Laboratory Investigation

Epinephrine-aminophylline-induced arrhythmias after midazolam or thiopentone in halothane-anaesthetized dogs

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The purpose of this study was to evaluate epinephrine-aminophylline-induced arrhythmias during halothane anaesthesia after induction with thiopentone or midazolam. Ten mongrel dogs were studied during 1 MAC halothane and 50% N_2O:O_2 anaesthesia while maintaining constant acid-base status. The minimal arrhythmogenic infusion rate of epinephrine (MAIRE) and the corresponding plasma concentration of epinephrine (MAPC) required to produce ventricular arrhythmias before and after aminophylline were higher following induction of anaesthesia with midazolam than with thiopentone ($P < 0.05$); the MAIREs decreased stepwise with aminophylline ($P < 0.05$). The correlation coefficient between individual MAIREs and MAPCs was 0.93 ($P < 0.001$). Epinephrine alone and in combination with aminophylline was less arrhythmogenic after induction with midazolam than with thiopentone.

Cette étude fut entreprise pour comparer l'effet de l'induction de l'anesthésie au midazolam à l'effet de l'induction au thiopentone sur l'arythmogénicité de l'épinéphrine tant en l'absence qu'en la présence d'aminophylline. Cinq chiens reçurent 10 $mg \cdot kg^{-1}$ de midazolam intraveineux. Cinq autres reçurent 25 à 30 $mg \cdot kg^{-1}$ de thiopentone. Après intubation trachéale, tous furent gardés sous anesthésie à l'aide de 1 MAC d'halothane dans un mélange de 50% de N_2O et d'O_2. Les taux minimaux d'infusion d'épinéphrine (MAIRE) requis pour produire des arythmies ventriculaires et les concentrations plasmatiques d'épinéphrine correspondantes (MAPC) diminuèrent graduellement après 10 et 20 $mg \cdot kg^{-1}$ d'aminophylline mais furent toujours plus élevés après l'induction au midazolam qu'après l'induction au thiopentone. Donc, sous nos conditions expérimentales et comparée au thiopentone, l'induction au midazolam atténue l'arythmogénicité de l'épinéphrine tant en l'absence qu'en la présence d'aminophylline.

Key words
ANAESTHETICS, INTRAVENOUS: midazolam, thiopentone;
ANAESTHETICS, VOLATILE: halothane;
HEART: arrhythmia;
PHARMACOLOGY: aminophylline;
SYMPATHETIC NERVOUS SYSTEM: epinephrine.

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Patients suffering from bronchial asthma and chronic obstructive pulmonary disease are often treated with epinephrine and theophylline (aminophylline) perioperatively. A serious problem with this potent bronchodilating combination is the potential to precipitate a fatal ventricular arrhythmia.[1,2] This is exacerbated when volatile halogenated anaesthetics and thiopentone are part of the anaesthetic regimen because of their tendency to sensitize the heart to the arrhythmogenic effect of catecholamines.[3–6] Halothane, enflurane, and isoflurane have been used successfully in the treatment of status asthma-

ticus.[7,8] Although halothane is more arrhythmogenic than enflurane and isoflurane, halothane may still be preferred[9] because it has some advantages over isoflurane during airway stimulation.[10]

In one approach to this problem, we tested the hypothesis that midazolam, compared with thiopentone for induction of anaesthesia, would result in less arrhythmogenicity of the epinephrine-aminophylline-halothane combination without interfering with its bronchodilating action.

Methods

Animals

We used two groups of five mongrel dogs each of either sex with a weight range of 17.0 to 21.5 kg.

Anaesthesia and monitoring

Anaesthesia was induced with either thiopentone (Group T), 25–30 $mg \cdot kg^{-1}$ *iv*, or midazolam (Group M), 10 $mg \cdot kg^{-1}$ *iv*, followed by succinylcholine, 2 $mg \cdot kg^{-1}$ *iv* to facilitate tracheal intubation. Anaesthesia was maintained with 50% N_2O in O_2 plus halothane (H) at 0.9% end-tidal concentration. Pulmonary ventilation was controlled to maintain $PaCO_2$ at 35–40 mmHg. A catheter was inserted into a saphenous vein for the administration of 5% dextrose in lactated Ringer's solution. The heart rate (HR) was recorded from lead II of the ECG using a Spacelabs monitor (Model 413A). A #8 Fr side port/haemostasis valve catheter to sheath adapter (Arrow AK-09801) was inserted percutaneously into a femoral artery for the rapid removal of blood for arterial blood gas (Radiometer Copenhagen (Model BMS MK2)) and blood chemistry analyses, and for retrograde catheterization of the femoral artery through the haemostasis valve with a #7 Fr NIH catheter to record aortic blood pressure. The arterial catheter was connected via a Bell & Howell transducer (Model 4-327-I) to a Gould amplifier module (Model 13-4218-00).

Physiological and biochemical measurements

All analogue signals were recorded on a Gould 6-channel strip recorder and on magnetic tape (Sabre tape deck, model II). Average values for R-R interval, systolic (SBP), and diastolic (DBP) aortic pressures were obtained from the analogue tracings of three consecutive beats. Heart rate (HR) was derived from the ECG, and mean aortic pressure (MAP) from a standard formula. End-expiratory PCO_2 was measured on-line with a Capnogard infrared analyzer, and arterial blood gas (ABG) analysis was determined intermittently to confirm appropriate ventilation and acid-base status. End-tidal concentrations of halothane were measured on-line by an Emma gas analyzer (LKB Medical Inc., Model 57-70110-30) and off-line by gas chromatography. Blood samples for the determination of plasma concentrations of catecholamines, theophylline and electrolytes were taken when appropriate. Plasma catecholamines were determined by HPLC with electrochemical detection[11] (coefficients of variation: exogenous, 5%; endogenous, 10%). Plasma theophylline was analyzed by a modification of Jatlow's HPLC method[12] (coefficient of variation 5%), and sodium and potassium were detected with an Instrumentation Laboratory Flame Photometer (Model 143, coefficient of variation 5%).

Arrhythmogenic state

This was defined by the occurrence of: (1) three consecutive premature ventricular contractions (PVCs), or (2) 10 or more $PVCs \cdot min^{-1}$, or (3) ventricular bigeminy. We chose this definition because it corresponds to the clinical concept of ventricular arrhythmias requiring immediate attention and treatment and is close to Dresel and Sutter's definition of minimal ventricular arrhythmia.[13]

Drugs

Except for the volatile anaesthetics, drugs were given *iv* either by bolus injection or by infusion using a calibrated Harvard infusion pump (Model 942).

EPINEPHRINE

The minimal arrhythmogenic infusion rate (MAIRE) and minimal arrhythmogenic plasma level (MAPC) were used to determine the arrhythmogenic threshold to epinephrine. This was done by infusing epinephrine in logarithmically spaced increasing doses starting at 0.37 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for five minutes each. The epinephrine infusions were stopped at the arrhythmogenic state after obtaining blood samples for physiological and biochemical analyses. The average time interval between induction of anaesthesia and the first dose of epinephrine was about two hours.

AMINOPHYLLINE

After haemodynamic variables had been stable for five minutes, aminophylline, 10 $mg \cdot kg^{-1}$, was injected over one minute. Five minutes later (A_{10}), haemodynamic measurements were recorded and blood samples taken. Then, the infusion schedule of epinephrine was repeated until the predetermined arrhythmic condition appeared, at which time blood samples again were taken. This aminophylline-epinephrine protocol was repeated with 20 $mg \cdot kg^{-1}$ of aminophylline (A_{20}).

Statistics

One-(ANOVAIR) and two-way analyses of variance, Newman-Keuls tests, unpaired t tests, and paired t tests

TABLE I Effect of induction of anaesthesia with midazolam (M, $n = 5$) and thiopentone (T, $n = 5$) on MAIRE and MAPC

		A_0	A_{10}	A_{20}
MAIRE	T	1.63 ± 0.27	0.74 ± 0.36#	0.41 ± 0.09#,+
$\mu g \cdot kg^{-1} \cdot min^{-1}$	M	2.52 ± 0.56*	1.57 ± 0.26#,**	0.87 ± 0.20#,+,**
MAPC	T	22.5 ± 10.5	09.4 ± 07.5#	04.2 ± 01.7#
$\mu g \cdot L^{-1}$	M	42.6 ± 16.1*	24.0 ± 07.6#,*	13.0 ± 06.6#,*
Plasma K^+	T	3.83 ± 0.59	3.13 ± 0.57#	2.98 ± 0.53#
$mEq \cdot L^{-1}$	M	3.77 ± 0.46	3.82 ± 0.26*	3.38 ± 0.65
Plasma A	T	0	10.98 ± 4.74	28.6 ± 15.3++
$mg \cdot L^{-1}$	M	0	9.02 ± 1.43	29.3 ± 4.3++
SBP	T	212 ± 24	166 ± 34#	124 ± 20#,++
mmHg	M	218 ± 31	200 ± 21	163 ± 8#,++,**

Mean values ± SD of minimal arrhythmogenic infusion rate of epinephrine (MAIRE), of minimal arrhythmogenic plasma concentrations of epinephrine (MAPC), of plasma potassium (K^+) and plasma aminophylline (A) concentrations and systolic blood pressure (SBP) prior to aminophylline (A_0), and following 10 $mg \cdot kg^{-1}$ (A_{10}) and 20 $mg \cdot kg^{-1}$ (A_{20}) aminophylline.
#Statistically significant difference from A_0 at $P < 0.01$ by Newman-Keuls test.
+,++Statistically significant difference between A_{20} and A_{10} at $P < 0.05$ and $P < 0.01$ respectively by Newman-Keuls test and by paired t test for plasma aminophylline.
*,**Statistically significant difference from T at $P < 0.05$, and $P < 0.01$ respectively by unpaired t test.

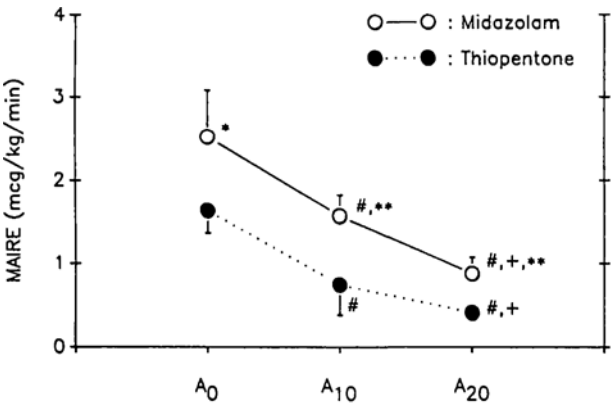

FIGURE 1 Mean values and SD of infusion rates of epinephrine without (A_0) and with 10 (A_{10}) and 20 (A_{20}) $mg \cdot kg^{-1}$-aminophylline in midazolam and thiopentone pretreated halothane-anesthetized dogs. Statistically significant differences from baseline (#, $P < 0.01$), from A_{10} (+, $P < 0.05$) and from midazolam (*, $P < 0.05$; **, $P < 0.01$).

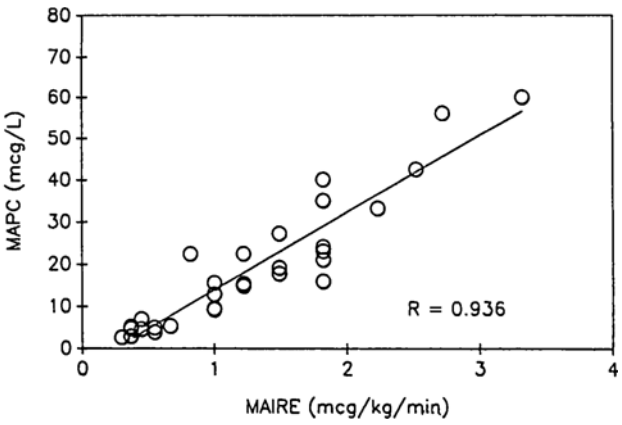

FIGURE 2 Linear regression of individual data points ($n = 30$) between MAIRE ($\mu g \cdot kg^{-1} \cdot min^{-1}$) and MAPC ($\mu g \cdot L^{-1}$).

were used to establish statistically significant differences among treatments.

Results

Pertinent data are listed in Table I.

At each measurement, MAIRE (Figure 1) and MAPC were lower after thiopentone than after midazolam ($P < 0.05$ for MAIRE at A_0, $P < 0.01$ for MAIRE at A_{10} and A_{20}, $P < 0.05$ for MAPC).

With aminophylline 10 $mg \cdot kg^{-1}$, MAIRE and MAPC decreased from A_0 in both groups ($P < 0.01$). With aminophylline 20 $mg \cdot kg^{-1}$, MAIRE decreased from A_{10} in both groups ($P < 0.05$).

Linear regression between all individual MAIRE and MAPC values (Figure 2) yielded a correlation coefficient of 0.93 ($P < 0.001$).

Overall aminophylline-induced changes in SBP were statistically significant both after thiopentone and midazolam induction ($P < 0.01$ by ANOVAIR). After thiopentone induction, SBP at MAIRE was lower after 10 and 20 $mg \cdot kg^{-1}$ aminophylline than before aminophyl-

TABLE II Acid-base chemistry

		A_0	A_{10}	A_{20}
pH	T	7.36 ± 0.06	7.33 ± 0.09	7.35 ± 0.07
(units)	M	7.35 ± 0.05	7.33 ± 0.03	7.35 ± 0.03
$PaCO_2$	T	38 ± 3	41 ± 5	35 ± 2
(mmHg)	M	40 ± 8	41 ± 2	38 ± 4

Mean values ± SD of pH and $PaCO_2$ at arrhythmogenic threshold without aminophylline (A_0) and after 10 (A_{10}) and 20 (A_{20}) mg · kg^{-1} aminophylline after thiopentone (T, $n = 5$) or midazolam (M, $n = 5$) induction.

line (A_0). After midazolam induction, SBP was lower only after A_{20} when compared to A_0 and A_{10}. At A_{20}, SBP was higher after midazolam than after thiopentone (163 vs 124 mmHg, $P < 0.01$).

There were no differences in plasma aminophylline concentrations at MAIREs between the midazolam and thiopentone groups.

With thiopentone plasma potassium levels at MAIRE declined after 10 and 20 mg · kg^{-1} aminophylline compared with A_0. Plasma potassium levels after 10 mg · kg^{-1} aminophylline were higher with midazolam than with thiopentone ($P < 0.05$).

The arterial blood pH and $PaCO_2$ values before (A_0) and after the injections of aminophylline (A_{10},A_{20}) were not different from each other within and between the two treatment groups (Table II).

Discussion

The arrhythmogenic thresholds to epinephrine were lower with thiopentone than with midazolam at each determination, and decreased after aminophylline in a dose-dependent manner (Figure 1 and Table I).

Compared with induction and maintenance of anaesthesia with halothane alone, thiopentone lowered the arrhythmogenic threshold to epinephrine[5] for at least four hours after injection.[14,15] The duration of midazolam's effect on arrhythmias is unknown.

Although we did not measure plasma thiopentone or midazolam concentrations, midazolam concentrations may have decreased much faster than thiopentone's throughout the study period, because midazolam has a shorter elimination half-life and faster clearance than thiopentone[16] (1.5–2.5 hr and 4–8 ml · kg^{-1} · min^{-1}, for midazolam vs 5–11.5 hr and 1.6–4.3 ml · kg^{-1} · min^{-1}, for thiopentone). Because of these pharmacokinetic differences and the time of measurements, we may have underestimated the thiopentone-midazolam differences in arrhythmogenic threshold to epinephrine. Based on the reported pharmacokinetic behaviour of thiopentone and midazolam,[16] the rapid decline in plasma levels of both drugs had already occurred when we began MAIRE measurements two hours after induction of anaesthesia, with plasma levels decreasing slowly during the time of measurements. We may also have underestimated thiopentone's arrhythmogenic potential, which may explain why our MAIRE (1.63 μg · kg^{-1} · min^{-1}) was higher than that reported by some.[17,18] Others found MAIREs higher than ours,[19–22] probably because our methodology included higher doses of thiopentone (25–30 mg · kg^{-1} vs 20 mg · kg^{-1}), N_2O (50% N_2O in O_2 vs 100% O_2), a lower halothane concentration (1 MAC vs 1.1 to 1.25 MAC), and a longer epinephrine infusion time (5 min vs 3 min). Ten-minute intervals separated consecutive infusions to allow haemodynamic variables to return to within 10% of control, as in the studies of Pace *et al.*[10] and Kapur *et al.*[20]

The arrhythmogenic threshold of epinephrine has been reported as infusion rate,[17,19,20,23,24] dose[5,14] (infusion rate × duration of infusion), or both.[25] We reported infusion rates and plasma levels of epinephrine, with the latter probably being more relevant.

In dogs anaesthetized with halothane after thiopentone induction, aminophylline 10 mg · kg^{-1} did not cause arrhythmias,[15] but did enhance the arrhythmogenicity of epinephrine.[18,19] To our knowledge, a dose-related arrhythmia-facilitating effect of aminophylline has not been clearly reported. Aminophylline 10 mg · kg^{-1} decreased MAIRE and MAPC; aminophylline 20 mg · kg^{-1} decreased MAIRE further, with a downward trend in MAPC (Table I). At each determination, both MAIRE and MAPC were higher after midazolam than after thiopentone (Table I). The midazolam/thiopentone MAIRE and MAPC ratios increased with aminophylline (M/T MAIRE and MAPC ratios: 1.54 and 1.89 at A_0; 2.12 and 2.55 at A_{10}; 2.12 and 3.09 at A_{20}), suggesting that midazolam-aminophylline was a less arrhythmogenic combination than thiopentone-aminophylline.

The arrhythmogenic threshold to epinephrine can be altered by *iv* anaesthetic induction agents,[5,18,21] halogenated volatile anaesthetics,[26] and aminophylline.[18,19] Our study was not designed to investigate if more complex cellular mechanisms such as the interaction of cAMP with free intracellular Ca^{++},[27] reuptake of adenosine,[28] sensitization of the A-V node[29] were responsible for alterations of the arrhythmogenic threshold to epinephrine. However, we were able to assess the role of the blood pressure response to epinephrine,[6] plasma potassium concentrations,[30] and acid-base status[31] in causing the observed MAIRE differences between thiopentone and midazolam induction.

Systolic blood pressure at the time of the arrhythmias was nearly identical between groups before aminophylline, although barbiturates and benzodiazepines may not have identical influences on the autonomic nervous system components. Thiopentone reportedly decreases the activity of baroreceptors[32] and the sympathetic activi-

ty of cutaneous nerves,[33] inhibits cervical sympathetic preganglionic activity,[32] and allows induction of anaesthesia without sympathetic activation[34] (thiopentone bolus plus infusion decreased plasma norepinephrine after ten minutes; giving thiopentone just before induction of anaesthesia by mask with halothane prevented the sympathetic activation seen with mask induction alone). Midazolam has been reported to decrease central sympathetic outflow, to lower circulating concentrations of catecholamines, and to decrease transiently baroreceptor activity.[35] To our knowledge, no systematic investigation exists comparing the autonomic nervous system effects of benzodiazepines and barbiturates. At A_{10} and A_{20}, systolic blood pressure was higher after midazolam than after thiopentone (Table I). This may have been more an effect than a cause since more epinephrine was required with midazolam to reach the arrhythmogenic threshold. Thus, increased midazolam/thiopentone MAIRE and MAPC ratios after aminophylline may explain the SBP differences between groups. Hypotension may be arrhythmogenic, but the lowest SBP at arrhythmias was 124 mmHg (group T at A_{20}). Neither hyper- nor hypotension appear to contribute to the inter-group differences in arrhythmogenic thresholds, reinforcing the conclusion of Atlee and Malkinson[5] that the systolic blood pressure response to epinephrine does not explain the increase in arrhythmogenicity after thiopentone.

Plasma potassium concentration was initially the same in both groups, then decreased after aminophylline 10 $mg \cdot kg^{-1}$ in group T, but with only a small downward trend after aminophylline 20 $mg \cdot kg^{-1}$ in group M (Table I). Hypokalaemia may have facilitated arrhythmias with the aminophylline-thiopentone combination.

Acid-base imbalance did not appear to contribute to the arrhythmias, since arterial pH and PCO_2 did not differ between groups nor change during the study (Table II).

In summary, if maintenance of anaesthesia with halothane is considered important when a potential aminophylline-epinephrine arrhythmogenic interaction may occur, then replacing thiopentone with midazolam as the induction agent could be advantageous.

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