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Alteration of Anesthetic Requirement by Amphetamine

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The effects of acute and chronic administration of dextroamphetamine (DA) on halothane MAC in dogs were evaluated. Acute intravenous administration of DA, 0.1, 0.5, and 1 mg/kg, during halothane anesthesia was associated with increases of MAC to 19 ± 8, 67 ± 11, and 96 ± 15 per cent above control values. Blood pressure increased 40, 112, and 109 per cent, respectively, at the three dose levels, and in 12 of 15 acute-administration trials the dogs developed cardiac arrhythmias. Body temperature increased 0.4 to 2.1 C following acute administration of DA. The large change in MAC produced by interaction of DA with halothane could be decreased by respiratory alkalosis. In contrast, chronically-treated dogs receiving 5 mg/kg/day of DA intramuscularly for seven days had decreases in MAC of 21 ± 3 per cent from control values. These data support the hypothesis that catecholamines that act on the central nervous system may alter anesthetic requirements. (Key words: Amphetamine; Central nervous system; Catecholamines; Anesthetic requirement; Drug interaction.)

AMPHETAMINE is a sympathomimetic drug that produces significant stimulation of the central nervous system (CNS). Because of this, the drug is appealing to drug abusers and clinically useful for weight reduction, for treatment of narcolepsy, and for use as an antidepressant. However, less well known is the fact that prolonged use of this drug results in lethargy or somnolence.[1] Interaction of this frequently-used drug with inhalational anesthetics has not been demonstrated. We evaluated the effects of acute and chronic administration of dextroamphetamine (DA) on the halothane requirement (MAC) in dogs. A further evaluation of the effect of respiratory alkalosis on the interaction of dextroamphetamine with halothane was suggested by an early observation in one dog that hyperventilation altered the DA effect.

Methods and Materials

The minimum alveolar concentration of anesthesia (MAC) was our standard of anesthetic potency.[2] In every study, esophageal temperature, femoral arterial pressure, end-tidal CO_2, and the electrocardiogram were monitored continuously. End-tidal halothane concentration was intermittently determined with a Beckman infrared analyzer. Pa_{CO_2}, Pa_{O_2} and pH_a were determined with appropriate electrodes. In all studies, blood samples for dextroampetamine determinations were drawn into unused disposable syringes, stored at 20 C in tubes with ethylenediaminetetraacetate, and later analyzed by the method of Rowland.[3]

ACUTE STUDIES

Five dogs, 9–16 kg in weight, each received one of three doses of dextroamphetamine, 0.1, 0.5, or 1 mg/kg, during an experiment. Three separate experiments were carried out with each dog at two-week intervals, so that every dog received all three doses. MAC studies were done after each DA administration, with each dog serving as its own control at all three dose levels. Anesthesia was induced with halothane–oxygen using a standard circle system. The trachea was intubated without the use of muscle relaxants and ventilation controlled to maintain pH_a between 7.28 and 7.40. After control MAC had been determined, DA was given intravenously over a two-minute period. Blood samples were drawn 5, 15, and 60 minutes after injection and hourly thereafter for determination of DA concentrations. An hour after DA injection, MAC was redetermined (MAC-1). A second MAC determination (MAC-2) was made three to four hours after injection of DA, and a third

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TABLE 1. Changes in Halothane MAC after Acute Administration of 0.1, 0.5, and 1.0 mg/kg of Dextroamphetamine

	Control MAC (Per Cent Halothane)	MAC-1 (An Hour after Injection)		MAC-2 (3 to 4 Hours after Injection)		MAC-3 (5 to 6 Hours after Injection)	
		Per Cent Halothane	Per Cent Increase	Per Cent Halothane	Per Cent Increase	Per Cent Halothane	Per Cent Increase
Dose 0.1 mg/kg							
Dog 1	0.94	1.14	24	0.95	1	—	
Dog 2	0.79	0.92	17	1.01	28	8	
Dog 3	0.76	0.76	0	—	—	—	
Dog 4	0.80	1.17	46	1.11	39	2	
Dog 5	1.18	1.29	9	1.34	12	—	
MEAN ± SE	0.89 ± 0.07	1.05 ± 0.09*	19 ± 8		20 ± 8		
Dose 0.5 mg/kg							
Dog 1	0.89	1.33	53	0.92	3	0.42	3
Dog 2	0.86	1.67	94	0.82	5†	1.30	51
Dog 3	0.79	1.52	93	1.42	80	1.56	98
Dog 4	0.89	1.36	53	1.27	43	0.86	3
Dog 5	1.17	1.68	44	1.56	33	1.45	24
MEAN ± SE	92 ± 0.07	1.51 ± 0.07*	67 ± 11	1.29 ± 0.14*	40 ± 16		
Dose 1.0 mg/kg							
Dog 1	0.85	1.64	93	—	—	—	—
Dog 2	0.83	1.85	153	1.89	154	1.74	138
Dog 3	0.64	1.14	79	1.00	56	0.62	3
Dog 4	0.94	1.76	87	1.68	79	0.91	3
Dog 5	1.19	2.00	70	1.72	46	1.52	29
MEAN ± SE	0.87 ± 0.09	1.67*	96 ± 15	1.57 ± 0.20*	84 ± 24	1.20 ± 0.26	43 ± 32

* ± SE.
† This value not included in calculations.

MAC determination (MAC-3) five to six hours after injection. Throughout the study, Ringer's lactate solution was infused at approximately 5 ml/kg/hour. Esophageal temperature was maintained at 37.2 ± 0.8 C.

Blood-pressure values represent the greatest changes in systolic pressure from control values. Control values for each animal were those recorded just prior to injection of DA at approximately control MAC halothane level. Temperature changes following injection represented the greatest rises in temperature from values just prior to injection. Raw data were analyzed by paired or unpaired t test, with $P < 0.05$ considered statistically significant.

CHRONIC STUDIES

Five dogs were anesthetized as described above and control MAC values determined. Twenty-five hours after recovery from anesthesia, DA, 2.5 mg/kg, was administered intramuscularly twice daily for seven days. MAC was then redetermined 18 to 24 hours after the last dose of DA. In addition to all the measurements made in the acute experiments, we indirectly evaluated norepinephrine depletion of peripheral postganglionic adrenergic neurons pre- and post-DA treatment by giving an injection of tyramine (100 μg/kg) intravenously and noting the blood-pressure response.

*p*H STUDIES

The effect of respiratory changes in *p*H on the MAC for halothane was determined in three dogs given acute administrations of DA. After determination of the control MAC, DA, 0.5 mg/kg, was given intravenously and MAC-1

TABLE 2. The Effects on Blood Pressure and Temperature of Acute Administration of Dextroamphetamine

	Dextroamphetamine, 0.1 mg/kg			Dextroamphetamine, 0.5 mg/kg			Dextroamphetamine, 1.0 mg/kg		
	Blood Pressure (torr)	Torr Δ	Temp. Δ	Blood Pressure (torr)	Torr Δ	Temp. Δ	Blood Pressure (torr)	Torr Δ	Temp. Δ
Dog 1	125–195	65	0.4	115–220	105	0.4	125–300	100	1.5
Dog 2	110–210	100	0.5	165–250	85	1.4	125–250	125	0.6
Dog 3	150–220	70	0.8	100–200	100	.5	125–200	75	2.1
Dog 4	125–200	75	1.0	110–230	70	1.2	125–250	125	0.5
Dog 5	95–150	55	0.4	100–200	100	.1	75–175	100	.3
MEAN ± SE		73.0 ± 7.5	0.62 ± 0.12		92.0 ± 6.4	0.72 ± 0.24		120 ± 16.6*	1.0 ± 0.77

* Indicates significance, $P < .05$.

was determined as in the acute studies. Following MAC-1, hyperventilation (Pa_{CO_2} 22 ± 2 torr, pH_a 7.55 ± 0.03) was initiated and MAC redetermined. Ventilation was then returned to normal (Pa_{CO_2} 34–44 torr, pH_a 7.32 ± 0.02) and MAC was again determined.

The effect of respiratory alkalosis on amphetamine–halothane interaction was evaluated further in four dogs by injecting DA during, rather than prior to, hyperventilation. After determination of control MAC, DA, 0.5 mg/kg, was injected while the animals were being hyperventilated (pH_a 7.54 ± 0.05 torr, Pa_{CO_2} 22 ± 2) and MAC was determined an hour later. Subsequently, MAC was redetermined after return to normal ventilation (Pa_{CO_2} 34–42 torr, pH_a 7.33 ± 0.03).

Results

Following acute administration of 0.1, 0.5, or 1.0 mg/kg of DA, increases in MAC of 19 ± 8, 67 ± 11, and 96 ± 15 per cent from control values were observed (table 1). In table 1 the actual values of the increases in halothane are given, in addition to the per cent changes in MAC. Dog 2 (at the 0.5 mg/kg dose) was the animal in which it was observed that blood *p*H alters DA increases in MAC. The MAC-2 value for this animal is not included in the calculations here, but is included with the *p*H changes. Although there was considerable variation at each dose level, all MAC-1 values were significantly different from the control values. There were also significant differences between the 0.1-mg/kg dose and the two higher doses, but not between the 0.5-mg/kg dose and the 1.0-mg/kg dose. The variability was more evident during MAC-2 and MAC-3 determinations, and some dogs showed little drug effect, *i.e.*, only small increases in MAC. Statistical analysis of the MAC-3 data at the 0.1-mg/kg dose level was not done because of the small number of studies completed.

Acute DA administration increased blood pressure 73.0 ± 7.5, 92.0 ± 6.4, and 120 ± 16.6 torr above control values (table 2). Blood pressure values in table 2 are systolic blood pressures just prior to (control) and after DA injection. The blood pressure increases were all significantly different from the control values. The effect of the 1.0-mg/kg dose was significantly different from those of the other two, but there was no significant difference between the effects of the 0.1-mg/kg and 0.5-mg/kg doses. In 12 of 15 dogs in the acute studies, atrial, nodal, and ventricular premature contractions were observed following DA administration, and revision to sinus tachycardia ensued in all 12 animals. Temperature increases (temp. Δ in table 2) usually appeared in 15 minutes; again, there were no significant differences among the temperature increases at the three dose levels. When temperatures rose more than 0.5 C, ice was applied to limit the increases and control temperatures during MAC determinations. With acute administration blood levels of DA (fig. 1) declined similarly at all three dose levels. Although there were significant differences among the three dose levels, there was little difference within a given dose at each time period. To obtain more stable blood levels and drug effects, an hour was allowed to elapse after injection before MAC determinations were made. There was more spontane-

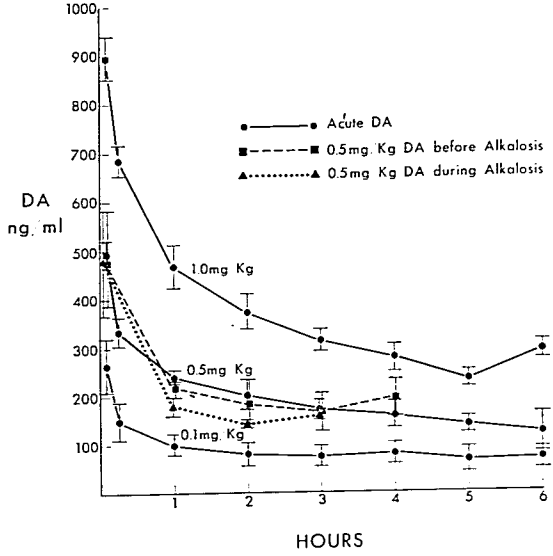

FIG. 1. Blood levels of dextroamphetamine (DA) during acute administration of three dose levels in dogs with normal *p*H., and at one dose during respiratory alkalosis. Each point represents the mean ±SE for three to five dogs.

ous movement, indicating increased MAC, with the higher blood levels after injection, since all dogs initially moved at more than 2 per cent halothane at the two larger doses of DA.

Chronically-administered DA was associated with a reduction of halothane MAC by 22 ± 3 per cent (table 3). No changes in blood pressure or rhythm were seen in these dogs. Challenge with tyramine resulted in increases in blood pressure of 5.6 ± 3.8 torr after DA, compared with 78.0 ± 14.1-torr increases prior to treatment. Blood levels of DA in the chronically-treated dogs are not shown, but ranged from 9.5 to 113.5 ng/ml and could not be correlated with individual decreases in MAC.

Alkalosis produced by hyperventilation consistently altered the MAC for halothane irrespective of whether the *p*H change was established after (Group I) or prior to (Group II)

TABLE 3. Changes in MAC and Response to Tyramine Following Chronic Administration of Dextroamphetamine

	Control Halothane MAC (Per Cent)	MAC after DA (Per Cent)	Per Cent Δ	Control Tyramine Response (torr)	Tyramine Response after DA torr Δ
Dog 6	1.13	0.90	−20	45	2
Dog 7	1.28	1.02	−20	55	20
Dog 8	1.28	1.11	−13	90	5
Dog 9	0.90	0.62	−31	75	5
Dog 10	1.19	0.91	−23	125	0
MEAN ± SE	1.15 ± 0.08	0.91 ± 0.07*	22 ± 3	78.0 ± 14.1	5.6 ± 3.8*

* Indicates significance, $P < .05$.

TABLE 4. The Effect of Respiratory Alkalosis on Increases in Halothane MAC Following Acute Administration of Dextroamphetamine

	Control MAC Per Cent Halothane	After DA		Per Cent Δ	After Alkalosis		Per Cent Δ from Control	After Normal pH	
		MAC	pH		MAC	pH		MAC	pH
Group I, pH normal on DA administration									
Dog 2	0.86	1.67	7.34	+77	0.96	7.57	−1	1.3	7.34
Dog 11	0.95	1.76	7.27	+87	0.92	7.56	−2		
Dog 12	0.94	1.64	7.34	+94	0.82	7.52	−5	1.3	7.30
MEAN ± SE	0.91 ± 0.02	1.69 ± 0.03*	7.31 ± 0.03	86 ± 5.0	0.90 ± 0.04	7.55 ± 0.03	−2.7 ± 0.07		

	Control MAC Per Cent Halothane	After DA		Per Cent Δ	After Normal pH		Per Cent Δ from Control
		MAC	pH		MAC	pH	
Group II, pH alkaline on DA administration							
Dog 13	0.85	1.08	7.53	+27	1.29	7.34	52
Dog 14	1.16	1.32	7.58	+13	1.54	7.36	33
Dog 15	1.05	1.28	7.49	+22	1.64	7.36	56
Dog 16	0.82	0.91	7.52	+11	1.08	7.30	32
MEAN ± SE	0.97 ± 0.08	1.15 ± 0.09*	7.54 ± 0.05	18.2 ± 1.6	1.38 ± 0.13*	7.33 ± 0.03	43 ± 3.1

* Indicates significance, $P < .05$.

injection of DA (table 4). In table 4, at levels other than control levels, each MAC value with DA administration is listed with the pH_a value obtained during that MAC period. Consistent with the acute studies, administration of 0.5 mg/kg of DA at a normal pH_a (7.31 ± 0.03) resulted in an increase in MAC of 86 ± 5.0 per cent. This increase was eliminated by hyperventilation (Pa_{CO_2} 22 ± 2, pH_a 7.55 ± 0.03). A return to normal pH_a suggested return of the previous DA effect in two of the three dogs, but this was not statistically analyzed because of the small number of dogs. Injection of DA during alkalosis resulted in an 18.2 ± 1.6 per cent increase in MAC, which is significantly different from the values obtained in other dogs with 0.5 mg/kg at normal pH_a. Decreased ventilation and consequent normal pH_a (7.33 ± 0.03) in these dogs were associated with a significant increase in MAC of 43 ± 3.1 per cent. Blood pressure and cardiac rhythm were altered little by changes in pH_a or ventilation.

Blood values of DA in dogs in which pH_a was normal (7.31 ± 0.03) when DA was injected were similar to the blood values in the acute studies. The values in dogs which received injections of DA during alkalosis (7.54 ± 0.05) were lower initially, but after two hours they were similar to those in the other dogs.

Altering P_{CO_2} and pH_a did not alter blood levels of DA, as evidenced by the small difference between DA levels in pre- and postventilation blood samples (fig. 1).

Discussion

Although DA is commonly used, there have been no reports of its effects on anesthetic requirements. We found that the results with acute and chronic use of DA differed: acute administration was associated with dose-dependent increases in halothane MAC, whereas chronic administration was associated with significant reductions in MAC. With acute DA administration, the increases in anesthetic requirement at all three dose levels are the largest reported with any pharmacologic or physiologic alteration during anesthesia. The durations of the changes in MAC, as evidenced in the MAC-2 and MAC-3 values, varied considerably. We have no explanation for the differences in the durations of MAC changes, because all conditions were the same in all experiments. MAC does not change with time,[2] and blood levels of DA were not

significantly different during the MAC-2 and MAC-3 periods. In contrast to the increases in MAC seen with acute DA use, chronic use may produce lethargy and somnolence and, therefore, might be anticipated to decrease MAC. The decreases in halothane MAC we observed with chronic administration of DA were similar to the values obtained by Miller *et al.*[4] in dogs given reserpine or alpha-methyldopa.

The alteration of anesthetic requirement by amphetamines may be related to catecholamine actions in the central nervous system (CNS). Carr,[5] measuring cerebrospinal fluid levels of metabolites of norepinephrine, has demonstrated that norepinephrine is released in the central nervous system after acute amphetamine administration. This evidence and the histochemical, biochemical, and pharmacologic evidence of others[6-8] suggest that the CNS stimulation that occurs with acute administration of amphetamine is related to release of catecholamines from the adrenergic nerve terminals in the CNS, as well as peripherally. If the effect of acute DA administration results from catecholamine release from nerve terminals, then our observations support the concept that an increase in the release of catecholamines in the CNS may increase anesthetic requirement. In contrast, chronic DA administration depletes CNS catecholamines[9] and decreases MAC, which further supports this hypothesis. Indirect evidence of peripheral depletion of the adrenergic nerve terminals, and hence, possible CNS depletion, was demonstrated by the failure of the chronically-treated dogs to respond to tyramine. Further evaluation of the mechanism by which MAC is increased by DA is needed.

In addition to the different alterations in anesthetic requirement we found in the acute and chronic experiments, the changes in the cardiovascular system differed. In acute experiments, the increases in blood pressure and the frequent arrhythmias we observed might have been related to the peripheral release of catecholamines by DA[10]; however, we could not attribute the increases in MAC to this peripheral catecholamine release. Eger[2] had previously demonstrated no significant changes in MAC from increasing blood pressure with phenylephrine. Evidence also indicates that catecholamines do not cross the blood–brain barrier[11]; thus, peripheral release of catecholamines by DA should not contribute to stimulation in the CNS. In contrast, the chronically-treated dogs were depleted of catecholamines, and responded without cardiovascular changes during anesthesia. The difference between the functional status of the peripheral adrenergic neurons in the acute and chronic experiments might explain the cardiovascular responses we observed, but peripheral changes cannot account for alteration in anesthetic requirement.

Body temperature frequently increases with amphetamine, although no description of this during anesthesia has appeared. The increases in body temperature observed in all dogs immediately after acute administration of DA were decreased to normal by application of ice prior to initiation of MAC determinations. As a result, the increases in MAC with acute DA cannot be attributed to increases in body temperature. Furthermore, the increase of 2.1 C that we saw in one dog would increase MAC approximately 10 per cent or less[12]—much less than the MAC changes at the higher dose levels.

In our study, the effect of acute DA administration to increase MAC was attenuated by respiratory alkalosis. Amphetamine is a weak base with a pK_a of 9.9[12]; thus, altering blood *p*H will alter the ratio of non-ionized to ionized amphetamine present. Feasibly, this could allow transfer of DA across membranes to more "active sites." Our blood concentrations of DA, although not indicative of DA in the central nervous system, were unchanged with ventilation, suggesting a small shift, if any, of the drug to other sites. Other studies are needed to determine whether *p*H changes other than respiratory alkalosis alter the interaction of DA with halothane.

In considering clinical applications of our study, it may be important to evaluate whether a patient would represent an acute or chronic amphetamine user. It is difficult to equate the dosages used in our dogs with those used by humans; however, dogs appear to respond in the manner described by patients. Acutely, patients respond to DA with CNS stimulation and increased alertness which is dose-dependent. Chronic use of DA, which occurs with patients on "diet pills," may lead to fatigue,

weight loss, and possible psychosis. Drug abusers experience stimulation with continued use of amphetamine, but sedation after withdrawal. In contrast to the stimulation that follows acute injection of amphetamine, the cyclical period of stimulation, then sedation, may become a life style for the amphetamine abuser.

The evaluation in our study may influence the management of clinical anesthesia for patients using DA in several ways. Patients first seen in a state of stimulation due to recent use are likely to be emergency cases. The halothane requirements of these patients may be significantly greater than normal, and they may have associated cardiovascular changes, as we saw in the acutely treated dogs. We did not allow temperatures to remain elevated; thus, we can only speculate that acute injection of DA could present hyperthermia problems for the anesthetist. The effect of respiratory alkalosis after acute administration suggests that *p*H changes may alter the amphetamine user's response to anesthesia. The chronic DA user or illicit drug user during withdrawal will require less anesthesia, increasing the possibility of anesthetic overdose if the usual doses of halothane are used. Additionally, patients using the drug chronically may have poor responses to the usual doses of indirect-acting sympathomimetic drugs, such as metaraminol, ephedrine, etc.

Many questions remain unanswered. Caution must be used in extrapolating our results with amphetamine to other anesthetics, because preliminary data suggest that acute administration of DA has little effect on fluroxene MAC.§ The mechanism of change in halothane MAC with DA, the change caused by hyperventilation, and the difference between halothane and fluroxene need further evaluation. Further experiments to answer some of these questions are in progress.

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