Epinephrine Arrhythmogenicity Is Enhanced by Acute, but Not Chronic, Aminophylline Administration during Halothane Anesthesia in Dogs

Philippe G. Prokocimer, M.D.,* Ethan Nicholls, B.A.,† David M. Gaba, M.D.,‡ Mervyn Maze, M.B., Ch.B.‡

The authors determined the effect of acute and chronic aminophylline treatment on the arrhythmogenicity of epinephrine during halothane anesthesia. The dose of epinephrine required to achieve an arrhythmia threshold (ADE) was determined in nine unpremedicated dogs anesthetized with halothane (1.5% v/v) in oxygen (A6). Aminophylline was then infused to achieve and sustain a therapeutic theophylline level (mean ± SD) of 17 ± 2 μg·ml−1 (A4), at which time the ADE was reassessed. The aminophylline infusion regimen was then adjusted to provide a supratherapeutic level of theophylline of 34 μg·ml−1 (A4) and the ADE was reassessed. In an additional seven dogs the ADE was assessed before and after 6 weeks of oral aminophylline treatment that yielded a plasma theophylline level of 18 ± 3 μg·ml−1. The ADE was significantly (P < 0.01) reduced from a basal value (mean ± SD) of 2.63 ± 0.97 μg·kg·min−1 to 1.39 ± 0.47 in the A4 state. There was no further decrement in the ADE at the A4 state (1.17 ± 0.36). The plasma epinephrine level at the arrhythmia threshold decreased commensurately from 50.7 ± 40.2 μg·ml−1 (A6) to 20.6 ± 7.9 and 19.2 ± 7.6 in the A4 and A2 states, respectively (P < 0.01). In contrast, these acute treatment experiments, neither the ADE (2.65 ± 0.95 vs. 2.97 ± 1.49 μg·kg·min−1) nor the plasma epinephrine levels at the arrhythmia threshold (47.2 ± 13.7 vs. 51.1 ± 22.0 μg·ml−1) were different after chronic aminophylline treatment. It is concluded that an important arrhythmia-enhancing effect is induced by a clinically relevant dose of acute intravenous aminophylline administration in a canine halothane-epinephrine arrhythmia model. However, this effect is reversed following chronic aminophylline treatment. The authors speculate that, in the acute state, the antiadenosine action of aminophylline potentiates the halothane-epinephrine arrhythmia interaction and that compensatory mechanisms normalize this effect following chronic aminophylline administration. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmia. Pharmacology: aminophylline. Receptors: adenosine. Sympathetic nervous system: catecholamines; epinephrine.)

Because asthma affects between 2–5% of the general population,1 patients with asthma are frequently encountered in the perioperative setting. While the clinical usefulness of treating bronchial asthma with parenteral theophylline-containing compounds has been well established,2 the literature is replete with reports of fatal cardiac complications in patients on drug combinations that include aminophylline.3,4 In selecting an appropriate anesthetic and adjunctive drugs for patients with asthma, a compromise has to be struck between the desired anti-bronchospastic effect and unwanted toxic manifestations. In this context, halothane has been recommended as an ideal agent because of its potent bronchodilatory properties that have been demonstrated both in animals5 and in humans.6 However, concurrent administration of aminophylline during halothane anesthesia may provoke ventricular ectopy,7 although the contribution of halothane to arrhythmia occurrence is only speculative because aminophylline, per se, can be arrhythmogenic.8 Stirr et al.9,10 have investigated the putative arrhythmogenic interaction between halothane and aminophylline in a dog model and have reported an increased propensity for ventricular arrhythmias in the presence of these two drugs. Unfortunately, it may not be possible to extrapolate their findings to the clinical setting because of the large dose and bolus mode of aminophylline administration that was used. Furthermore, their experiments only addressed the situation in which aminophylline is acutely administered while most asthmatic patients present for anesthesia and surgery with a long history of aminophylline treatment. This study was designed to: 1) determine the effect of acutely administered aminophylline, at two steady-state levels, on the threshold for arrhythmias in an accepted halothane-epinephrine arrhythmia model11; and 2) determine the arrhythmia potential following chronic aminophylline treatment.

Methods

Anesthesia was induced and maintained in nine unpremedicated male mongrel dogs with halothane in oxygen at an end-tidal halothane concentration of 1.5% v/v. Tracheal intubation was performed without muscle relaxants, and ventilation was controlled to achieve normocarbia (PaCO₂ 54–44) as determined by continuous end-tidal CO₂ monitoring and confirmed by intermittent PaCO₂ determination at 2-h intervals. A foreleg vein and femoral artery were cannulated percutaneously. Maintenance fluid consisted of 5% dextrose in 0.2% NaCl supplemented with 89 mEq l−1 sodium bicarbonate to prevent the metabolic acidosis seen with repeated epinephrine
infusions. No additional correction of metabolic acid-base status was required in any dog. Nasal temperature was monitored and maintained at 38°C with warming blankets and heating lamps. End-tidal CO₂ and halothane concentrations (Beckman), arterial blood pressure, and lead II of the ECG were continuously recorded on a strip chart recorder (Beckman, Palo Alto, CA).

The arrhythmogenic dose of epinephrine (ADE) was measured in the absence of aminophylline (A₀) according to the method of Pace et al. A fresh 100 µg·ml⁻¹ solution of epinephrine in 5% dextrose was infused via a syringe pump (Harvard) for 3 min at a constant rate. If an arrhythmia threshold (four or more ventricular ectopic beats in a 15-s period) was not achieved, the animal was allowed to recover from the epinephrine infusion for 7 min before a subsequent dose, 1.4 times higher than the previous one, was infused. This process of progressively larger doses of epinephrine was continued until the ADE was established and expressed as a dose of epinephrine in µg·kg⁻¹·min⁻¹. Aminophylline was then infused, according to known canine pharmacokinetic parameters (volume of distribution of 0.82 l·kg⁻¹ and a clearance rate of 1.66 ml·kg⁻¹·min⁻¹), to achieve and maintain a steady-state plasma level of 15 µg·ml⁻¹ (A₂), which was confirmed by the fluorescence polarization immunoassay technique (Abbott Laboratories Diagnostic Division, North Chicago, IL). The ADE determination was reassessed, after which aminophylline infusion regimens were adjusted after an additional loading dose to achieve and sustain a second steady-state aminophylline level (A₂) of 30 µg·ml⁻¹. The ADE was reassessed at this state. Circulating catecholamine concentrations were determined before and after each loading dose of aminophylline by high-performance liquid chromatography with electrochemical detection procedure. Plasma epinephrine levels were also determined at the time the arrhythmia threshold was achieved to investigate whether lower plasma levels of epinephrine caused arrhythmia occurrence in the presence of aminophylline.

For the chronic experiments, the ADE was assessed in an additional seven dogs in an aminophylline-free state. Aminophylline was orally administered in these animals at an average dose of 45 mg·kg⁻¹·day⁻¹, in two divided doses, for 6 weeks. The dose was adjusted at weekly intervals, as necessary, to sustain a plasma theophylline level between 15–25 µg·ml⁻¹. The ADE assessment was then repeated, at which time the plasma theophylline levels were determined.

**DATA ANALYSIS**

The ratio of the infused dose (D) to the plasma level (L) was calculated for each arrhythmia threshold. This ratio (D/L), which is dimensionally equivalent to volume, approximates the apparent volume of distribution for the infused arrhythmogenic dose of epinephrine. This was calculated to determine whether aminophylline altered the disposition of infused epinephrine. Analysis of variance was used to compare the ADE and catecholamine values for the different aminophylline states (A₀, A₁, and A₂). When the F statistic exceeded the critical value ($F_{0.05}$ [2, 18] = 3.55), differences among groups were tested by the paired $t$ test with Bonferroni correction. For the chronic experiments, the ADE values before and after aminophylline treatment were compared by the paired $t$ test. A $P$ value $< 0.05$ was considered statistically significant. Data are presented as the mean ± SD.

**Results**

No ventricular arrhythmias were observed in the absence of exogenously administered epinephrine, regardless of the plasma theophylline level achieved. During acute aminophylline treatments, the infusion regimens yielded an observed plasma theophylline concentration of 17 ± 2 and 34 ± 4 µg·ml⁻¹ for the A₁ and A₂ states, respectively (table 1). The ADE decreased markedly in each animal after aminophylline infusion (fig. 1; table 1). Plasma epinephrine levels at the time of arrhythmia were significantly lower in the presence of aminophylline (table 1). No significant increase in basal plasma catecholamines were noted following the aminophylline treatments (table.
AMINOPHYLLINE AND EPINEPHRINE ARRHYTHMIAS

Discussion

Acute aminophylline administration enhanced the arrhythmogenic effects of epinephrine in the halothane-anesthetized dogs, even at therapeutic levels ($A_1$). Thus, data from earlier animal studies,\textsuperscript{9,10,17} which were performed in the presence of very high and possibly toxic theophylline levels, are now confirmed in the setting of a standardized, more clinically relevant aminophylline infusion regimen that provided stable therapeutic ($A_1$) and toxic ($A_2$) theophylline levels. In contrast to these findings with acute administration, chronically treated dogs did not manifest any increased tendency to halothane-epinephrine arrhythmias, as reflected by the unchanged ADE in these animals.

Increase in the sensitivity to halothane-epinephrine arrhythmias by acute administration of aminophylline may have its basis on either a pharmacodynamic or pharmacokinetic effect of this treatment on the two interacting drugs, halothane and epinephrine. An effect by aminophylline on halothane disposition is unlikely because the uptake of halothane is not affected by aminophylline,\textsuperscript{16} additionally, there is no halothane dose dependency for myocardial sensitization to epinephrine arrhythmias between 0.5% and 2.0% end-tidal halothane concentration.\textsuperscript{11} Our data also discount the likelihood that aminophylline alters epinephrine disposition because the derived ratio between the infused epinephrine dose and the epinephrine level at arrhythmia, which corresponds roughly to the apparent volume of distribution of the central compartment for epinephrine, was not different between the aminophylline states (table 1).

We suggest that aminophylline induces a pharmacodynamic change in myocardial sensitization by a mechanism that probably involves a known pharmacologic property of this drug. Methylxanthine compounds, of which aminophylline is an example, are sympathomimetic agents and may, therefore, further potentiate the halothane-epinephrine interaction through an endogenous release of catecholamines. Aminophylline induces catecholamine release in isolated adrenal preparations\textsuperscript{19} and papillary muscle preparations.\textsuperscript{20} Aunis et al.\textsuperscript{21} reported that the intravenous administration of as little as 200 mg of theophylline in human subjects can enhance exocytosis of catecholamines from storage vesicles, as evidenced by an increase in dopamine  $\beta$-hydroxylase activity in the plasma. Recently Vestal et al.\textsuperscript{22} reported an aminophylline-induced elevation in circulating catecholamines in human volunteers. Surprisingly, we did not observe any increase in plasma catecholamines at the initiation of the therapeutic aminophylline state ($A_2$). We speculate that the known sympatholytic properties of halothane\textsuperscript{23,24} are effective in blunting the sympathomimetic properties of theophylline. Alternatively, aminophylline might cause an increase in endogenous catecholamine release in the heart that is not reflected in the arterial blood because of dilution from other unstimulated vascular beds or uptake by the lung. Other pharmacologic properties of aminophylline may account for our findings.

While it has been fashionable to ascribe many of aminophylline's effects to its inhibitory action on phosphodiesterase (PDE) activity,\textsuperscript{25} this does not occur to any significant extent within theophylline's therapeutic range.\textsuperscript{26} However, in the presence of catecholamine stimulation, the PDE activity is enhanced,\textsuperscript{27} and inhibition of its activity, however minor, may result in a physiologic effect. Thus, it is possible that the anti-PDE effect of aminophylline may be a relevant explanation for our findings. Another tenable mechanism for aminophylline's effect in

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heightening the halothane–epinephrine arrhythmogenic interaction is through competitive antagonism of the receptor for the endogenous purine, adenosine. This substance is a hydrolytic product of adenosine triphosphate (ATP) and, as such, it is found as ubiquitously as its parent compound. Under physiologic conditions adenosine acts as a general regulatory substance in much the same manner as the prostaglandins. Its effects are mediated by a receptor–effector mechanism that is capable of producing diametrically opposite actions, depending on the organ and the subclass of receptor involved. One type of extracellular receptor, variously termed the A1 or R1 receptor, has a very high affinity for adenosine (dissociation constant \( K_d \) of \( 10^{-9} \) M) and in some cells (e.g., lipocytes, cardiocytes) it couples to adenylyl cyclase in an inhibitory manner. The other class of receptors has a lower affinity for adenosine (\( K_d = 10 \) \( \mu \)M) and in many cell types (e.g., platelets, vasculature) it couples to adenylyl cyclase in a stimulatory manner and is referred to as the \( A_2 \) or \( R_5 \) receptor. A further acceptor site for adenosine that is normally disposed is called the “P” site and is extremely sensitive to changes on the ribose moiety of the nucleoside. Its kinetic binding parameters and effector molecule remain uncertain.

In the heart, adenosine may affect the arrhythmogenic interaction through four separate mechanisms: 1) presynaptic inhibition of neurotransmitter release; 2) coronary artery vasodilation; 3) postreceptor adinergic effect; and 4) direct effects on cardiac impulse formation and conduction. The first effect is probably not pertinent to theophylline’s sensitization because its antiadenosine action should “disinhibit” neurotransmitter release and increase circulating catecholamine levels, which were not observed in our studies (table 1). However, it is important to recognize that circulating catecholamine levels may not accurately reflect the rate of release, especially if release is altered on a regional basis. It is possible that the vasodilatory effect of adenosine on the coronary artery, which would otherwise counteract any constricting influence of epinephrine, is antagonized by aminophylline, resulting in ischemia-induced ventricular ectopy. However, because halothane–epinephrine arrhythmias can be demonstrated in cell culture, it does not appear that alterations in coronary blood flow are relevant to the pathogenesis of these arrhythmias. Adenosine’s antiadrenergic effect has been demonstrated best for β-adrenergic-mediated myocardial events and can be overcome by clinical concentrations of theophylline; therefore, the methyloxanthine-induced, antiadenosine effect may be more critical in the presence of epinephrine when the responsiveness of β-adrenoceptor-mediated events are enhanced. While a dominant role for the myocardial α-adrenoceptor has been identified for halothane–epinephrine arrhythmias, there is, in addition, a significant mediation of this interaction through the β-adrenoceptor. Data from recent studies suggest a decrease in ventricular automaticity by adenosine and of adenosine-mediated antiarrhythmic effect on ischemia-induced ventricular arrhythmias. In an experimental setting similar to ours, Sohn et al. reported on the antiarrhythmic activity of ATP, and it is reasonable to expect that this effect is mediated via adenosine, an active metabolite of ATP. Thus, we suggest that it is aminophylline’s antagonism of the adenosine receptor that is instrumental in its arrhythmia-enhancing effects following acute administration in the halothane–epinephrine model.

Effects of drugs administered acutely may be counteracted by adaptive responses when given chronically. Earlier studies demonstrated sensitization of the arrhythmogenic halothane–epinephrine interaction by acute imipramine therapy that was not evident after chronic treatment. In the setting of a receptor antagonist (e.g., the adenosine antagonist, aminophylline), up-regulation of receptor density has been documented in many biological systems, including the adenosine receptor, which will tend to overcome the antagonist effect and restore the normal response. Thus, Rotenberg et al. reported that rats treated with long-term oral caffeine (another antiadenosine compound) had a higher ventricular arrhythmia threshold than controls, while a reduction in the arrhythmia threshold was caused by a single injection of caffeine.

If we assume the β-adrenoceptor–effector mechanism mediates an important contribution of the arrhythmia-enhancing effect of acute aminophylline treatment (see previous discussion), then it is relevant that following chronic theophylline treatment, a down-regulation of β-adrenoceptors occurs. While this observation was demonstrated in the hippocampus, it is noteworthy that the same subtype of adenosine receptor exists in the hippocampus as in the hippocampus. If a down-regulation of myocardial β-adrenoceptors were to occur in our chronic model, this might result in an attenuation of β-mediated adrenergic responses, perhaps including halothane–epinephrine arrhythmias.

Halothane is frequently selected as an anesthetic in patients with obstructive pulmonary disease because of its potent bronchodilatory action. If our animal data are extrapolated to the clinical paradigm, the acute, concurrent administration of halothane and aminophylline will result in an increased risk for the development of ventricular arrhythmias. It is worth noting that the original clinical report of halothane–aminophylline arrhythmias concerned patients who had received their initial aminophylline treatment just prior to halothane administration. Intraoperative administration of aminophylline to treat severe acute bronchospasm in the halothane-anesthetized patient could constitute an even greater risk if endogenous catecholamine levels are elevated due to re-
spiratory insufficiency. It appears that these same concerns should not apply to patients in whom the drug is chronically administered, which is the most frequently encountered clinical situation.

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