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Effects of Pharmacologic Alterations of Adrenergic Mechanisms by Cocaine, Tropolone, Aminophylline, and Ketamine on Epinephrine-induced Arrhythmias during Halothane–Nitrous Oxide Anesthesia

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The purpose of this study was to examine the effects of pharmacologic alterations of adrenergic terminating mechanisms by cocaine, tropolone, aminophylline, and ketamine on the ability of epinephrine to induce arrhythmias during halothane–nitrous oxide anesthesia in dogs. Because the first three drugs inhibit intraneuronal uptake of catecholamines, extraneuronal catechol-O-methyl transferase (COMT), and phosphodiesterase, respectively, they might be expected to potentiate epinephrine-induced arrhythmias. To evaluate this possibility, the authors devised a technique for determining the minimal arrhythmic dosage of epinephrine that permitted graded assessment of changes in the sensitivity of the heart to epinephrine-induced arrhythmias. When the first three drugs were administered to the same dog in the order listed at intervals of 60 minutes, they sequentially increased the ability of epinephrine to induce arrhythmias. Ketamine, according to several investigators, also appears to block reuptake of catecholamines, and when studied was also found to enhance the arrhythmogenicity of epinephrine. The extent of enhancement was comparable to that seen with cocaine. These results indicate that drugs like cocaine and ketamine that interfere with intraneuronal uptake can facilitate the development of epinephrine-induced arrhythmias and that the successive pharmacologic interference of intraneuron. uptake, COMT, and phosphodiesterase leads to a stepwise increase in the arrhythmogenicity of epinephrine. (Key words: Heart, arrhythmias; Sympathetic nervous system, epinephrine; Anesthetics, local, cocaine; Anesthetics, volatile, halothane; Anesthetics, intravenous, ketamine.)

THE ABILITY of epinephrine to produce arrhythmias is attributed to its action at adrenergic receptors. According to Katz, the evidence available indicates that the beta receptors are primarily, if not completely, responsible for the arrhythmias produced by catecholamines. This conclusion is based primarily on the specificity and consistency of certain beta-adrenergic blockers in abolishing these arrhythmias.[1–3]

The response to epinephrine can be considered to be dependent in large part on the activity of certain catecholamine-terminating mechanisms involved in reducing the concentration of endogenous and exogenous catecholamines in the area of the receptor and modulating cellular responses to receptor activation. Primarily, reuptake into the adrenergic nerve endings and, secondarily, extraneuronal uptake with O-methylation by catechol-O-methyltransferase (COMT) are adrenergic mechanisms that help to lower the concentrations of epinephrine and norepinephrine in the area of the receptor.[4] Following beta-receptor stimulation there is an increase in the intracellular level of cyclic 3′,5′-adenosine monophosphate (cAMP) that is considered to be responsible for many of the cellular responses that follow receptor activation.[5] However, the intracellular cyclic nucleotide phosphodiesterase, by inactivating cAMP, influences the extent and duration of cellular responses initiated by an increase in cAMP.[6]

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Interference with each of the above adrenergic terminating mechanisms can be achieved pharmacologically. Intraneuronal uptake of catecholamines can be blocked by cocaine[4,7-9] and ketamine.[10,11] COMT can be inhibited by tropolone,[12-14] and the cyclic nucleotide phosphodiesterase can be inhibited by aminophylline, a theophylline salt.[6]

These drugs are also known to enhance certain cardiovascular responses to epinephrine.[10,15-17] As for the arrhythmogenicity of epinephrine, it is markedly increased in the presence of halothane.[18] Is this arrythmogenicity further increased by drugs that interfere with the intraneuronal uptake of epinephrine by cocaine, and what further effect on arrhythmogenicity is caused by additionally blocking COMT by tropolone and then blocking cyclic nucleotide phosphodiesterase by aminophylline?

Thus, the aims of the study were essentially twofold. One was to evaluate and compare the effects of cocaine and ketamine on the arrhythmogenicity of epinephrine because of their common property of interfering with the primary adrenergic terminating mechanism, intraneuronal uptake. The second was to demonstrate via an increase in the arrhythmogenicity of epinephrine the susceptibility of the adrenergic terminating mechanisms to successive pharmacologic interference. It was decided that this susceptibility could be demonstrated best by interfering with the adrenergic mechanisms in a sequence that corresponds to the probable physiologic importance of the mechanisms: intraneuronal uptake, COMT, and phosphodiesterase.

Materials and Methods

Twenty-four mongrel dogs of either sex, mean weight 15 kg (range 14–20 kg) were studied. Anesthesia was induced with thiopental, 20 mg/kg, intravenously, followed by endotracheal intubation.

Anesthesia was maintained with an inspired concentration of 1 per cent halothane and 60 per cent nitrous oxide in oxygen. The nitrous oxide and oxygen were delivered via a Foregger anesthesia machine at a total flow of 6 l/min and passed through a calibrated Fluotec vaporizer. Ventilation was controlled with a Harvard dual-phase respirator, and a nonrebreathing system was used in all experiments. The inspired halothane concentration was monitored with a Fluothane Monitor, Model 10, Analytic Systems Co.

Bilateral cervical vagotomy was performed on all animals to prevent parasympathetic reflex influences. A polyethylene cannula was inserted into the left femoral artery and connected to a Statham P23b pressure transducer calibrated with mercury at the beginning of each experiment. Cannulas were also placed in the right femoral artery and vein for arterial sampling and drug administration, respectively. Rectal temperature was monitored and maintained at 37 ± 1 C by external means. By repetitive blood-gas measurements and appropriate adjustments of ventilatory volume and rate, Pa_{CO_2} was maintained at 32–40 torr. Lead II of the electrocardiogram was used to monitor heart rate and rhythm. Arterial pressure and lead II were registered continuously on a Hewlett-Packard recorder (Model 7700).

After a 45-min equilibration period, epinephrine was administered as an intravenous bolus every 30 seconds until either a minimal ventricular arrhythmia occurred or a maximum of six injections had been given, whichever occurred first. The process of administering epinephrine according to this schedule is referred to as an "epinephrine bolus series." The intervals between series were at least 10 minutes to allow blood pressure and heart rate to return to control values. In this study the term "minimal ventricular arrhythmia," used by Dresel and Sutter, included bigeminal rhythms at least 4 seconds in duration or three or more premature ventricular contractions within a 4-second period.[19]

For any one epinephrine bolus series the dose of epinephrine in each bolus, numbered 1 through 6, was constant and was determined by the dosage level assigned to a series. The stepladder column on the left of figure 1 depicts the doses of epinephrine for epinephrine bolus series at successive dosage levels. Note that at each successive dosage level the dose was doubled.

For this study the minimal arrhythmic dosage of epinephrine was defined as the lowest dosage level and bolus number in that level that elicited a minimal ventricular arrhythmia. The general approach for determining the first minimal arrhythmic dosage of epinephrine is illustrated in the hypothetical experiment in figure 1 for Dog 50. Here, an epinephrine bolus series was first done at the .0625 μg/kg dosage level. This dose was given as a bolus every 30 seconds until bolus 6 had been given without a minimal ventricular arrhythmia occurring. Therefore, 10 minutes later an epinephrine bolus series was done at the next higher dosage level, and so on until at the .25 μg/kg dosage level a minimal ventricular arrhythmia occurred at bolus 5. This dosage level and bolus number were then taken as the minimal arrhythmic dosage of epinephrine. This technique of the constant-interval administration of epinephrine at different dosage levels was devised to permit the consistent detection of the lowest epinephrine dosage that would elicit a reproducible, transient arrhythmia.

The concentration of epinephrine used in all experiments was 10 μg/ml. With this concentration the volumes of boluses of epinephrine ranged from .08 to 2 ml. Each bolus was injected into a 3-ml intravenous cannula and immediately flushed with 4 ml of physiologic saline solution.

In Phase I of the study, the effect of sequentially administering cocaine, tropolone, and aminophylline on the minimal arrhythmic dosage of epinephrine during halothane–nitrous oxide anesthesia was de-

termined in 16 dogs. Each dog in Phase I received all three drugs intravenously in the order listed. The intervals between drug administrations were approximately 60 minutes.

The minimal arrhythmic dosage of epinephrine was first determined while the dog received only halothane and nitrous oxide in oxygen. Epinephrine bolus series were done until a minimal ventricular arrhythmia was elicited by the same lowest dosage level and bolus number in that level in at least two consecutive series. This dosage level and bolus number were then taken as the minimal arrhythmic dosage of epinephrine for halothane. Consistency in the lowest dosage level and bolus number eliciting a minimal ventricular arrhythmia was usually not achieved until after the first two epinephrine bolus series eliciting a minimal ventricular arrhythmia had been done.

Cocaine, 2 mg/kg, was then administered over 10 minutes. One minute after administration, the first epinephrine bolus series was done at one dosage level lower than the control dosage level which was taken as the lowest dosage level eliciting a minimal ventricular arrhythmic during the 20 minutes previous to giving the drug, in this case cocaine. Subsequent runs were repeated over the next 40 to 50 minutes at the same, lower, and if necessary, higher dosage levels in order to detect the lowest dosage level and bolus number in that level that would elicit a minimal ventricular arrhythmia. Accordingly, this lowest dosage level and bolus number became the minimal arrhythmic dosage after cocaine. The dosage level of the first epinephrine bolus series after administering a drug in Phase I was chosen to be one lower than the control dosage level to avoid excessively overshooting the minimal arrhythmic dosage (which was usually lowered by these drugs) and eliciting ventricular fibrillation with the first bolus of epinephrine at the control dosage level, which for cocaine was the same as the dosage level denoting the minimal arrhythmic dosage for halothane.

Next, tropolone, 20 mg/kg, was administered over 6 minutes and the minimal arrhythmic dosage after tropolone determined in the same manner as that after cocaine.

This was followed by one fourth the previous doses of cocaine and tropolone and by 10 mg/kg aminophylline over an 8-minute period. The additional doses of cocaine and tropolone were considered necessary in order to maintain an "effective" plasma concentration of these drugs, which had been administered initially 120 and 60 minutes, respectively, before the injection of aminophylline. The minimal arrhythmic dosage after aminophylline was determined in the same manner as that after cocaine.

In Phase II of the study, the effects of ketamine at 2 mg/kg and 6 mg/kg on the minimal arrhythmic dosage of epinephrine were determined in eight

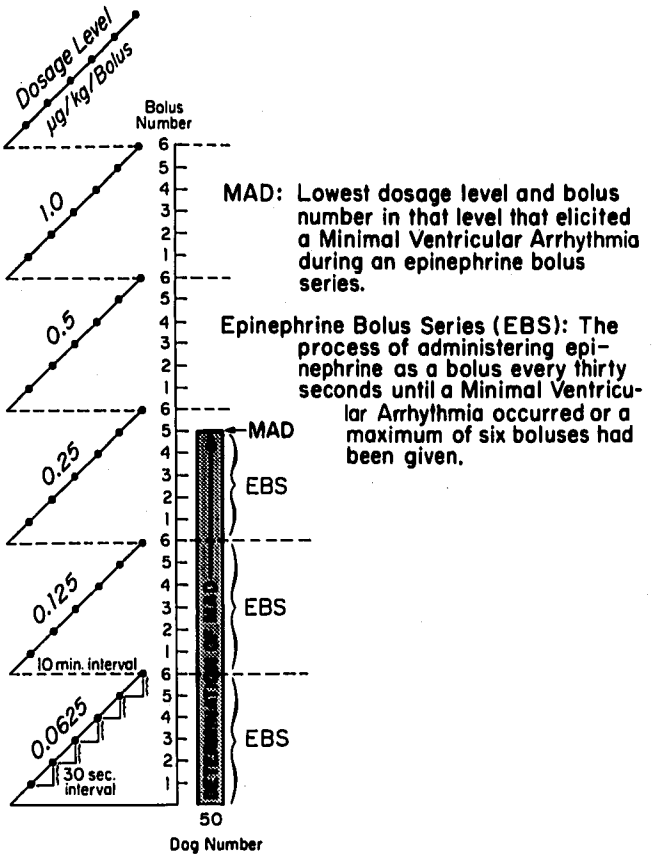

FIG. 1. Determination of the minimal arrhythmic dosage of epinephrine. An example of the initial sequence of events in determining the minimal arrhythmic dosage for halothane is illustrated for Dog 50. The relative positions of the minimal arrhythmic dosages of epinephrine according to bolus number and dosage level are depicted on the left by the vertical arrangement of bolus numbers 1 through 6 at successive dosage levels.

dogs. The interval between ketamine doses was 60 minutes. Every dose of ketamine was given intravenously over 1 minute, with the first epinephrine bolus series always beginning 1 minute after the dose had been administered. The preparation of the dog and the determination of the minimal arrhythmic dosage of epinephrine for halothane were identical to those in Phase I.

Each dog received first 2 mg/kg ketamine. The first epinephrine bolus series was done at the control dosage level. Otherwise, the same procedure was followed as after cocaine. If the bolus number denoting the minimal arrhythmic dosage after 2 mg/kg happened to be 1, a second 2 mg/kg ketamine dose was given and the minimal arrhythmic dosage again determined as before except that the first epinephrine bolus series was done at one dosage level lower than the control dosage level.

Following the 2 mg/kg ketamine dose, each dog received 6 mg/kg ketamine and the minimal arrhythmic dosage was determined in the same manner as after cocaine. Next, a second 6 mg/kg

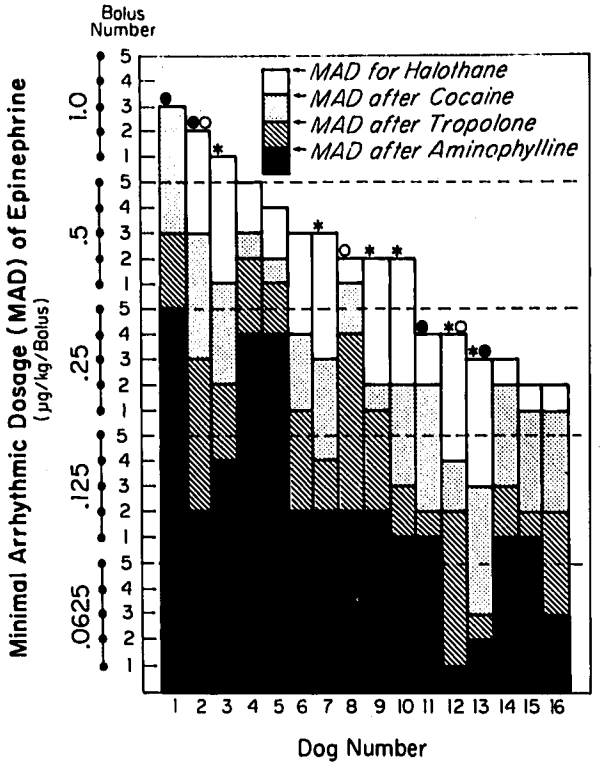

FIG. 2. Effect of sequentially administering cocaine, tropolone, and aminophylline on the minimal arrhythmic dosage (MAD) of epinephrine during halothane–nitrous oxide anesthesia. Each bar represents the results for one dog. The minimal arrhythmic dosages for halothane are represented by the top of each bar and are arranged in descending order. The order in which a dog is listed was determined by his minimal arrhythmic dosage for halothane and not according to when he was studied. * Dogs that showed the maximum 50 per cent decrease in MAD after cocaine; ° dogs that showed the maximum 50 per cent decrease in MAD after tropolone; ° dogs where the maximum decrease in the MAD after aminophylline was slightly greater than 50 per cent.

dose of ketamine was administered to every dog and the minimal arrhythmic dosage again determined as before except in those few instances when a minimal ventricular arrhythmia had not been elicited by the first epinephrine bolus series following the first 6 mg/kg dose. When this occurred, the first epinephrine bolus series after the second 6 mg/kg dose was done at the control dosage level instead of one lower.

Because the occurrence of a minimal ventricular arrhythmia at bolus 6 was rare regardless of dosage level in both Phase I and Phase II, it was possible to omit this bolus when depicting the results of the minimal arrhythmic dosage for halothane and after each drug.

In six of eight dogs in Phase II of the study, continuous minimal ventricular arrhythmias were produced 60 to 90 minutes after the second 6 mg/kg dose of ketamine by steady infusion of epinephrine via a Harvard infusion pump. The infusion was started at approximately .1 to .3 μg/kg/min and the rate increased at intervals of 3 minutes until a minimal ventricular arrhythmia appeared. After multifocal ventricular extrasystoles (five dogs) and bigeminy (one dog) had developed, the rate of infusion remained constant for the remainder of the experiment. The rates of administration used to produce the above-described arrhythmias ranged from .11 to 3.8 μg/kg/min. After the arrhythmias had persisted for 4 minutes, ketamine, 6 mg/kg, was administered rapidly to three dogs and thiopental, 10 mg/kg, to three other dogs.

Before the administration of cocaine and then after the administration of each drug, 1-ml arterial blood samples for potassium determinations were drawn during at least one epinephrine bolus series eliciting a minimal ventricular arrhythmia. The samples were drawn in heparinized syringes 1 minute before the start of the series and within 30 seconds of the onset of an arrhythmia.

Statistical analyses of blood pressure, heart rate, potassium and time measurements were performed using the t test for paired data. Differences in minimal arrhythmic dosages of epinephrine were analyzed statistically by the Sign Test.[20] A P value of <0.05 was considered significant. Values are presented as means ±SE.

Cocaine hydrochloride was dissolved in physiologic saline solution to a final concentration of 10 mg/ml; tropolone (K & K Laboratories, Plainview, New York) was dissolved with slight warming in distilled water to a final concentration of 15 mg/ml; aminophylline (aminophylline—G.D. Searle & Company) was diluted to 1.5 per cent with physiologic saline solution; ketamine hydrochloride (Parke-Davis) was used as the 100 mg/ml commercial preparation; epinephrine (Adrenalin—Parke-Davis) in 1-ml ampules of 1/1000 was diluted in 99 ml of physiologic saline solution. General anesthetics used were halothane (Fluothane—Ayerst) and thiopental (sodium Pentothal, 2.5 per cent—Abbott).

Results

The duration of an experiment on any one dog was five to six hours. Each animal was used as its own control. Pa_{O_2}'s ranged from 100 to 150 torr and the pH's from 7.32 to 7.46. Control values of potassium averaged 3.1 ± .07 mEq/l; in samples drawn within 30 seconds of the onset of an arrhythmia the mean value was 3.4 ± .08 mEq/l.

It was established in several ways that when a decrease in the minimal arrhythmic dosage occurred, it reflected a drug effect and not a time-dependent change in sensitivity. First, epinephrine bolus series were repeated at 10- to 15-minute intervals over a four-hour period in four dogs while they received only 1 per cent halothane and 60 per cent nitrous oxide in oxygen. After the first or second epinephrine bolus series eliciting a minimal ventricular arrhythmia, there was remark-

able stability in the minimal arrhythmic dosage of epinephrine. Where there was deviation with time, the tendency was for a small increase rather than a decrease in the minimal arrhythmic dosage. Second, in three of four dogs examined three hours after administration of the last drug in the sequence, aminophylline, there was almost a complete return to the minimal arrhythmic dosage for halothane. Likewise, in Phase II of the study, it was found that within 40 to 60 minutes after each dose of ketamine the minimal arrhythmic dosage of epinephrine was generally the same as the initial minimal arrhythmic dosage for halothane.

Effects of Cocaine, Tropolone, and Aminophylline on the Minimal Arrhythmic Dosage of Epinephrine

The bar graph in figure 2 shows the sequential decrease in the minimal arrhythmic dosage of epinephrine that occurred after the administration of each drug in Phase I. The minimal arrhythmic dosages of epinephrine during halothane alone extended from the .25 μg/kg to the 1 μg/kg dosage level. Note that while there was wide individual variability in the minimal arrhythmic dosages for halothane among dogs, the direction of change in the minimal arrhythmic dosage after each subsequent drug was always toward a decrease or, in other words, an increase in the arrhythmogenicity of epinephrine.

Cocaine decreased the minimal arrhythmic dosage of epinephrine in every animal except Dog 1. In this animal there was no change from the control value. The maximum decrease was 50 per cent, which was seen in six of the 16 animals. A decrease of 50 per cent was calculable when the minimal arrhythmic dosage decreased by one dosage level while retaining the same bolus number.

Tropolone, administered 60 minutes after cocaine, further decreased the minimal arrhythmic dosage in every animal. The maximum decrease was again 50 per cent and was seen in four of the 16 animals.

After aminophylline the minimal arrhythmic dosage was decreased even further in every animal. In three animals the maximum decrease was slightly greater than 50 per cent. The minimal arrhythmic dosage after aminophylline, reflecting the combined effects of all three drugs, was generally at the .125 μg/kg dosage level or lower.

The maximum decrease in the minimal arrhythmic dosage after cocaine was usually not observed until 20 to 40 minutes after its administration, whereas the maximum effects after tropolone and aminophylline were usually apparent within 1 to 15 minutes of administration. The decrease in the minimal arrhythmic dosage after each drug was statistically significant.

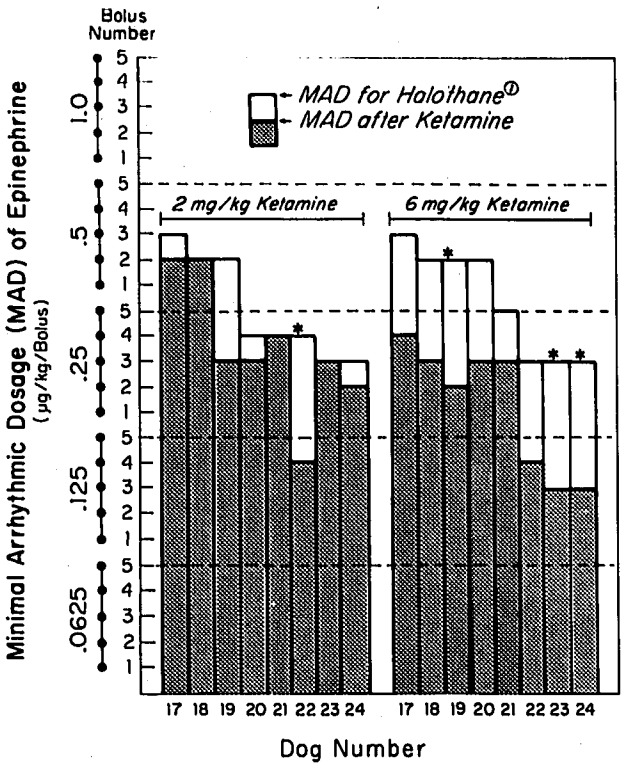

Fig. 3. Effects of administering ketamine first at 2 mg/kg, then at 6 mg/kg, on the minimal arrhythmic dosage (MAD) of epinephrine during halothane–nitrous oxide anesthesia. The results after 2 mg/kg in the second group of bars. The minimal arrhythmic dosage for halothane for the 6 mg/kg dose was the lowest dosage level and bolus number in that level eliciting a minimal ventricular arrhythmia 40 to 60 minutes after the last 2 mg/kg dose. * Dogs that showed the maximum 50 per cent decrease in MAD after ketamine.

Effect of Ketamine on the Minimal Arrhythmic Dosage of Epinephrine

After 2 mg/kg ketamine decreases in the minimal arrhythmic dosage were seen in five of eight dogs (fig. 3). After 6 mg/kg ketamine every dog showed an obvious decrease in the minimal arrhythmic dosage. The maximum decrease in the minimal arrhythmic dosage was 50 per cent, seen in three animals after 6 mg/kg but in only one animal after 2 mg/kg ketamine.

The decrease in the minimal arrhythmic dosage after a dose of ketamine was maximal only for the first epinephrine bolus series, or 1 to 4 minutes after the injection of ketamine. When the second epinephrine bolus series was done 10 minutes later, the minimal arrhythmic dosage had, in most instances, returned to the pre-ketamine-injection control levels. Generally, the decrease in the minimal arrhythmic dosage after the second 6 mg/kg dose was not as great as that after the first 6 mg/kg dose. The decreases in minimal arrhythmic dosage were statistically significant after both 2 and 6 mg/kg ketamine.

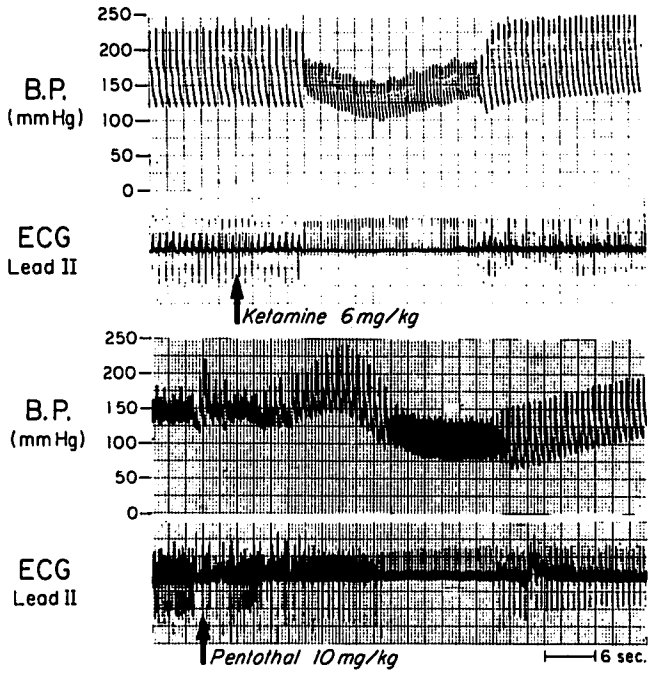

FIG. 4. The effect of ketamine administered during bigeminal rhythm produced by infusion of epinephrine at 1.4 μg/kg/min is depicted in the upper half of the figure. The effect of administering thiopental during multifocal ventricular extrasystoles produced by an epinephrine infusion at 1.4 μg/kg/min is depicted in the lower half. Both dogs were anesthetized with halothane–nitrous oxide. The two panels for each dog are blood pressure and ECG, lead II.

EFFECTS OF KETAMINE AND THIOPENTAL ADMINISTERED DURING CONTINUOUS MINIMAL VENTRICULAR ARRHYTHMIAS

Continuous minimal ventricular arrhythmias produced by constant infusion of epinephrine during halothane–nitrous oxide anesthesia could be temporarily abolished by rapid injection of 6 mg/kg ketamine or 10 mg/kg thiopental. The antiarrhythmic effect of ketamine in this situation is depicted in the upper half of figure 4. Ketamine, 6 mg/kg, abolished the bigeminal rhythm for 20 seconds. The blood pressure during the period of normal rhythm first dropped momentarily and then increased. As it increased to a level approximating that present at the onset of the normal rhythm, the arrhythmia reappeared. In two other dogs continuous multifocal ventricular extrasystoles were similarly abolished by 6 mg/kg ketamine for only a brief period. Blood pressure again declined momentarily during the period of normal rhythm. The same arrhythmia reappeared when the blood pressure had risen to a level near that present at the beginning of the normal rhythm.

In three other dogs in which continuous multifocal ventricular extrasystoles were produced, 10 mg/kg thiopental had a similar antiarrhythmic effect. The response in one dog is shown in the lower half of figure 4. Following injection of thiopental, the multifocal ventricular extrasystoles were first converted to a bigeminal rhythm for 11 seconds and then to a normal rhythm as the blood pressure declined. After 14 seconds of normal rhythm the bigeminal rhythm reappeared as the blood pressure started to rise. In the two other dogs in which the same dose of thiopental was given, the multifocal ventricular extrasystoles were converted immediately to a normal rhythm without an intervening begeminal rhythm. Blood pressure again declined briefly during the period of normal rhythm. The reappearance of multiple ventricular extrasystoles coincided with a rise in blood pressure.

After ketamine the duration of normal rhythm was 10 to 22 seconds and after thiopental, 14 to 20 seconds. Except in the one dog whose response to thiopental is shown in figure 4, all conversions to normal rhythm occurred within 12 seconds of injection of either drug. The average pre-epinephrine infusion blood pressure for the six dogs was 124/80 torr, with the blood pressures just before the onsets of arrhythmias averaging 188/130 torr.

TABLE 1. Effects of Cocaine, Tropolone, Aminophylline, and Ketamine on the Control and Peak Heart Rate and Systolic Blood Pressure in Phases I and II of the Study

		Systolic Blood Pressure (torr)		Heart Rate (/min)	
		Control	Peak	Control	Peak
Phase I	Halothane	117 ± .2	176 ± 4.9	133 ± 4	165 ± 4.9
	Cocaine	122 ± 5.7	178 ± 4.5	132 ± 3	170 ± 4.5
	Tropolone	152 ± 5.8*	188 ± 5.3	143 ± 5.3*	176 ± 6.7
	Aminophylline	140 ± 3.1	156 ± 6.3*	177 ± 6.1*	189 ± 7.1*
Phase II	Halothane	114 ± 5	176 ± 8.7	132 ± 7.8	168 ± 4.9
	Ketamine (2 mg/kg)	109 ± 5.2*	176 ± 8.3	133 ± 9.1	162 ± 6.2
	Ketamine (6 mg/kg)	97 ± 5.1*	173 ± 6.2	128 ± 8.9	151 ± 4 *

* Statistically significant change compared with previous drug.

Effects of Cocaine, Tropolone, Aminophylline, and Ketamine on Blood Pressure and Heart Rate

To evaluate the effects of these drugs on the heart rate and blood pressure at which a minimal ventricular arrhythmia occurred and on the control values present just before the start of an epinephrine bolus series, control and peak heart rates and systolic blood pressures were recorded for the epinephrine bolus series, establishing the minimal arrhythmic dosage after each drug. Excluding the arrhythmic period, the maximum heart rate and blood pressure attained in response to epinephrine almost always occurred within 5 seconds of the onset of an episode of arrhythmia. Therefore, the peak heart rate and systolic blood pressure were taken as the maximum response attained in the 5-second period before the onset of the minimal ventricular arrhythmia.

The control and peak heart rates and systolic blood pressures for halothane and after the administration of each drug are presented in table 1. In Phase I the peak systolic blood pressures ranged from 156 torr following aminophylline to 188 torr after tropolone. In Phase II the peak systolic blood pressure was relatively unaffected by either dose of ketamine, but the control systolic blood pressure was significantly decreased after either 2 or 6 mg/kg ketamine. The control values after ketamine represented the mean of measurements taken 1 minute after its injection. Systolic blood pressures just before the injections of 2 and 6 mg/kg (not given in table) were 116 ± 6 and 115 ± 5 torr, respectively, and differed only marginally from the Phase II halothane control value of 114 ± 5 torr.

Effects of Cocaine, Tropolone, and Ketamine on the 50 Per Cent Recovery Times of Blood Pressure and Heart Rate

If cocaine, tropolone and ketamine interfere with mechanisms that help reduce the concentration of epinephrine in the area of the receptor to an extent sufficient to increase the arrhythmogenicity of epinephrine, then an increase in the duration of the blood pressure and heart rate responses to epinephrine might also be expected after each drug. To evaluate this possibility the duration of heart rate and blood pressure responses was measured as the time in seconds for 50 per cent recovery from peak values obtained during an epinephrine series. As shown in figure 5, the increases in 50 per cent recovery times of blood pressure and heart rate were significant after cocaine, tropolone, and ketamine. The extents of the increases after cocaine and 6 mg/kg ketamine was similar.

The increases in the 50 per cent recovery times

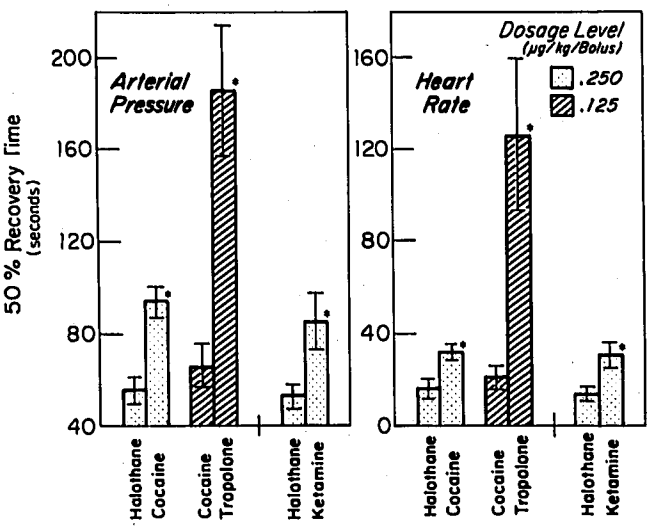

FIG. 5. The pairs of bars represent the 50 per cent recovery times (mean ±SE) of systolic blood pressure and heart rate for the epinephrine bolus series from the same dosage level of adjacently administered drugs: halothane–cocaine, cocaine–tropolone, halothane–ketamine. The ordinate is the time in seconds for 50 per cent recovery, and the drug whose effect on the recovery time was measured is indicated below the appropriate bar. The recovery time after ketamine was for the 6 mg/kg dose. * Significant increase in recovery time compared with the first drug in a pair.

after cocaine and tropolone remained relatively stable during the time periods studied. However, after 6 mg/kg ketamine the increase in the 50 per cent blood pressure recovery time was greatest for the first epinephrine bolus series begun 1 minute after injection of ketamine; by 12 minutes the blood pressure had recovered to half the original increase, and at 60 minutes the recovery time was the same as the preinjection 50 per cent recovery time (fig. 6). This time course of recovery was reproducible after the second 6 mg/kg dose.

Duration of Arrhythmias

The mean durations of the minimal ventricular arrhythmias elicited by epinephrine bolus series establishing the minimal arrhythmic dosages in Phase I were 15 ± 1.9 seconds for halothane, 17 ± 1.9 seconds after cocaine, 17 ± 3.5 seconds after tropolone, 37 ± 1.4 seconds after aminophylline. In Phase II the durations of the minimal ventricular arrhythmias were 14 ± 2 seconds for halothane and 20 ± 2 seconds after both 2 mg/kg and 6 mg/kg ketamine.

Discussion

The technique used in this study to determine the minimal arrhythmic dosage of epinephrine permitted the graded assessment of changes in the sensitivity of the heart to epinephrine-induced arrhythmias and eliminated the accidental initiation

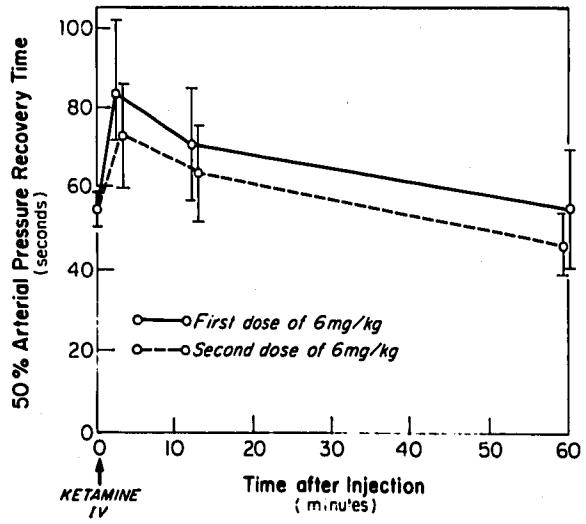

FIG. 6. The 50 per cent systolic blood pressure recovery time for the epinephrine bolus series done 1, 12, and 60 minutes after 6 mg/kg ketamine. The ordinate is the time in seconds for 50 per cent recovery of blood pressure. The abscissa is the time in minutes after the injection of ketamine when recovery times were measured. The recovery times were taken from the epinephrine bolus series from the .25 μg/kg dosage level. Data are shown as mean ± SE with N = 4 for first dose and N = 5 for second dose.

of persistent major ventricular arrhythmias, which would prevent the study of a sequence of drugs in the same animal. With this technique the mean durations of the minimal ventricular arrhythmias for halothane and after cocaine, tropolone, and ketamine were in the limited range of 14–20 seconds, suggesting that the method was relatively sensitive in detecting just that amount of epinephrine necessary to influence a uniform transient arrhythmia. This sensitivity may be related in part to the finding by Ferreira and Vane that in the dog epinephrine has a half-life in the circulation of less than one circulation time.[21] The circulation time in the dog is about 20 seconds.[22] Therefore, by administering boluses of epinephrine at 30-second intervals, the maximum response to a bolus was achieved before the next injection was to be given, thereby avoiding marked overshoot of the minimal arrhythmic dosage.

The results in Phase I indicate that the sequential administration of cocaine, tropolone, and aminophylline causes a corresponding sequential increase in the arrhythmogenicity of epinephrine. This observation is consistent with the known effects of these drugs on specific catecholamine terminating mechanisms and their ability to increase other epinephrine responses.

Although other effects of these drugs may be involved, they can in most instances be either related indirectly to the catecholamine terminating action of the drug or considered to be unimportant or even opposed to the production of arrhythmias.

For example, cocaine, in addition to inhibiting intraneuronal uptake, has local anesthetic action. This property is generally cardiodepressant[23] and would presumably impart an antiarrhythmic effect to cocaine. Cardiac depression by cocaine has been found at 10 mg/kg and even at 5 mg/kg when administered rapidly.[24] Such depression, however, was not apparent at the dose and rate of administration employed in this study. What did occur was a significant increase in the 50 per cent recovery times of blood pressure and heart rate, implying that cocaine was affecting a catecholamine terminating mechanism, namely inhibition of intraneuronal uptake. It seems reasonable to suspect that inhibition of intraneuronal uptake was also primarily responsible for the increase in the arrhythmogenicity of epinephrine that occurred after cocaine.

Tropolone, besides being an inhibitor of COMT, has also been reported to have beta-receptor blocking activity.[25] The latter effect would be expected to oppose the arrhythmia-inducing action of epinephrine. Rather, it was found that following cocaine, tropolone caused an additional increase in the arrhythmogenicity of epinephrine and the 50 per cent recovery times. Inhibition of COMT has been found by Kalsner and Nickerson to increase the duration of the vasoconstrictor response to epinephrine and norepinephrine[26] and by Giles and Miller to potentiate in rabbit atria the inotropic responses to epinephrine and isoproterenol but not to norepinephrine.[27] However, when cocaine was present Kaumann found that COMT inhibition potentiated the effects of norepinephrine in cat papillary muscle.[28]

Trendelenburg has concluded that blocking COMT will be more likely to result in potentiation of a catecholamine when neuronal uptake is of little importance or the sensitivity of the receptor to the catecholamine is very high.[4] Hence, in these experiments where cocaine had already been given and halothane sensitization of the myocardium to epinephrine was present, it was not expected that tropolone enhanced the arrhythmogenicity of epinephrine.

The last drug in the sequence, aminophylline, further enhanced the arrhythmia-inducing action of epinephrine. Aminophylline has several actions besides inhibition of phosphodiesterase that could be responsible for this increase. For example, it is known to stimulate catecholamine release from the adrenal medulla[29] and to alter calcium accumulation by the sarcoplasmic reticulum.[30] However, because cAMP may also affect these processes,[31,32] they could in turn be susceptible to the effects of phosphodiesterase inhibition by aminophylline. The inhibitory action of aminophylline on phosphodiesterase assumes further importance when consideration is given to the possibility that cAMP may also mediate the effects of epinephrine on automaticity in Purkinje fibers. Tsien, from results comparing the effects of epinephrine and theo-

phylline on the electrical activity of Purkinje fibers, proposed that the two drugs have a common mechanism of action beginning with elevation of intracellular cAMP.[33] In addition, Danilio *et al.* found that the increase in automaticity induced by epinephrine in canine Purkinje fibers was associated with an elevation of cAMP.[34] From such studies it appears quite probable that cAMP is involved in the electrophysiologic effects of epinephrine on Purkinje fibers. Such a relationship supports the contention that the additional increase in the arrhythmogenicity of epinephrine after aminophylline is at least in part associated with phosphodiesterase inhibition.

Although a rise in arterial blood pressure has been found to promote the induction of epinephrine-induced arrhythmias,[35,36] an increase in blood pressure is not necessary for the production of arrhythmias by epinephrine.[37,38] That the mean systolic blood pressure at which minimal ventricular arrhythmias occurred after aminophylline was significantly lower compared with the other drugs and that the range of the means of the peak systolic pressures was 156 to 188 torr suggest that the absolute peak of the blood pressure was not necessarily the critical determinant in the development of the arrhythmias in this study.

In Phase II the increases in arrhythmogenicity of epinephrine and the 50 per cent recovery times after ketamine were comparable to those seen after cocaine and, hence, are consistent with a cocaine-like action of ketamine's being responsible for the increase. Nevertheless, this does not rule out the possibility that other effects of ketamine may also be involved. Nedergaard found that ketamine, besides possessing a cocaine-like action, may interfere with COMT and monoamine oxidase.[10] The suggestion that ketamine may release endogenous catecholamines has also been made.[39–41] However, Nedergaard and Traber were not able to demonstrate such an effect.[10,42,43] Also, Yamanaka and Dowdy concluded from their data on rabbit aorta strips that ketamine does not stimulate alpha- or beta-adrenergic receptors.[44]

Ketamine has been said to produce centrally mediated effects that increase blood pressure and heart rate.[42,43,45] However, during halothane–nitrous oxide anesthesia, only a depressor response was found by Stanley, with the maximum decrease observed between the fourth and seventh minute following intravenous injection of 2 mg/kg ketamine.[46] In our study the dominant response 1 minute after the injection of ketamine was also a decrease in blood pressure after either 2 or 6 mg/kg, with the heart rate either remaining unchanged or decreasing slightly. Stanley proposed that this inhibition of the pressor response of ketamine was due to the depressant effects of halothane on the central nervous system and its sympatholytic action. This explanation can be extended by encompassing the action of ketamine at the adrenergic neuroeffector junction with the depression by halothane of the release of catecholamines from the adrenergic nerve ending and the adrenal medulla.[47–49] As suggested by Miletich *et al.* and Nedergaard, the increases in blood pressure and heart rate seen after ketamine may be due in part to its ability to block the intraneuronal uptake of catecholamines.[10,11] Consequently, during halothane anesthesia when the release of catecholamines is depressed, there would be a corresponding decrease in the quantity of catecholamines that could be prevented by ketamine from being taken up into the adrenergic nerve endings. As a result, less than the usual amount of catecholamines would be diverted back to or prevented from leaving the area of the receptor, thereby allowing the direct depressant effects of ketamine on the heart to predominate.[50]

The direct effects of ketamine on Purkinje fibers have been found by Hamilton and Bryson to be dose-related and to be consistent with both antiarrhythmic and arrhythmogenic effects.[51] The latter effect was evident at the highest ketamine concentration studied. At this concentration in electrically driven preparations, the duration of an action potential between evoked potentials was shortened and the ability of epinephrine to elicit spontaneous action potentials was markedly augmented. These effects were interpreted as predisposing to the development of arrhythmias and are in agreement with our finding that ketamine can increase the arrhythmogenicity of epinephrine. The effect on arrhythmogenicity in this study was more prominent at 6 mg/kg than at 2 mg/kg ketamine.

The increases in the arrhythmogenicity of epinephrine and the 50 per cent blood pressure recovery time after 6 mg/kg were characteristically short-lived, in that the initial increases observed 1 to 4 minutes after injection of ketamine with the first epinephrine bolus series were greatly diminished or absent 12 minutes later when the second series was done. Thus, the increase in arrhythmogenicity of epinephrine is time- as well as dose-related, and can be explained as follows: Miletich found in the isolated rat heart that although on an equal-dose basis ketamine was only about 80 per cent as effective as cocaine in preventing uptake of norepinephrine, this cocaine-like action was increased by increasing the concentration of ketamine in the perfusate.[11] However, *in vivo* the plasma concentration of ketamine decreases rapidly after an intravenous injection, with the initial decrease in the plasma level having a half-life of 10 minutes.[52] Our results suggest that the duration of an effective plasma and myocardial level of ketamine with sufficient cocaine-like action to cause potentiation of epinephrine arrhythmogenicity is less than 12 minutes after 6 mg/kg ketamine.

In contrast to the increase in arrhythmogenicity of epinephrine seen 1 to 4 minutes after injection

of 6 mg/kg ketamine, the same dose would, when administered during a continuous epinephrine-induced arrhythmia, transiently abolish the arrhythmia. This antiarrhythmic effect was evident within 12 seconds of injecting ketamine and lasted less than 30 seconds. Dowdy and Kaya previously described this ability of ketamine to abolish epinephrine-induced arrhythmias during halothane anesthesia.[53]

In addition, however, we were also able to produce a similar antiarrhythmic effect with 10 mg/kg of thiopental, a potent cardiovascular depressant at high concentrations.[54] The immediate but short-lived antiarrhythmic effects of both drugs would coincide with the high but briefly maintained plasma levels of these drugs that follow their intravenous injection.[55–58] Ketamine, like thiopental, is also a cardiovascular depressant at high concentrations.[43,50] Hence, the immediate but brief duration of the antiarrhythmic effects after both drugs, and the return of the arrhythmia with a rise in blood pressure, suggest that cardiovascular depression by ketamine could account in part for its antiarrhythmic action in this situation.

Thus, after intravenous injection of 6 mg/kg ketamine there is a very short interval of arrhythmia suppression, followed by a period in which the ability of epinephrine to induce arrhythmias is increased. The order and duration of each event can be considered to be determined by the net effect of opposing concentration-dependent actions of ketamine.

Thus, the results of this study indicate that drugs like cocaine and ketamine, which interfere with intraneuronal uptake, facilitate the development of epinephrine-induced arrhythmias, and that the successive pharmacologic interference with intraneuronal uptake, COMT, and phosphodiesterase leads to a stepwise increase in the arrhythmogenicity of epinephrine. The implication of the results of these interactions further emphasizes the need to be knowledgeable concerning all the drugs a patient may be taking and all the actions of these drugs. That is, what might be considered a safe dose of epinephrine in so-called "normal circumstances" may be far from safe in situations where adrenergic terminating mechanisms are not functioning optimally because of pharmacologic interference.

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