

Adenosine Decreases the Minimum Alveolar Concentration of Halothane in Dogs

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Adenosine has sedative properties, and adenosine-receptor agonists have been found to reduce anesthetic requirements in rodents. This study determined whether adenosine, in hypotensive doses, reduces anesthetic requirements in halothane-anesthetized dogs. In seven animals, minimum alveolar concentration (MAC) for halothane was determined by a tail-clamp technique at three time points: after 2 h of halothane anesthesia, during adenosine-induced hypotension (mean arterial pressure: 55 mmHg), and 1 h after adenosine was discontinued. In other dogs, the effects of aminophylline, dipyridamole, or the specific adenosine-receptor antagonist 8-phenyltheophylline (8-PT) on the halothane-adenosine interaction were studied. Adenosine significantly reduced halothane MAC, by 49%, from 0.76 ± 0.05 to 0.39 ± 0.05 vol% (mean \pm SEM). This effect was blocked by the concurrent administration of aminophylline ($n = 5$, $P < 0.05$) or 8-PT ($n = 4$ of 4). When dipyridamole, which increases the plasma concentrations of endogenous adenosine, was administered alone, halothane MAC was reduced from 0.79 ± 0.03 to 0.67 ± 0.05 vol% ($n = 5$, $P = 0.09$). We conclude that exogenous adenosine substantially reduces halothane MAC in dogs and that this effect is blocked by the concurrent administration of the adenosine-receptor antagonists aminophylline or 8-PT. Relatively small alterations of endogenous adenosine concentrations, however, do not substantially reduce halothane MAC. (Key words: Anesthetic techniques: hypotension, adenosine. Anesthetics, volatile: halothane. Pharmacology: adenosine, dipyridamole, aminophylline. Potency, anesthetic: minimum alveolar concentration.)

ADENOSINE is a naturally occurring, purine nucleoside currently being investigated for use as a hypotensive agent during controlled arterial hypotension.¹ A distinctive feature of this compound is that the plasma half-life is very short, less than 10 s in humans.² Endogenous adenosine is a potent vasodilator, slows cardiac electrical conductivity, possesses anti-adrenergic activity, and has sedative and anti-convulsant properties.³ These pharmacologic effects are mediated by at least two subpopulations of specific

and saturable, extracellular membrane-bound adenosine receptors, which are classified according to their ability after activation to inhibit (A_1) or stimulate (A_2) adenylate cyclase.⁴

We speculated that exogenously administered adenosine would reduce anesthetic requirements because of the following considerations. Adenosine reduces central nervous system (CNS) norepinephrine concentrations and is a CNS depressant.^{5,6} An association between CNS catecholamine concentrations and anesthetic sensitivity has been observed: decreased CNS catecholamine concentrations are associated with a reduced minimum alveolar concentration (MAC).⁷ Although CNS drug interactions involving anesthetic agents and adenosine *per se* have not been described, supramaximal doses of the adenosine receptor agonist L-phenylisopropyladenosine (L-PIA) have been shown to reduce anesthetic requirements in rodents.⁸

The CNS stimulatory properties of methylxanthines, such as theophylline and caffeine, are believed to be mediated by blockade of adenosine receptors.^{9,10} At high concentrations, some methylxanthines also inhibit the intracellular phosphodiesterase enzyme system. With theophylline, no alterations in halothane requirements (MAC) have been found in rodents or dogs.¹¹ Likewise, other methylxanthines are not known to affect sensitivity to anesthetic agents.

The principal objectives of the study were to determine whether exogenous adenosine reduces halothane MAC in dogs and whether these effects are blocked by the adenosine-receptor antagonists theophylline or 8-phenyltheophylline (8-PT). 8-PT is a potent, highly specific adenosine-receptor antagonist that has negligible effects on the phosphodiesterase enzyme system.¹² This study also was designed to determine whether dipyridamole administration reduces halothane MAC. Dipyridamole increases concentrations of endogenous adenosine by two-fold, by inhibition of the membrane-bound nucleoside active transport mechanism.¹³

Materials and Methods

This experimental protocol received the approval of the local institutional animal welfare committee. Animal resource facilities in which this research was conducted are fully accredited by the American Association for Accreditation of Laboratory Animal Care. Studies were performed in 14 healthy mongrel dogs of either sex weighing 17–28 kg. Animals were fasted overnight before tests and

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received no preanesthetic medication. Five of these animals were studied on a second occasion, with dipyrindamole, 7–14 days after an initial study involving adenosine. Two dogs were studied with both adenosine and adenosine plus aminophylline in separate investigations.

Anesthesia was induced with halothane in O₂ via mask. Animals then were placed supine; tracheas were intubated; and mechanical ventilation was begun. Arterial carbon dioxide tension (PaCO₂) was maintained between 35 and 40 mmHg. Anesthesia was maintained with halothane in O₂. Catheters were inserted percutaneously into a peripheral vein and femoral artery; a triple-lumen catheter was inserted into the superior vena cava via the right external jugular vein. Femoral arterial and central venous pressures were measured continuously, and arterial blood gas values were determined intermittently. Isotonic saline solution was administered at 10 ml · kg⁻¹ · h⁻¹, and sodium bicarbonate was given to maintain normal acid–base status.¹⁴

During anesthesia, end-tidal CO₂, arterial O₂ saturation (SaO₂) (Novamatrix, model 7000), esophageal temperature, lead-2 electrocardiogram (ECG), heart rate, and inspired halothane concentration (volume %) (Siemens, model 120) were monitored continuously. End-tidal halothane concentration was measured every 15–30 min by mass spectroscopy (Perkin-Elmer). Stable body temperature was maintained with heating lamps and warming blankets.

DRUG ADMINISTRATION

Adenosine (Sigma), 9.6 mg/ml, was administered through the central venous catheter by a constant rate syringe infusion pump at a rate that maintained mean arterial pressure (MAP) at 55 mmHg. The target blood pressure was deliberately achieved stepwise by increasing the adenosine infusion gradually until the target MAP was reached. Aminophylline (Invenex) (n = 5) or 8-PT (Sigma) (n = 4) was slowly administered via a peripheral intravenous catheter: for each drug, an initial bolus dose of 5 mg · kg⁻¹ was followed by an infusion of 1–2 mg · kg⁻¹ · h⁻¹. Dipyrindamole (Sigma) was administered at a dose of 250 μg · kg⁻¹ iv over 5 min.

DETERMINATION OF MAC

In seven dogs after 2 h of halothane administration, baseline halothane MAC was determined by a tail-clamp technique.¹⁵ Briefly, a 10-in clamp was applied to the dog's tail 2–4 in from the base to the first ratchet and was moved continuously for 60 s. A positive response was gross purposeful movement, usually of the head (jerking or twisting) or extremities (clawing). Halothane concentration was decreased stepwise by approximately 0.05 to 0.10 vol% with an equilibration period of at least 15 min before

each tail clamping. MAC was calculated as the halothane concentration midway between that which allowed and that which prevented movement. A second halothane MAC was determined during adenosine administration, and a third determination was performed 1 h after termination of adenosine administration.

In nine animals, halothane MAC was measured at three time points: at baseline, during adenosine administration, and then after 1 h during co-administration of adenosine and either aminophylline (n = 5) or 8-PT (n = 4). In a separate study, in order to determine the effects of endogenous adenosine on halothane sensitivity, halothane MAC was determined at baseline and then 1 h after dipyrindamole administration.

DATA ANALYSIS

Unless stated otherwise, results are expressed as mean values ± SEM. Statistical testing was performed with a randomized-design analysis of variance (ANOVA) and with two-tailed paired *t* tests or Wilcoxon signed-rank tests where appropriate. *P* < 0.05 was considered statistically significant.

Results

The baseline MAP in these animals was 105 ± 5 mmHg. The target MAP of 55 mmHg was easily achieved in all animals by adenosine in doses of 1.5 ± 0.3 mg · kg⁻¹ · min⁻¹. Tissue perfusion, as evaluated from urine production, SaO₂, and acid–base status remained normal during adenosine-induced hypotension. There were no cardiac conduction abnormalities or arrhythmias associated with adenosine administration.

In seven animals, adenosine reduced halothane MAC by 54% from 0.82 ± 0.06 to 0.38 ± 0.06 vol% (*P* < 0.05, fig. 1). Once the adenosine infusion was discontinued,

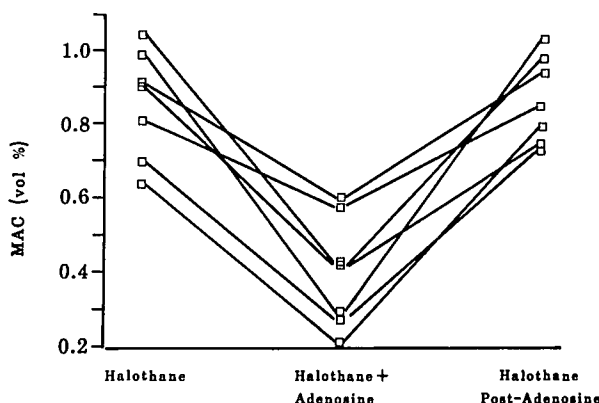


FIG. 1. Effect of adenosine on the MAC of halothane before (control), during, and after adenosine was given to seven dogs (data presented for individual animals). *P* < 0.05 for halothane + adenosine compared with halothane alone.

systemic blood pressure rapidly returned to normal values. Within 1 min after discontinuation of adenosine, most animals spontaneously opened their eyes or showed other clear, clinical signs of emergence from anesthesia. One hour afterward, halothane MAC had returned to baseline values (0.83 ± 0.04 vol%, $P < 0.05$, fig. 1).

The effect of adenosine on halothane MAC was antagonized by aminophylline ($P < 0.05$, fig. 2) or by the specific adenosine-receptor antagonist 8-PT (fig. 3). During concomitant administration of adenosine and either aminophylline or 8-PT, arterial pressure increased to approximately 85% of baseline values. For animals that received adenosine with and without aminophylline or 8-PT, a constant dose of adenosine was administered throughout both testing periods.

Halothane MAC values from all 14 animals with and without adenosine demonstrated that adenosine significantly reduced halothane MAC, by 49%, from 0.76 ± 0.03 to 0.39 ± 0.05 vol% ($P < 0.05$, fig. 4).

Intravenously administered dipyridamole produced a small decrease, of approximately 5–10 mmHg, in blood pressure. After acute dipyridamole administration, halothane MAC was reduced in all five dogs by an average of 15%, from 0.79 ± 0.03 to 0.67 ± 0.05 vol%. This difference was small when compared with the effects produced by exogenous adenosine ($P = 0.09$, fig. 5).

Discussion

The physiologic properties of adenosine initially were described more than 60 yr ago by Drury and Szent-Gyorgyi.¹⁶ Adenosine is a potent vasodilator in most vascular beds; intravenous adenosine administration decreases systemic arterial pressure in a dose-dependent manner, whereas cardiac output is increased or unaffected.³ Large doses of adenosine slow atrioventricular conduction. This

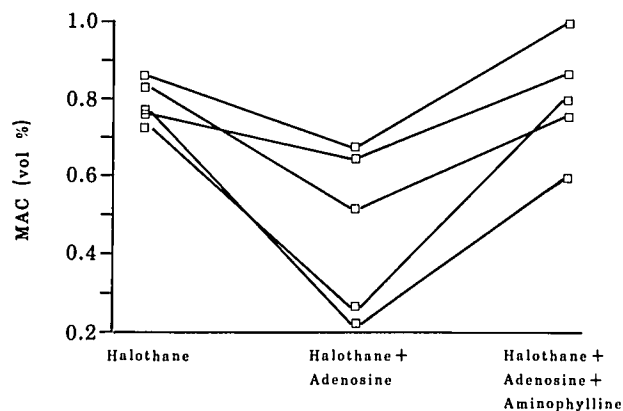


FIG. 2. Effect of adenosine and aminophylline on MAC of halothane in 5 dogs during halothane anesthesia (data presented for individual animals). $P < 0.05$ for halothane + adenosine compared with halothane + adenosine + aminophylline.

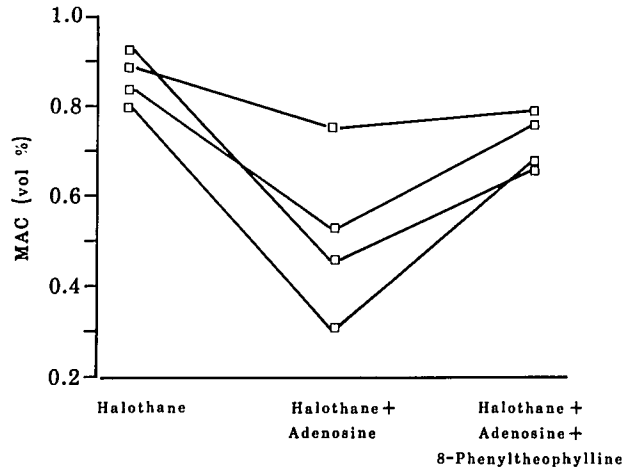


FIG. 3. Effect of adenosine and 8-phenyltheophylline on MAC for halothane in four dogs during halothane anesthesia (data presented for individual animals).

compound has been recently approved by the Food and Drug Administration for the treatment of paroxysmal supraventricular tachyarrhythmia.¹⁷ Adenosine does not increase catecholamine production or renin release¹⁸ and has anti-aggregatory effects on platelets.¹⁹ Adenosine also produces sedation and has been found to have anticonvulsant properties.²⁰

This study demonstrates another CNS effect of adenosine; namely, when administered in doses that produce moderate arterial hypotension, adenosine reduces halothane MAC by approximately 50% in dogs. Previous investigations have demonstrated that moderate systemic hypotension *per se* does not alter MAC.²¹ We observed that, consistent with an extremely short plasma half-life, the anesthetic sparing effects of adenosine terminated within 1–2 min after discontinuation of the adenosine

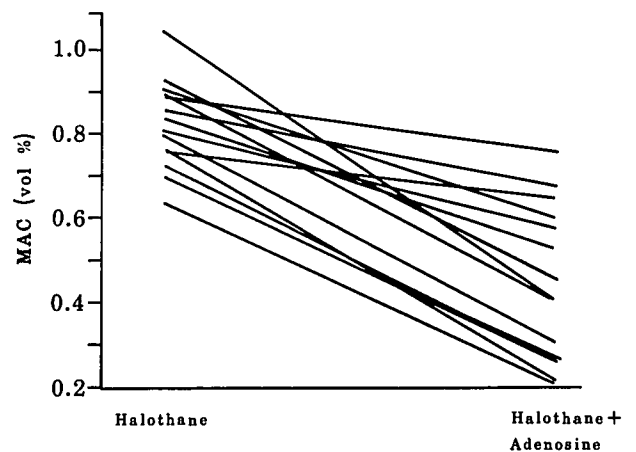


FIG. 4. Effect of adenosine on MAC for halothane in 14 dogs (data presented for individual animals). $P < 0.05$ for halothane + adenosine compared with halothane.

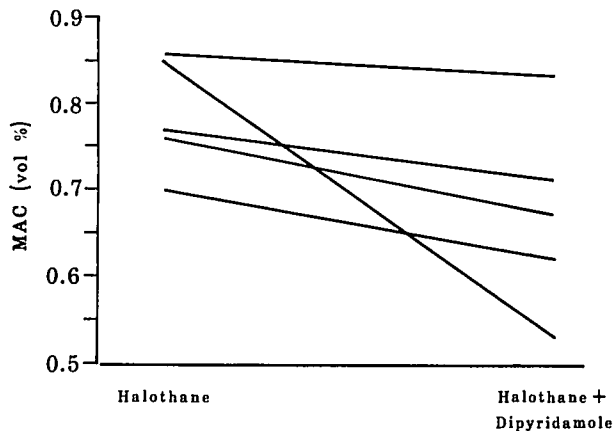


FIG. 5. Effect of dipyridamole on halothane MAC in five dogs (data presented for individual animals). $P = 0.05$ for halothane + adenosine compared with halothane alone.

infusion. The doses of adenosine used in these studies to induce hypotension were less than those associated with clinically significant cardiac conduction effects.³

Results from this investigation are consistent with earlier adenosine studies on central neuromodulation and neurodepression^{4,22-24} and with the recent demonstration that L-PIA diminishes halothane MAC in rats.⁸ As a CNS neuromodulator, adenosine tonically inhibits excitatory central noradrenergic neurons *via* presynaptic adenosine A₁ receptors.⁶ Central noradrenergic pathways appear to contribute to modulation of the depth of anesthetic response.²⁵ Interventions that decrease central noradrenergic neurotransmission decrease MAC.⁷ For example, alpha-2 adrenergic agonists such as clonidine, azepexole, and dexmedetomidine, which similarly inhibit release of central norepinephrine, also lower MAC.²⁶⁻²⁸ Inhibition of central norepinephrine probably is involved in the adenosine-induced decrease in halothane MAC, but this may not be the sole mechanism. Studies in rats have shown that decreased CNS norepinephrine alone decreased MAC by 40%.²⁹⁻³⁰ Additional factors, such as a post-junctional effect or contributions from other neuromodulators such as endorphins, remain to be evaluated.

Dipyridamole has been shown to double the circulating concentration of endogenous adenosine.³¹ Results of our investigation suggest that, when dipyridamole is administered acutely, halothane MAC is virtually unaffected. We infer that relatively small increases in endogenous adenosine concentration do not substantially alter halothane MAC.

We found that reduction of halothane MAC by adenosine was blocked by aminophylline. We believe that this effect of aminophylline is mediated specifically by adenosine-receptor blockade and not by phosphodiesterase enzyme inhibition, for two reasons. 1) Intracellular phosphodiesterase is inhibited by aminophylline concentrations

that are much higher than therapeutic concentrations known to block adenosine receptors.¹² 2) The methylxanthine 8-PT, which blocks adenosine receptors but not CNS phosphodiesterase enzymes,¹² also blocked adenosine reduction of halothane MAC in this study.

It is noteworthy that the adenosine antagonist aminophylline, when administered alone, has not been reported to affect halothane MAC in dogs.¹¹ This indicates that blocking the action of endogenous adenosine does not substantially alter halothane sensitivity and suggests that endogenous A₁ stimulation does not contribute to depth of anesthesia in the basal state. However, there are situations in which methylxanthines could have a clinically significant effect on CNS adenosine response. For example, patients taking aminophylline or caffeine would be expected to be resistant to the CNS depressant effects of *exogenous* adenosine. Also, during chronic theophylline use, CNS adenosine receptors are increased,^{32,33} and the CNS response to exogenous adenosine would likely be exaggerated during the withdrawal period.

The findings of this investigation may have important clinical implications for the intraoperative use of adenosine. The pharmacokinetics of this compound are unusual. The fast onset and duration of action of adenosine are associated with a plasma half-life of less than 10 s. In addition, adenosine plasma elimination is independent of cardiac output or organ blood flow. Use of adenosine would be expected to allow rapid alteration in anesthetic depth and emergence from anesthesia. The latter may be especially valuable for evaluation of neurologic function in the early postoperative period or during surgical procedures of the spine that require intraoperative wake-up testing. Future studies involving drugs that interact with adenosine receptors³⁴ may provide clues for the development of new intravenous anesthetic agents or provide insight into the mechanism of anesthesia.

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