal was discarded.

After administration of MDA, the animals were transferred to separate Plexiglas cages and kept under close observation for five to six hours. A careful record of behavioral effects was made, and if the animal died, the time and nature of death was recorded. Animals which survived more than eight hours were kept under intermittent observation for four days.

In the studies of the interactions of other agents with MDA, animals were selected at random and assigned alternately to a control or an experimental group. Both groups received MDA by intraperitoneal injection at a dose of 90 mg/kg. The experimental group received phenobarbital (30 mg/kg) by intraperitoneal injection shortly after administration of MDA, and in some experiments this was followed, after an interval of 45 min, by intraperitoneal administration of phentolamine (10 mg/kg). In further experiments the procedure was repeated with the omission of the phenobarbital. The doses of these agents are similar to those suggested by Barnes and Eltherington [4].

The LD_{50} and the corresponding confidence limits were obtained from the probit analysis [5] as modified for the APL computer system [6]. The computer employed was the IBM 360/67. Probabilities were obtained from the χ^2 test [7].

RESULTS

Effects of MDA

Shortly after administration of MDA, the animals show marked piloerection and exopthalmos which sometimes persists for several hours. There may be ejaculation in males. Rarely, the animals may develop corneal opacity shortly before death.

High doses of MDA are accompanied by clonic convulsions, which may occur intermittently for up to two hours. The convulsions are initially interspersed with periods of quiescence, but as the convulsions become less frequent, they are separated by periods of violent but coordinated motor activity. Characteristic behavior during this period includes protracted hand-and face-washing activity accompanied by twisting of the head. This latter effect is believed to be characteristic of hallucinogenic drugs [8]. In addition the animal tends to move backward round the cage, and if confronted with an obstacle, will back away from it. These behavior patterns may persist for several hours, finally giving way to a period in which the animal becomes comatose. Normal behavior starts to reappear six to 12 hours after administration, and the survivors appear to be normal after 24 hours.

Death may occur at anytime during the course of the intoxication but is frequent during the convulsions. Some animals fail to recover from the comatose state, and others, although apparently normal at 24 hours after administration of MDA, die during the ensuing 24 hours. Death appears to be due to respiratory failure.

Estimations of LD_{50}

The LD_{50} value using the intraperitoneal, intravenous, and oral administration of MDA are shown in Table 1, together with the corresponding data for amphetamine [9, 10]. It appears that the agent is slightly more toxic than amphetamine in this species. It should be noted that the 1 hour intravenous LD_{50} is in some doubt since the χ^2 test, which is routinely applied, suggests that the probit transformation is inappropriate for the data. This may arise because death by intravenous injection is very rapid. In general an animal which survives more than three minutes will

TABLE 1. LD_{50} Values for MDA and Amphetamine, by Different Routes in Mice[a]

	MDA, 1 hr	MDA, 4 hr	MDA, 36 hr	Amphetamine
Intraperitoneal	92.7 ± 1.9	90.1 ± 1.6	82.3 ± 1.4	120 [9]
Intravenous	32.9 ± 2.8	33.2 ± 1.4	33.2 ± 1.4	25 [8]
Oral	62.9 ± 5.4	53.0 ± 5.0	13.3 ± 2.9	22 [8]

[a]Values for MDA shown ± standard error. LD_{50} values expressed as milligrams free base per kilogram of mouse.

survive up to four days, and the individual tolerances to large intravenous doses of MDA appear to vary widely.

Protection Studies

The effects of phenobarbital, the short-lasting α-adrenergic blocking agent, phentolamine, and a combination of these agents on mice poisoned with MDA is shown in Table 2. Phenobarbital increased the percentage survival over the control group which had received MDA alone. Phentolamine alone had little effect, but the combination of phenobarbital and phentolamine increased the percentage survival both over the control group and the group treated with phenobarbital alone. These results suggest that the toxicity of MDA arises from both central and autonomic effects, and to maximize the chance of survival, it is necessary to deal with both effects.

DISCUSSION

The administration of MDA to mice is accompanied by physiological effects similar to those encountered with amphetamine. The behavioral effects differ from those of amphetamine, and this may be attributed to the probable hallucinogenic effects of this agent. In particular the animals appear unresponsive to their

TABLE 2. Effects of Phenobarbital and Phentolamine on Survival of Mice Poisoned with MDA

	No. tested	% survival after 4 days
MDA (90 mg/kg)	48	14.3
MDA (90 mg/kg) + phentolamine (10 mg/kg)	12	16.7
MDA (90 mg/kg) + phenobarbital (30 mg/kg)	12	50[a]
MDA (90 mg/kg) + phentolamine (10 mg/kg) + phenobarbital (30 mg/kg)	34	89[a,b]

[a]Significantly ($P<0.01$) different from controls.
[b]Significantly ($P<0.01$) different from MDA + phenobarbital alone.

surroundings and to the presence of other animals in the cage. The toxicity of MDA in mice is similar or rather higher than that of amphetamine itself, and this fact is of some interest in view of the widely held belief that MDA can be classified with LSD, which has a relatively low acute toxicity relative to the dose for hallucinosis, rather than amphetamine which is generally known to be toxic. The very low oral LD_{50} at 36 hr is a particularly alarming observation, and if a similar phenomenon pertains to man, it is not surprising that deaths from MDA overdose have been encountered.

The attempted therapy of MDA overdose was suggested by the recommended therapy of amphetamine overdose [11] and appears to be effective in the case of MDA also. It is apparent that some component of the toxicity of MDA arises from its sympathomimetic effects, and these may be antagonized by the short-lasting α-adrenergic blocking agent phentolamine.

These studies suggest the possibility that MDA intoxication may be successfully treated in the same way as amphetamine intoxication, and parenthetically, it would be expected that further measures [11] that may be applied to amphetamine overdose, such as osmotic diuresis with ammonium chloride, would also be beneficial, although we have no direct evidence of this at present.

Finally, it is important to bear in mind that "street" MDA may be contaminated with other materials or may, in fact, contain a totally different compound. The experience reported by Solursh and Clement [12] indicates the care necessary in the therapy of overdose of drugs of abuse; intoxication with STP (DOM, 2,5-dimethoxy-4-methyl amphetamine, an amphetamine closely related to MDA), was treated with chlorpromazine with fatal results owing to contamination of the street STP with a belladonna alkaloid. Thus if MDA overdose is reported, it is necessary to establish the diagnosis of overdose with a sympathomimetic amine before instituting therapy. It would seem reasonable that therapy similar to that employed in the case of amphetamine overdose should be employed, and this suggestion is supported by the study on experimental animals reported here.

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