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EFFECTS OF AN i.v. LETHAL DOSE OF 3,4-METHYLENEDIOXYAMPHETAMINE (MDA) IN THE DOG AND ANTAGONISM BY CHLORPROMAZINE

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Abstract—1. A high intravenous (i.v.) dose of MDA (20 mg/kg) to mongrel dogs elevated body temperature, heart rate, mean arterial pressure and other cardiovascular parameters initially, but only the 1st two remained high. Other functions soon became quite depressed, and death shortly ensued.

2. Arterial pO_2 decreased, but pH and pCO_2 showed a biphasic response after an initial decrease,

3. Dogs that received chlorpromazine (10 mg/kg, i.v.) after MDA showed stabilization of physiological parameters, and survival through 48 hr.

INTRODUCTION

3,4-Methylenedioxyamphetamine (MDA) was repeatedly involved in life-threatening or fatal overdose reactions arising from its nonmedical use in the late 1960's and early 1970's (Jackson and Reed, 1970; Richards and Borgstedt, 1971; Cimbura, 1972; Reed *et al.*, 1972). Similar reports recurred in the late 1970's and early 1980's (Lukaszewski, 1979; Poklis *et al.*, 1979; Simpson and Rumack, 1981) as seizures of illicit drugs in the U.S.A. began to include not only MDA, but also the *N*-methyl (Anonymous, 1983) or *N*-ethyl (Vallejo, 1982) analogs of MDA. Persons receiving medical attention for MDA overdosing have exhibited both CNS effects—agitation, hallucinations, delerium, convulsions and coma—and autonomic disturbances—elevation of arterial pressure, heart rate and respiratory rate, diaphoresis, mydriasis and diarrhea (Cimbura, 1972; Richards and Borgstedt, 1971; Simpson and Rumack, 1981). Perhaps quite significant is the tendency for a marked hyperthermia that has been attributed to combined central and peripheral actions (Simpson and Rumack, 1981).

Previous large-animal studies on MDA have determined the LD_{50}'s and toxic symptomatology for dogs and rhesus monkeys (Hardman *et al.* 1973) and the cardiovascular responses in anesthetized dogs and cats (Nichols *et al.*, 1975; Paton *et al.*, 1975; Marquardt *et al.*, 1978). Other researchers have analyzed the electroencephalographic activity of the cat after MDA, compared to amphetamine, mescaline and other methoxyamphetamines (Fairchild *et al.*, 1967) and have compared MDA to amphetamine and to LSD in the intact or chronic spinal dog (Nozaki *et al.*, 1977). The latter work also tested cyproheptadine, phenoxybenzamine, and chlorpromazine for antagonism of the physiological responses to subtoxic behavioral doses of MDA. We have recently reported the effects of behavioral (sublethal) doses of MDA on cardiovascular/pulmonary responses of conscious and anesthetized dogs, plus the blocking of such effects by phenoxybenzamine pretreatment (Waters *et al.*, 1985).

The objective of the present study was to obtain data concerning the pathophysiologic response pattern of dogs to a highly toxic (LD_{100}) dosage of MDA, and to determine the capacity of chlorpromazine to antidote such toxicity. In order for the results to have maximal applicability to clinical poisonings, the conscious dog preparation was employed and the putative antagonist compound was given after, not before, the lethal injection of MDA.

MATERIALS AND METHODS

Either male or female adult mongrel dogs were restrained gently on an operating table and cannulae were placed appropriately under procaine local anesthesia so that arterial systolic and diastolic pressures, cardiac output, left ventricular systolic pressure and heart rate could be measured. Mean arterial pressure and total peripheral resistance were calculated from these measurements. Blood samples were drawn from these cannulae for the measurement of arterial pH, lactate, pCO_2 and pO_2. Body temperature was measured by a rectal thermistor. A more detailed description of methods may be found in Catravas *et al.* (1977).

Control measurements of all parameters were taken, and then each animal was given a 20 mg/kg i.v. dose of MDA at 1.4 mg/kg/min. This was chosen to be 2.5 times the LD_{50} of 8.1 mg/kg we had determined and reported elsewhere (Waters *et al.*, 1985). The physiological measurements were repeated at various time intervals until death ensued. The time to death varied among the animals receiving only MDA: six animals died at 28 ± 4 min, while the mean ($\pm$SE) time to death of 5 other animals was 107 ± 26 min. Consequently, for statistical analysis the data from MDA-treated animals were divided into two groups depending on their average time to death.

Another group of animals was given the same i.v. lethal dose of MDA; immediately after MDA infusion was terminated, chlorpromazine was administered intravenously at a dose of 10 mg/kg during the second stage of toxicity as

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Table 1. Responses of several physiologic parameters to a lethal dose of MDA in the conscious dog and antagonism by chlorpromazine (CPZ)

	Control	Time after MDA injection (min) 5	15	25	35	45	55	70	90
MDA Group 1									
Art. sys. pr. (mmHg)	167 ± 9	347 ± 7	294 ± 24	249 ± 32	135 ± 15				
Art. dias. pr. (mmHg)	92 ± 7	167 ± 7	128 ± 12	96 ± 20	30 ± 6				
Heart rate (bpm)	124 ± 14	139 ± 18	220 ± 11	245 ± 19	177 ± 73				
Stroke vol. (ml)	29 ± 3	28 ± 6	28 ± 5	25 ± 3	13 ± 7				
Rt. atr. pr. (mmHg)	3.8 ± 1	19 ± 4	12 ± 4	8 ± 6	3 ± 0				
pCO_2 (mmHg)	32 ± 2	40 ± 4	59 ± 9	55 ± 11	38 ± 6				
pO_2 (mmHg)	85 ± 1	71 ± 6	49 ± 7	46 ± 6	53 ± 10				
MDA Group 2									
Art. sys. pr. (mmHg)	161 ± 9	313 ± 6	303 ± 12	281 ± 12	236 ± 11	186 ± 8	176 ± 8	158 ± 8	144 ± 8
Art. dias. pr. (mmHg)	83 ± 8	160 ± 11	123 ± 8	106 ± 13	98 ± 15	60 ± 20	61 ± 16	54 ± 23	64 ± 0
Heart rate (bpm)	103 ± 13	181 ± 26	196 ± 18	228 ± 15	225 ± 22	235 ± 13	226 ± 23	166 ± 79	240 ± 20
Stroke vol. (ml)	32 ± 4	12 ± 2	30 ± 5	20 ± 2	24 ± 4	22 ± 3	17 ± 3	11 ± 1	9 ± 3
Rt. atr. pr. (mmHg)	3.6 ± 0.4	16 ± 3	14 ± 3	13 ± 3	6 ± 2	5 ± 2	4 ± 3	2 ± 2	2 ± 1
pCO_2 (mmHg)	38 ± 1	44 ± 2	49 ± 4	44 ± 3	36 ± 8	29 ± 5	29 ± 5	31 ± 10	23 ± 1
pO_2 (mmHg)	85 ± 1	62 ± 7	50 ± 4	43 ± 2	42 ± 9	48 ± 5	48 ± 4	33 ± 15	48
MDA plus CPZ									
Art. sys. pr. (mmHg)	177 ± 10	306 ± 7	203 ± 19	184 ± 11	161 ± 12	142 ± 8	128 ± 8	109 ± 8	100 ± 11
Art. dias. pr. (mmHg)	90 ± 8	168 ± 12	120 ± 12	119 ± 6	90 ± 11	85 ± 11	79 ± 9	51 ± 7	57 ± 13
Heart rate (bpm)	112 ± 15	185 ± 33	220 ± 24	187 ± 16	195 ± 20	184 ± 20	182 ± 19	194 ± 15	188 ± 15
Stroke vol. (ml)	25 ± 1	19 ± 4	21 ± 5	17 ± 3	12 ± 2	14 ± 3	13 ± 3	10 ± 1	10 ± 1
Rt. atr. pr. (mmHg)	4 ± 1	25 ± 3	8 ± 6	2 ± 2	0.6 ± 1	0.4 ± 0.7	0 ± 1	0.5 ± 2	−0.4 ± 1
pCO_2 (mmHg)	34 ± 2	38 ± 5	41 ± 5	37 ± 4	32 ± 1	32 ± 2	32 ± 2	29 ± 1	NA
pO_2 (mmHg)	85 ± 2	75 ± 7	67 ± 6	61 ± 7	55 ± 8	61 ± 7	60 ± 9	58 ± 11	59 ± 9

described for amphetamine by Zalis *et al.* (1967), and physiological parameters were monitored for at least another 45 min. Those animals which were protected by the antagonist were returned to their cages after appropriate care of their surgical wound and were observed for 48 hr, after which they were sacrificed and autopsied.

Statistical comparisons between the chlorpromazine-treated and the MDA-treated groups were performed by means of one-way analysis of variance followed by Scheffe's multiple comparisons test at the 0.05 probability level. Body temperatures (initial and terminal) were compared between the two MDA-only subgroups by Student's t-test. The relationship between their initial body temperatures and their survival times was tested by Spearman's rank correlation coefficient.

RESULTS

All dogs treated only with MDA exhibited severe excitation and muscular hyperactivity progressing to frank convulsions, which lasted until death. All MDA + chlorpromazine-treated animals survived without convulsing.

Arterial systolic pressure increased immediately under the influence of MDA (Table 1). Thereafter, pressure in both sub-groups of MDA-treated animals declined until all animals eventually died. A sharper rate of decline in systolic pressure was observed in the short-lived MDA-treated animals. A similar pattern prevailed for diastolic pressure (Table 1) and for mean arterial pressure and left ventricular pressure (Fig. 1). Chlorpromazine-treated animals showed an early return to control values, and most post-antagonist measurements differed significantly from the corresponding MDA-treated values.

Total peripheral resistance increased immediately in all three groups (Fig. 1); this can largely explain the prompt increase in arterial pressures noted above. Following this initial rise, total peripheral resistance fluctuated in the MDA-treated groups, while an early return to pre-drug levels was achieved in the chlorpromazine-treated animals. Total peripheral resistance values in the chlorpromazine group differed significantly from their corresponding controls only at the 45 and 55 min measurements.

A delayed but relatively sustained increase in cardiac output was observed in both MDA-treated groups (Fig. 2). After an initial rise, cardiac output in chlorpromazine-treated animals returned to and stabilized at physiologically normal levels.

Body temperature rose sharply in both MDA-treated groups (Fig. 2). The mean rectal temperatures of the two MDA sub-groups both exceeded 43°C before death; the average of 45°C for the short-survival group at their last reading was significantly higher ($P < 0.005$) than the peak of 43.5° for the longer-surviving sub-group. However, there also was a significant difference ($P < 0.01$) in their initial body temperatures, 38.3°C for the long-surviving and 39.6°C for the short-surviving subgroups. Moreover, there was a significant ($P < 0.05$) negative correlation coefficient, $R_s = -0.65$, among all 11 dogs receiving only MDA for initial body temperature vs survival time. Chlorpromazine-treated animals maintained normal body temperature, apparently because they were protected against convulsive seizures.

Arterial pH declined significantly in all MDA-treated animals (Fig. 2). However, those with a shorter time to death experienced a more severe decrease in pH. Arterial pH was relatively constant in the chlorpromazine-treated dogs. Blood lactate increased greatly in both MDA-treated groups (Fig. 2). Increased lactic acid production by hyperactive skeletal muscles appears likely to be the cause of the severe acidemia observed after MDA treatment. Lack of abnormal muscular activity could account for the normal arterial pH levels observed in the chlorpromazine-treated animals.

antagonism by chlorpromazine

	70	90
:8	158 ± 8	144 ± 8
:16	54 ± 23	64 ± 0
:23	166 ± 79	240 ± 20
:3	11 ± 1	9 ± 3
±3	2 ± 2	2 ± 1
±5	31 ± 10	23 ± 1
±4	33 ± 15	48
±8	109 ± 8	100 ± 11
±9	51 ± 7	57 ± 13
±19	194 ± 15	188 ± 15
±3	10 ± 1	10 ± 1
±1	0.5 ± 2	−0.4 ± 1
±2	29 ± 1	NA
±9	58 ± 11	59 ± 9

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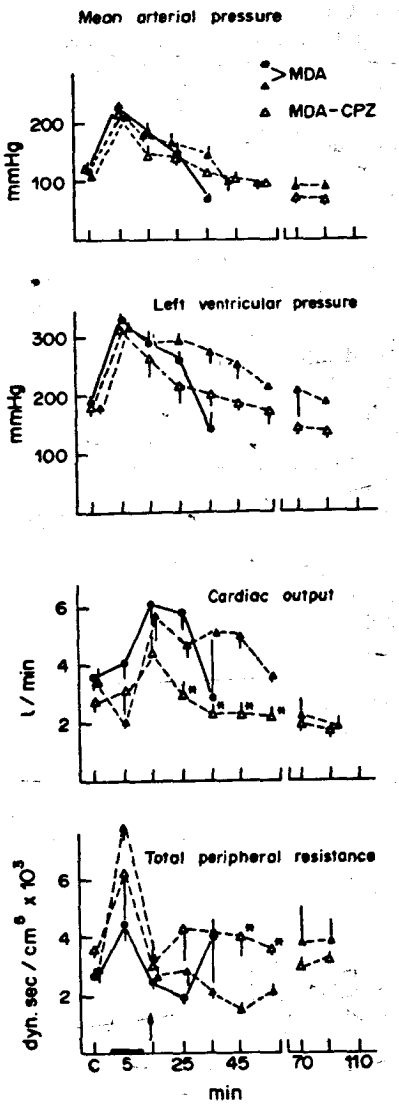

Fig. 1. Effects of MDA (20 mg/kg, i.v.) alone on canine cardiovascular parameters, and the antagonistic action of CPZ (10 mg/kg, i.v.). Circles and filled triangles indicate the short-survival and long-survival groups, respectively, receiving only MDA, whereas the open triangles indicate the group receiving CPZ after MDA. Data are expressed as mean ± SE, with the stars indicating statistically significant ($P < 0.05$) differences of MDA + CPZ group from group(s) receiving only MDA.

Findings upon autopsy of the dogs receiving MDA alone were as follows: (a) cardiac apical hemorrhage of varying size (1–10 mm); (b) frequent petechial epicardial hemorrhages, usually along the coronary sulcus; (c) frequent left and right ventricular subendocardial hemorrhages; (d) absence of transmural cardiac hemorrhages; (e) hemorrhagic and moderately congested lungs; (f) contracted spleen; (g) no gross changes in the liver, small or large intestine, gall bladder, and kidneys; (h) moderate brain hemorrhages around the area of the occipital cortex in two animals. No remarkable changes were noted at sacrifice in the dogs treated with chlorpromazine and MDA.

DISCUSSION

The differences in the magnitude of the cardiovascular, hyperthermic and acidemic responses to a lethal dose of MDA encountered among the population of dogs tested in this study cannot be readily explained. However, the factor of a higher initial body temperature in the case of the short-surviving dogs may have been responsible for the greater sensitivity of this population of dogs, as their terminal mean temperature showed an equal or greater difference from the other subgroup. A dichotomization into shorter- and longer-surviving dogs was not observed during similar previous studies in this laboratory on (+)-amphetamine and cocaine lethal intoxications in dogs (Catravas *et al.*, 1977, 1978).

It might also be postulated that the prior exposure to substances inhibiting or inducing the enzymes of biotransformation could have differed between the two groups of dogs. Marquardt *et al.* (1978) found that inhibition of microsomal metabolism via treatment with SKF 525-A caused a 53% decrease in the lethality of the (S)-isomer of MDA in mice. Conversely, the LD_{50} of (R)-MDA was decreased as lethality was increased 20% after SKF 525-A, whereas the racemic mixture, such as we have administered, showed a 19% decrease in lethality and increase in LD_{50}. Assuming a similar relationship to

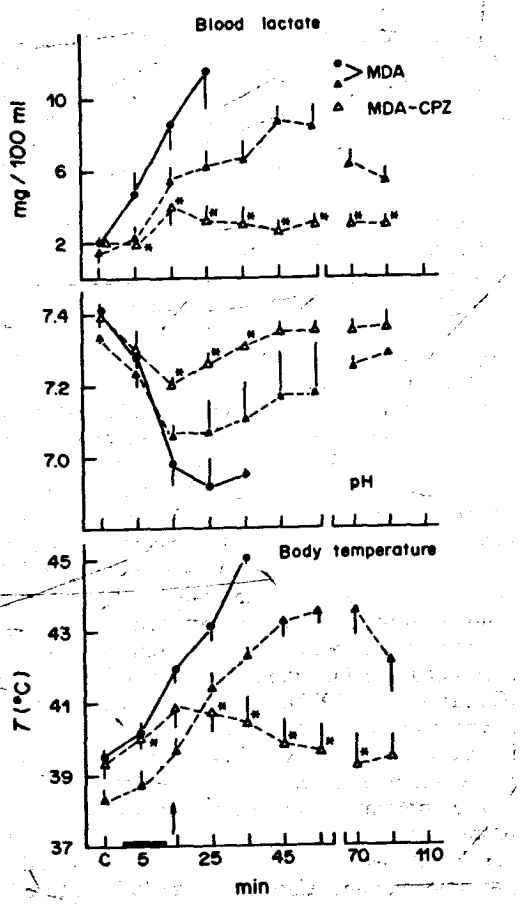

Fig. 2. Effects of MDA on canine body temperature, blood pH and lactate with or without CPZ treatment following the MDA infusion. Dosages and symbols are as indicated for Fig. 1.

that prevalent in the mouse, our dog data could represent a comparable enzyme inhibition in the case of the longer-surviving subgroup. Conversely, it could represent an induction of drug-metabolizing enzymes in the short-surviving dogs. Biotransformation of MDA in the dog is known to produce chiefly an active metabolite, α-methyldopamine (Midha *et al.*, 1978), which could contribute to the effects of toxic doses of MDA treatment.

Changes in cardiovascular parameters observed in this study confirm MDA to be a potent sympathomimetic agent, which has been indicated by various prior observations. The pressor responses demonstrated in all MDA-treated animals appear to be of mixed cardiac and vascular origin, since both cardiac output and total peripheral resistance were significantly elevated.

The cause of death in acute MDA poisoning is not clear, but the severe hyperthermia and acidemia both appear likely to be contributory. A critical role of hyperthermia in the lethal action of cocaine was demonstrated via data showing that protection against hyperpyrexia was an effective means of preventing death (Catravas and Waters, 1981). The lethality of hyperthermia has been studied in various species; swine succumb at a rectal temperature of 43°C (Marple *et al.*, 1974), rats die at a core temperature of 42°C (Hubbard *et al.*, 1977) and mongrel dogs showed 100% mortality at rectal temperatures of 43°C (Shapiro *et al.*, 1973). Zalis *et al.* (1967) found the same sort of epicardial and subendocardial hemorrhages after lethal doses of (+)-amphetamine as we report after MDA. They also cited numerous observations of such hemorrhages in human cases of fatal heat stroke.

Chlorpromazine is a recognized antagonist of central dopaminergic and peripheral α-adrenergic receptors. The effective antagonism that we observed with chlorpromazine toward the elevation of all cardiovascular parameters measured might be explained by its peripheral α-adrenergic blocking properties alone, but the contribution of the prominent sedative effects of this compound on the CNS cannot be disregarded. However, previous work has demonstrated that blockade of CNS dopaminergic receptors by haloperidol proved to be ineffective (Lopatka *et al.*, 1976) or only slightly effective (Davis *et al.*, 1978) in protecting mice from MDA lethality. Preliminary studies in our laboratory have shown haloperidol to be inadequate also in the conscious dog for preventing MDA lethality. This contrasts with the good activity of haloperidol in antagonizing the acute effects of a lethal i.v. dose of amphetamine in the dog (Catravas *et al.*, 1977). Thus, a central dopaminergic receptor blockade does not seem to benefit MDA intoxication, whereas it is helpful in (+)-amphetamine poisoning.

The present study demonstrates that chlorpromazine can serve as an effective antagonist of the lethal actions of MDA as it also did for (+)-amphetamine (Catravas *et al.*, 1977). Moreover, it had such protectiveness against a supralethal dose of MDA even by *post*-treatment, which supports the supposition that it could be an effective antidote for MDA poisoning in the emergency room. Presently accepted treatment of such incidents emphasizes support of vital functions, with no specific antidote recognized. Chlorpromazine combines a central sedative component with a peripheral α-adrenergic blocking action, providing the benefits offered in previous rodent and dog studies for a combination of two agents acting so (Thiessen and Cook, 1973; Waters *et al.*, 1985).

SUMMARY

1. A lethal dose of racemic 3,4-methylenedioxyamphetamine HCl (MDA) 20 mg/kg, administered intravenously (1.4 mg/kg/min) to conscious mongrel dogs elevated body temperature, heart rate, mean arterial pressure, left ventricular pressure, total peripheral resistance and cardiac output.

2. The increases in body temperature and heart rate were sustained, but the remaining parameters showed an initial increase followed by a profound depression; death occurred shortly thereafter.

3. Arterial pO_2 was decreased significantly, but arterial pH and pCO_2 responded in a biphasic manner.

4. A second group of animals received chlorpromazine (10 mg/kg, i.v.) at the termination of the MDA infusion. In these dogs all physiological parameters showed an early return toward control values, and all animals survived a 48-hr observation period.

5. These data indicate a definite protective action of chlorpromazine against MDA-induced lethality in this species, and suggest a clinical treatment for overdoses of MDA or closely related agents.

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