Aminophylline

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Since its first use in man in 1902 (84), aminophylline (theophylline ethylenediamine) has become a mainstay in the treatment of asthma and bronchospasm. This review of the copious and often conflicting results of research involving aminophylline emphasizes the findings most important to anesthesiologists. It is organized as follows: drug characteristics, mechanism of action, physiologic effects, anesthesia-related use, dosage and administration, metabolism and elimination, toxicity, and summary.

Drug Characteristics

Aminophylline is the ethylenediamine salt of theophylline, one of a group of closely related alkaloids present in plants widely distributed throughout the world. Tea leaves are the source from which theophylline is extracted.

Theophylline, caffeine, and theobromine are closely related methylated xanthines. Xanthine itself is 2,6-dioxopurine, and is structurally related to uric acid. Caffeine is 1,3,7-trimethylxanthine; theophylline is 1,3-dimethylxanthine; and theobromine is 3,7-dimethylxanthine (112). The structural formulas of purine, uric acid, xanthine, and the three pharmacologically important xanthine derivatives are shown in Fig. 1. Studies of the actions of congeners of the methylxanthines have revealed that inhibition of cyclic nucleotide phosphodiesterase, a possible mode of action of the methylxanthines, is associated with small nonpolar substitutions at positions 1 and 3 (7).

The solubility of methylxanthines is quite low; thus compounds combining them with various salts are utilized therapeutically. When theophylline is combined with the salt ethylenediamine to form aminophylline, its solubility increases 20-fold (112). Intravenous preparations of aminophylline contain from 75% to 85% theophylline by weight, depending on their manufacturer (92).

Mechanism of Action

Three major hypotheses currently exist regarding the mechanism of action of theophylline. These center around (a) cyclic adenosine 3',5'-monophosphate (cAMP), (b) catecholamines, and (c) calcium.

CAMP is today considered central to cellular function. Almost all enzyme systems are believed to utilize CAMP as an intermediary, or "second messenger," in effecting cellular functions initiated by various hormones, drugs, and other substrates (138).

In the CAMP system, a hormone or drug acts as the "first messenger," carrying the initial extracellular signal. Once attached to the appropriate (and specific) receptor site, the hormone causes activation of adenylyl cyclase, which has been located in the cell membrane (26). In the presence of magnesium ion (Mg2+), adenylyl cyclase then causes intracellular conversion of adenosine 3',5'-triphosphate (ATP) into CAMP. The breakdown of CAMP has been shown to be governed by a magnesium-dependent phosphodiesterase, which catalyzes CAMP at the 3' position, yielding adenosine 5'-phosphate (138). Inhibition of phosphodiesterase by theophylline, demonstrated in the late 1950s, would...
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lead to increased levels of cAMP and resulting physiologic responses (137).

Increases in cAMP by this pathway may become clinically important when viewed against the background of the molecular mechanism of catecholamine action. Catecholamines do not stimulate cellular function directly, but activate adenyl cyclase, causing accumulation of cAMP (136, 152). Thus, increased catechol levels together with theophylline would seem to lead to increased effector activity and possibly synergism if cAMP were indeed a common mediator.

Furthermore, there is evidence that intravenous aminophylline causes significantly increased urinary excretion of the catecholamines epinephrine and norepinephrine in man (4). The increase is considered to be due to stimulation of catecholamine release by the adrenal medulla and extra-adrenal chromaffin tissue (4).

Further work in intact rats has investigated the precise biochemical pathways involved in catecholamine synthesis and how they are affected by theophylline (130). It has been shown that theophylline activates tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, causing significant increases in adrenal dopamine, a precursor of epinephrine. No increase was found in the total amount of epinephrine plus norepinephrine present after theophylline, in spite of apparently increased dopamine synthesis. This was attributed to increased catechol release caused by theophylline (130).

Support for this hypothesis was the finding that bovine adrenal glands perfused in vitro responded to single injections or continuous infusions of aminophylline by increased release of catecholamines (106). Other studies (98) in in vitro cat adrenal glands perfused with theophylline confirmed its efficacy in releasing catecholamines. It has even been suggested that theophylline is of use in treating bronchial asthma because of its epinephrine-releasing effects (9).

The precise role of calcium in theophylline action remains unclear. One study of catecholamine release induced by theophylline, cAMP, and dibutyl cAMP (a molecular form which more easily enters the cell than cAMP and so may mimic the actual effects of cAMP, presumed to be intracellularly based, more accurately than extracellularly applied cAMP) compared effects in the presence and absence of extracellular calcium (98). Exposure to a calcium-free medium for 180 minutes had no effect on adrenal catecholamine secretory responses to either cyclic nucleotides themselves or theophylline. It was concluded that theophylline does not require extracellular calcium in order to release adrenal catecholamines, but may either be independent of calcium or may translocate intracellular bound calcium (98).

Another study (106), however, found that extracellular calcium concentration did indeed seem to parallel the amount of aminophylline-induced catecholamine release. However, this study also found catecholamine release, although slightly depressed from control values, still occurred with a high aminophylline concentration in the absence of calcium. It was proposed that two mechanisms for theophylline-induced catecholamine release were present, one dependent and one independent of extracellular calcium.

Theophylline could simply depolarize the adrenal chromaffin cell, causing increased calcium influx from the surrounding medium, thereby explaining the dependence of theophylline on extracellular calcium concentration (106). Release of intracellular calcium from membrane stores in the sarcoplasmic reticulum

Fig. 1. Structural formulas of purine, uric acid, xanthine, and the three pharmacologically important xanthine derivatives.
would provide a mechanism independent of extracellular calcium (106).

Work on theophylline’s effects on cardiac tissue seems to support the evidence noted above (98, 106), regarding calcium and mechanisms of catechol release. Studies of theophylline in rat papillary and atrial muscle found intensification and prolongation of the active contractile state, leading to the conclusion that methylxanthines exert two effects on excitation-contraction coupling: (a) cell membrane changes leading to increased calcium entry, and (b) inhibition of calcium sequestration by sarcoplasmic reticulum (10).

Other work on cardiac mechanics suggests that, in addition to theophylline-induced increases in myocardial catecholamine release, theophylline may also directly influence calcium kinetics and thereby alter myocardial function (78). Evidence supporting this theory is indirect, at best. Studies measuring calcium transport in cardiac muscle cells and subcellular components such as mitochondria and sarcoplasmic reticulum are needed to verify this hypothesis.

Studies of theophylline and dibutyryl cAMP-induced release of catecholamines in vitro from electrically stimulated sympathetic nerves in the presence and absence of calcium have shown enhanced catechol release in the presence of calcium, although release was also present in calcium-free medium (167). These investigators proposed that cAMP acts as a mediator of theophylline activity, either in parallel with calcium or by mobilizing intracellular, bound calcium as suggested above (167).

There is evidence that theophylline and epinephrine modify internal cardiac Purkinje fiber surface charges, and thus cause voltage shifts which would allow the increased calcium flux proposed above (148). The proposed cause of this change in surface charges is an elevation in intracellular cAMP caused by theophylline or epinephrine (148). Thus, both cAMP and calcium would be involved as mediators of theophylline action.

In summary, the mechanism of action of theophylline, once believed to be simply due to the inhibition of phosphodiesterase (6), no longer appears so straightforward. It seems likely, from studies in a variety of tissues, that phosphodiesterase inhibition with a subsequent increase in cAMP levels is involved, along with theophylline-mediated catecholamine release and subsequent catecholamine-related increases in cAMP. In addition, the action of theophylline appears related to, but not dependent on, extracellular calcium concentration, and theophylline may directly influence calcium kinetics.

**Physiologic Effects**

The physiologic effects of aminophylline will be considered in four broad groups: respiratory, cardiac and circulatory, cerebral, and miscellaneous.

**Respiratory Effects**

The first clinical use of theophylline, in 1902 (84), was for the treatment of congestive heart failure. As experience with aminophylline has accumulated over the ensuing eight decades, the majority of its clinical applications have involved some aspect of the cardiopulmonary system. Indeed, in 1981, the primary indication for and most frequent use of aminophylline is in the treatment of respiratory problems.

Successful aminophylline therapy of Cheyne-Stokes respiration in man was first reported in Germany in 1927 (157). Further investigations (79, 161) determined the mechanism of its action in Cheyne-Stokes respiration to be either direct stimulation of the medullary respiratory center or the result of increased sensitivity to CO₂. More recently (28) it has been shown in patients with Cheyne-Stokes respiration that aminophylline decreases the respiratory threshold for CO₂ without altering CO₂ sensitivity.

Several years after these studies, aminophylline was introduced into pediatrics as therapy for neonatal apnea (69). Subsequently its use has become widespread and it is now a mainstay of therapy for this condition (125, 150). Recent work (44) indicates that, in premature infants, aminophylline decreases the threshold of the central chemoreceptor to CO₂ increasing respiratory center output. In conjunction with its observed effects in treating Cheyne-Stokes respiration and neonatal apnea of prematurity, it has recently been shown (70) that aminophylline increases the hypoxic ventilatory response in normal man.

Alveolar hypoxia causes inconsistent changes in pulmonary blood flow distribution in normal man, although preferential lower lung zone vasoconstriction is frequently seen (36). Hypoxic stimulation of the carotid and aortic chemoreceptors, direct adrenergic vasomotor innervation, release of such intrinsic chemical mediators as histamine, prostaglandins, and angiotensin, and direct effects of hypoxia on pulmonary vascular smooth muscle have been postulated as mechanisms of pulmonary vasoconstriction (33). As most gas exchange in man occurs in the lower lung, preferential lower zone vasoconstriction would provide a significant defense against hypoxia.

During an asthmatic episode hypoxemia is commonly present (81). Hypoxemia is characteristically a
feature of chronic obstructive pulmonary disease (COPD) as well. Such hypoxemic patients might tend toward lower zone pulmonary vasoconstriction as self-protection against further hypoxemia. However, the concomitant bronchoconstriction characteristic of asthma would decrease ventilation even to relatively nonhypoxic lung zones. Aminophylline is a bronchodilator, relaxing airway smooth muscle (90). Thus, in asthmatic patients an improvement in arterial oxygenation might well be expected after administration of aminophylline if there were no concomitant alteration in pulmonary blood flow.

Varying results have been obtained in studies of the effect of aminophylline on arterial oxygenation in conscious humans with asthma and other obstructive pulmonary diseases (Table 1) (25, 50, 110, 139, 164, 171). No definite change in arterial oxygenation followed intravenous aminophylline in either group. The seeming efficacy of aminophylline in these conditions seems to result from its ability to decrease $P_{aO_2}$ by mechanical ventilatory improvement through bronchodilation (25, 139, 164, 171).

Many studies of aminophylline in asthmatic patients support this hypothesis (Table 2). In every trial (39, 57, 62, 105, 149, 162) aminophylline produced significant decreases in airway resistance and improvement in ventilatory function.

Reports of asthma therapy contain frequent mention of positive subjective responses to therapy on the part of patients, whether the therapy is placebo, aminophylline, or another drug (39, 110). In few other medical conditions is the psychological background as important in initiating, perpetuating, and resolving the problem. From the data noted above, however, aminophylline would seem to be of definite objective benefit in the treatment of asthma and bronchospasm in man.

### Table 1

| Reference | Dose | $P_{aO_2}$ | Time after administration | No. of patients | Clinical diagnosis |
|-----------|------|------------|---------------------------|----------------|-------------------|
| 139       | 250  | (1–5 torr) | 30                        | 5              | Asthma            |
| 139       | 250  | (5–10 torr)| 30                        | 5              | Asthma            |
| 110       | 500  | (4–12 torr)| 15                        | 4              | Status asthmaticus |
| 110       | 500  | No change  | 30                        | 10             | Status asthmaticus |
| 50        | 400  | (10–12 torr)| 40                        | 6              | COPD              |
| 25        | 250  | (15–20 torr)| 20                        | 8              | COPD              |
| 164       | 300  | No change  | 30                        | 6              | COPD              |
| 171       | 500  | (7 torr)   | 20                        | 1              | COPD              |

* $S_{aO_2}$

| Reference | Dose and route | Serum theophylline | Change in indices (no. of patients) | Type of study |
|-----------|----------------|--------------------|-------------------------------------|---------------|
| 149       | 600 orally     | 6–14               | $VC (5/6)$                          | Prospective   |
| 57        | 500 orally     | 9–12               | $VC (6/6)$                          | Prospective   |
| 62        | 500–1000 orally| 8–20               | $Specific airway resistance (6/7)$  | Prospective, blind |
| 162       | 6–11/kg orally | 7–25               | $FEV_1$, $FVC$                      | Prospective, double-blind crossover |
| 39        | 250 IV         | —                  | $FVC (6/9)$                         | Prospective, double-blind |
| 120       | 4.8/kg IV      | —                  | $FEV_1 (21/63)$                     | Prospective, blind |

* Abbreviations used are: $VC$, vital capacity; $FEV_1$, forced expiratory volume in 1 second; $FVC$, forced vital capacity.

† Data from Halmagyi and Cotes (50).

### Table 2

Cardiac and Circulatory Effects

Results of studies on the myocardial effects of aminophylline in animals (1, 8, 20, 34, 47, 91, 95, 166) are summarized in Table 3. Aminophylline is a chronotrope in animal hearts. The lack of inotropic response to aminophylline in transplanted canine hearts, along with the positive response in situ, indicates that aminophylline acts on the heart via catecholamine release from intact cardiac adrenergic nerve terminals (95). Aminophylline appears to have no consistent effect on canine coronary blood flow (1, 34, 47, 91).

In man (Table 4), aminophylline consistently exerts a chronotropic effect (35, 96, 97, 107, 109). Increases in heart rate, stroke volume, and cardiac output are accompanied by decreases in systemic vascular resistance, right and left ventricular end-diastolic pres-
TABLE 3
Cardiac Effects of Aminophylline in Anesthetized Animals*

| Reference | Effects | Anesthetic | Species | Remarks |
|-----------|---------|------------|---------|---------|
| 20        | ↑HR     | Pentobarbital | Dog     | Propanol blocked ↑HR |
| 166       | ↑HR     | Heart-lung preparation | Dog     | Reserpine blocked ↑HR |
| 95        | HR unchanged↑ | Not specified | Dog     | Propanol and phenox ybenzamine caused no change in CBF |
| 8         | ↑HR     | Isolated heart | Guinea pig | Theophylline uptake lagged behind, ↑HR |
| 34        | CBF unchanged, ↑Coronary A – V̇O₂, ↑myocardial O₂ uptake | Pentobarbital | Dog     | |
| 1         | ↑Posthypoxic CBF | Pentobarbital | Dog     | |
| 47        | ↑Posthypoxic CBF | Pentobarbital | Dog     | |
| 91        | ↑CBF    | Chloralose | Dog     | |

* Abbreviations used are: HR, heart rate; CBF, coronary blood flow; AV, atrioventricular.
† Transplanted hearts.

pressures, pulmonary capillary wedge pressure, and arterial pressure (35, 96, 97, 107, 109, 131, 151). The use of aminophylline in congestive heart failure, common practice in Europe, would therefore seem clinically valid.

Cerebral Effects

Aminophylline is a central nervous system stimulant. Early work (75, 76) showed a striking improvement in neurologic status in unconscious, comatose, and hemiplegic patients given intravenous aminophylline, which produces a global decrease in cerebral blood flow (87); its analeptic effect appeared due to increased blood flow in damaged brain (129). More recently (42), a double-blind prospective trial of intravenous aminophylline in patients with acute cerebral infarction showed significantly greater immediate improvement in patients who received aminophylline than in those receiving placebo (38% vs 15%). However, after 3 weeks there was no difference in neurologic status and residual disability between the aminophylline and placebo groups. The authors concluded that in ischemic stroke aminophylline can bring immediate symptomatic relief without appreciably influencing ultimate recovery.

Miscellaneous Effects

Cerebral metabolic rate increased along with cerebral cAMP concentrations in young mice given aminophylline (144). The same study also found that anoxic survival in vivo was greatly decreased in neonatal mice given therapeutic aminophylline doses compared to those not receiving aminophylline (0% vs 62%). The implications for aminophylline use in human neonates with apnea, currently routine as noted earlier in this section, are obvious.

Aminophylline has been shown to be a direct renal vasodilator in vivo (18). It increases renal blood flow and decreases tubular sodium reabsorption (74, 156). However, increases in tubular sodium reabsorption have also been documented (66). Theophylline increases renal vein renin concentration (156).

Aminophylline has been reported to decrease venous tone in man (160). Decreases in tone have been observed in dogs in vivo, yet in vitro venous distensibility in dogs was not affected by aminophylline (173). Decreased tone may account for the previously
noted decreased vascular resistance induced by aminophylline.

Reduction in pulmonary transvascular filtration due to decreased lung vascular pressures has been reported after administration of aminophylline (37). Histamine-induced pulmonary edema is antagonized by aminophylline, even in the presence of propanolol (100). Thus, the antiedema effect of aminophylline, noted clinically through its efficacy as an adjunct in the therapy of congestive heart failure (see above), does not seem dependent on pulmonary beta-adrenergic receptors.

Aminophylline inhibits platelet aggregation in human plasma (12). Aminophylline also has an inhibitory action on uterine motility in women, perhaps related to increases in cAMP and the subsequent inhibition of uterine motility by cAMP (24). Theophylline increases sensitivity to pain in rats, its effects being proportional to plasma theophylline concentrations (93, 94).

Theophylline stimulates the neuromuscular junction (132). In vitro studies with myasthenia gravis muscle preparations have shown marked augmentation of neuromuscular function (60). In patients with myasthenia gravis refractory to anticholinesterase medication, theophylline increases muscle strength and improves function (14). Antagonism of pancuronium-induced neuromuscular block in the presence of supratherapeutic serum theophylline concentrations has been reported (27).

These studies indicate that aminophylline facilitates neuromuscular transmission, perhaps by increasing cAMP level at the neuromuscular junction through phosphodiesterase inhibition. cAMP at the prejunctional level may cause neurotransmitter release (29).

### TABLE 5

| Reference | No. of patients | Recommendations | Side effects (no. of patients) | Remarks |
|-----------|----------------|----------------|-------------------------------|---------|
| 21        | 280            | Useful before surgery | None noted                 | 4% asthmatics in total patient population |
| 128       | 687            | Useful before surgery; possibly useful during surgery | None noted | 1.2% asthmatics in total patient population; halothane advocated during surgery |
| 48        | Not stated     | Possibly useful during surgery | None noted | Halothane advocated during surgery |
| 6         | 89*            | Useful before surgery | Cardiac arrhythmias 4/89; 3/4 had preoperative aminophylline + halothane anesthesia | PaCO₂ < 35, PaO₂ > 100 shortly after onset of arrhythmias |
| 113       | 2              | Avoid halothane for 13 hours | Multiform ventricular tachycardia (2/2) | PaCO₂ < 42, PaO₂ > 100 at onset of arrhythmia in each patient |
| 172       | Not stated     | Perioperative use safe and effective | None noted | Anecdotal comments |

* Eighty-nine anesthetics in 67 patients.

### Anesthesia-Related Use

Perioperative use of aminophylline is controversial (114, 172), due to its reported arrhythmogenic effects during general anesthesia (6, 113). Surprisingly little objective information exists on the efficacy of aminophylline in the prevention or resolution of asthmatic episodes associated with anesthesia and surgery (Table 5). Generalizations that aminophylline is useful in the preoperative preparation of asthmatic patients fail to cite objective evidence of its efficacy in treating or preventing intraoperative bronchospasm (6, 21, 48, 128, 172).

In two reports of arrhythmogenic effects of aminophylline in conjunction with general anesthesia in man (6, 113), the anesthetic agent used in all patients with arrhythmias was halothane. Halothane is considered the anesthetic of choice for the asthmatic patient (48, 128), so it would most likely be the agent involved in aminophylline-anesthetic interactions.

The first of these reports (6) noted intraoperative cardiac arrhythmias during four of 67 halothane anesthetics administered to asthmatic patients. The arrhythmias consisted of supraventricular tachycardia (one patient), bigeminy (two patients), and multifocal premature ventricular contractions (one patient). Two of the three patients with ventricular arrhythmias had received preoperative aminophylline, as had the patient with supraventricular tachycardia. No information on doses or serum theophylline levels was presented. However, arterial blood gases at the onset of ventricular arrhythmias showed no evidence of hypoxemia or hypercarbia.

Tachycardia during halothane anesthesia after preoperative aminophylline was significantly more fre-
quent than in patients not receiving this combination (6). Nine of 45 patients (20%) given aminophylline and halothane developed heart rates greater than 145 beats per minute; none of the 22 patients having halothane anesthesia without aminophylline had a heart rate greater than 140 beats per minute. Only one of 21 other patients anesthetized with methoxyflurane, ether, fluroxene, or fentanyl had a heart rate greater than 140 beats per minute; this patient had received preoperative aminophylline.

The second report (113) cited two cases of patients who had received preoperative aminophylline and subsequently developed multifocal ventricular tachycardia 5 minutes after induction of halothane anesthesia. Serum theophylline levels were not measured at the time arrhythmias occurred, but in one case a toxic level was almost certainly present during induction. Arterial gases at the onset of arrhythmias again showed no evidence of hypoxemia or hypercarbia.

We performed a prospective study in dogs of intravenous aminophylline administration followed 2 minutes later by the induction of halothane anesthesia (Table 6). After administration of thiopental and succinylcholine, and endotracheal intubation, three groups of six dogs each were given intravenous aminophylline in doses of 10, 25, and 50 mg/kg, respectively. Serum theophylline levels were measured and found to be in the human therapeutic range after 10 mg/kg and in the toxic range after 25 and 50 mg/kg of aminophylline. Two of six dogs given 10 mg/kg of aminophylline developed ventricular arrhythmias (premature ventricular contractions and bigeminy) during induction of halothane anesthesia. One of six dogs given 25 mg/kg of aminophylline developed an arrhythmia (bigeminy), and three of six dogs given 50 mg/kg of aminophylline developed arrhythmias (bigeminy in two and premature ventricular contractions and bigeminy in the third) during induction of halothane anesthesia.

Neither arterial hypoxemia nor hypercarbia was present in any of the animals studied. Serum levels of ionized calcium and potassium were within normal limits. All arrhythmias resulting from the combination of aminophylline followed by halothane occurred 5 minutes or more after induction of halothane anesthesia, and persisted for the duration of the experiments (30 minutes). This time course was quite different from that of arrhythmias seen when aminophylline is administered to dogs during halothane anesthesia (see below).

A number of studies of the effects of aminophylline administered during general anesthesia in dogs (54, 127, 134, 135, 140, 141, 152), have shown that toxic doses of aminophylline consistently cause ventricular arrhythmias when administered during 1% halothane anesthesia (Table 7). However, the majority of the studies (127, 140, 141, 152) did not report arterial blood gas values, serum theophylline levels, or potassium and ionized calcium concentrations before or at the time arrhythmias occurred, and so it is not possible to eliminate conclusively causes other than aminophylline-halothane interaction as possible sources of arrhythmogenicity.

In our study of aminophylline administration during halothane anesthesia in dogs, we reported serum theophylline levels and arterial blood gas tensions (134). We observed no arrhythmias after aminophylline administration which produced serum theophylline levels corresponding to the therapeutic range in conscious man. The only significant changes noted were a 10% increase in heart rate and transient decreases in systemic vascular resistance and pulmonary capillary wedge pressure after aminophylline. No change in arterial oxygenation was noted.

We then studied the arrhythmogenic effects of both therapeutic and toxic aminophylline doses during induction and maintenance of halothane anesthesia in dogs (135). We again found that therapeutic theophylline levels were not arrhythmogenic, but showed that toxic levels produce ventricular arrhythmias in

### Table 6

| Aminophylline dose mg/kg | Theophylline level mg/L | Ventricular arrhythmias (frequency) | Time of onset of arrhythmias after halothane min | At onset of arrhythmia |
|-------------------------|------------------------|-----------------------------------|-----------------------------------------------|------------------------|
| 10                      | 11                     | PVCs, bigeminy (2/6)              | 5/11                                          | P<sub>O2</sub> 78–97 74–7.45 4.2–4.4 2.09–2.21 |
| 25                      | 34                     | Bigeminy (1/6)                    | 8                                             | P<sub>CO2</sub> 29–33 7.44–7.45 4.2–4.4 2.09–2.21 |
| 50                      | 44–63                  | PVCs, bigeminy (3/6)              | 8.5–18                                        | pH 7.51 4.7 2.14 |
|                         |                        |                                   |                                               | K<sup>+</sup> 4.0–4.5 2.14–2.31 |
|                         |                        |                                   |                                               | Ca<sup>2+</sup> 2.14–2.31 |

*Abbreviation used is: PVCs, premature ventricular contractions.
Intravenous Aminophylline in Anesthetized Dogs

| Reference | Dose | Anesthetic | Anesthetic-amino- | Ventricular arrhythmia | Remarks |
|-----------|------|------------|------------------|------------------------|---------|
| 152       | 50   | Pentobarbital | 15 min | PVCs (2/4) | Sinus tachycardia (2/4) |
| 140       | 50   | 1% halothane | 10 min | PVCs (12/20) | Sinus tachycardia (6/8) |
| 141       | 50   | None | — | PVCs (1/10) | |
| 50        | 75 min | Pentobarbital | PVCs (2/6) | | |
| 50        | 30 min | 3% ether | PVCs (1/6) | | |
| 50        | 10 min | 3% halothane | PVCs (0/6) | | |
| 50        | 15 min | 1% halothane | PVCs (12/16) | | |
| 127       | 50   | 1% halothane | 30 min | PVCs (2/7), ventricular tachycardia (4/7) | Spontaneous ventilation |
| 54        | 7    | Pentobarbital | Not stated | Direct electrical stimulation to heart to produce arrhythmias | |
| 134       | 10   | 1% halothane | 90 min | (0/11) | Therapeutic theophylline levels, heart rate |
| 135       | 10   | 1% halothane | 2 hr | (0/8) | Therapeutic theophylline levels |
| 25        | 6 hr | 1% halothane | PVCs (4/8) | | Toxic theophylline levels |
| 50        | 15 min | 1% halothane | Bigeminy (2/6) | | Toxic theophylline levels |

Dosage and Administration

Since the development of an accurate spectrophotometric assay for theophylline in 1949 (121), numerous other assays have been developed, including high pressure liquid chromatography (142), radioimmunoassay (22), and enzyme immunoassay (49). Thus, obtaining accurate serum theophylline levels has become routine in most major medical centers in the United States.

Aminophylline toxicity continues to be seen and reported (31, 52, 58, 59, 119, 168, 174) even though a well defined therapeutic range (10 to 20 mg/L) for serum theophylline has been established (86). Causes of this problem include failure to appreciate the pharmacokinetics of aminophylline, effects of disease and altered physiologic states on theophylline disposition, and drug interactions.

Theophylline pharmacokinetics can best be described by a two-compartment, open system model (85). Simplified, this means that the drug is distributed initially into the first compartment (plasma) and then gradually disperses into the second compartment (tissues). In man, the half-time for plasma compartment decay is 30 to 45 minutes, whereas the slower decay of theophylline in the tissue compartment is reflected in a half-time of approximately 4.5 hours (92). Con-
siderable variability in the tissue compartment half-time with altered physiologic states may often lead to overdose and toxicity.

Each 1 mg/kg of theophylline administered in a rapidly absorbed form (intravenous, oral solution, or rapid dissolution tablet) results in a 2-mg/L increase in serum theophylline concentration (86). Infusion of theophylline is then necessary to maintain a constant level (86).

Many studies relating clinical effects to serum theophylline concentration have shown a consistent bronchodilator response to serum theophylline levels of 10 to 20 mg/L (39, 57, 62, 105, 120, 162). This has become the accepted therapeutic range (118). Toxicity has usually been associated with levels greater than 20 mg/L (62, 86).

From the information above, it becomes evident that to achieve a serum theophylline level of 10 mg/L, an average 70-kg adult requires 350 mg (5 x 70) of theophylline as a loading dose. Recalling that aminophylline is approximately 80% theophylline, this patient would require 438 mg (1.25 x 350) of aminophylline as a loading dose.

Alterations in physiologic status may produce differences in theophylline disposition and kinetics sufficient to cause toxicity or, in some cases, relative underdosage (Tables 8 and 9). The apparent volume of distribution of theophylline in the steady state averages 0.5 L/kg of body weight in healthy adults (103).

Earlier work (86) established an aminophylline infusion rate of 0.9 mg/kg/hr after a 5.6-mg/kg loading dose to maintain plasma theophylline levels of 10 mg/L in 95% of patients studied. However, rigid adherence to this dose schedule, often without adequate monitoring of serum theophylline levels, has led to overdose and toxicity (see "Toxicity").

As information has accumulated on altered theophylline disposition, new guidelines for safe therapy have been established. Thus, after an initial loading dose of 5.6 mg/kg, theophylline infusion rates designed to achieve and maintain a serum theophylline level of 10 mg/L are: for children 1 to 9 years old, 0.85 mg/kg/hr; for children more than 9 years old and otherwise healthy adult smokers, 0.7 mg/kg/hr; for otherwise healthy nonsmokers, 0.4 mg/kg/hr; in patients with cardiac decompensation or liver dysfunction, 0.2 mg/kg/hr (53). These guidelines must be combined with measurement of serum theophylline levels within 12 hours of starting an infusion in order to individualize the dose to particular patient requirements.

Theophylline interacts with a number of drugs other than halothane, creating the possibility of unwanted or diminished drug action and effects. In addition, there is evidence that chronic theophylline treatment inhibits its own elimination (92).

Theophylline directly stimulates the myocardium and may enhance sensitivity to digitalis as well as increase vulnerability to digitalis toxicity (126). Aminophylline seems to increase the excretion of lithium ions and possibly may impair therapeutic responses to lithium carbonate, necessitating higher lithium doses during aminophylline therapy (143). The antibiotics troleandomycin and erythromycin double expected theophylline levels, although no mechanism for this effect has been determined (68, 163). A recent study (101), however, showed no significant interaction between theophylline and tetracycline, erythromycin, or cephalixin.

Aminophylline may be administered by intravenous, intramuscular, oral, aerosol, or rectal routes. The intravenous route is most reliable and rapid in the acute situation (92). The drug should always be administered via a peripheral vein and never through

### TABLE 8

| Reference | Pathology | Change in Vd | Effect on serum theophylline | Species |
|-----------|-----------|--------------|------------------------------|---------|
| 2         | Premature neonates | ↑ | ↑ | Man |
| 104       | Cirrhosis | ↑ | ↓ | Man |
| 40        | Obesity   | ↓ | ↑ | Man |
| 65        | ↓pH       | ↑ | ↓ | Dog |
| 111       | ↓pH       | ↑ | ↓ | Man, multiple drugs |

### TABLE 9

| Reference | Physiologic change | Change in theophylline clearance | Effect on serum theophylline |
|-----------|--------------------|----------------------------------|------------------------------|
| 55        | Cigarette smoking  | ↑                                | ↓                            |
| 63        | Marihuana          | ↑                                | ↑                            |
| 108, 156  | Acute fever        | ↑                                | ↑                            |
| 155       | Cor pulmonale      | ↓                                | ↑                            |
| 103       | Pulmonary edema    | ↓                                | ↑                            |
| 52        | Hepatic disease    | ↓                                | ↑                            |
| 52, 153   | Congestive heart failure | ↓ | ↑ |
| 40        | Obesity            | ↓                                | ↑                            |
| 69        | Old age            | ↓                                | ↑                            |
| 64        | Eating charcoal-broiled meats | ↑ | ↓ |
a central catheter (17, 102) (see “Toxicity”). Aminophylline should be administered over 10 to 20 minutes (102), diluted in 25 to 50 ml of saline, preferably, although not necessarily, with a constant infusion pump (85, 103).

Intramuscular administration is painful and produces low plasma concentrations (123). Oral administration is common but not always reliable. Nausea and vomiting, occasionally seen after toxic doses administered orally, are also seen after rectal and intravenous use, suggesting that gastrointestinal disturbances after aminophylline administration do not arise solely from local irritation of the gastric mucosa, but rather reflect systemic toxicity due to stimulation of central vomiting centers and effects on gastric acid secretion and mucosal tissue concentrations (30, 118, 124, 169). The aerosol route is ineffectual (133). Rectal administration results in variable and unpredictable serum concentrations, and proctitis is frequent (56, 73, 124, 145, 147).

**Metabolism and Elimination**

Theophylline is rapidly distributed throughout extracellular fluids and body tissues after intravenous administration (92) (see “Dosage and Administration”). It is found not only in plasma and extracellular fluid, but also in erythrocytes (85), saliva (67), and breast milk (170). Theophylline can cross the placenta to produce high fetal concentrations (3). The disposition of theophylline depends primarily on protein binding in serum, metabolism in the liver, and excretion in urine.

Theophylline in plasma is reversibly bound to circulating plasma proteins (92). On the average, approximately 55% of theophylline is protein bound in healthy adults, but in neonates only 36% of theophylline is bound (2, 67). In patients with hepatic cirrhosis, approximately 35% is protein bound (77, 104). As unbound drug in plasma is generally considered to be the pharmacologically active fraction, a more intense pharmacologic response would be expected in the newborn or the patient with liver disease than in a normal adult with the same total serum theophylline concentration.

Theophylline is mainly eliminated from the body by biotransformation in the liver and by urinary excretion (61). Approximately 7% to 15% of a given dose of theophylline is excreted unchanged in the urine (13, 23, 61). Renal clearance is proportional to urine flow (72).

The major metabolites of theophylline (1,3-dimethylxanthine) in man are 3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid (146) (Fig. 2). In one study of theophylline disposition (61), 8% was excreted unchanged in urine, 40% appeared as 1,3-dimethyluric acid, 36% as 3-methylxanthine, and 17% as 1-methyluric acid.

The enzymes responsible for oxidation and demethylation in the liver have not yet been identified, although the microsomal enzyme system is involved and not the mitochondria (92, 146). The system of microsomal enzymes involved contains three main components: cytochrome P-450, a nicotinamide-adenine dinucleotide phosphate (NADPH)-dependent reductase, and phosphatidylcholine. Cytochrome P-450 activity is inducible by phenobarbital, but administration of phenobarbital in man does not lead to increased theophylline clearance (146). Cytochrome P-450 activity is also inducible by polycyclic hydrocarbons (146). This may explain the increase in theophylline clearance associated with cigarette smoking, which increases tissue levels of polycyclic hydrocarbons (55, 146). Increased theophylline clearance in subjects eating a diet high in charcoal-broiled meats (64) can be explained on the same basis.

Premature infants have extremely low plasma theophylline clearance values which increase progressively over several weeks of continuous aminophylline infusion (2, 45), suggesting either maturation of hepatic oxidative enzyme activity or self induction of the biotransformation process (92). Removal of dietary methylxanthine in three normal subjects resulted in more rapid elimination of theophylline and its metabolites (16). Increasing plateau concentrations of theophylline have resulted in correspondingly decreased clearance values with each increase in serum level (92).

In examining the pathways for theophylline deg-
radiation, it is evident that xanthine oxidase, responsible for the production of uric acid from xanthines and fundamental in the pathogenesis of gout, plays a significant role in theophylline metabolism. As noted above, 1-methyluric acid makes up 17% of the end product of theophylline degradation. Because of the lack of complete demethylation, however, no increase in uric acid excretion would be expected after theophylline administration (112). This is indeed the case (92).

Allopurinol, a potent and commonly used clinical inhibitor of xanthine oxidase, did not alter theophylline clearance in five normal volunteers (159). On the basis of the metabolic pathways noted above, however, one would certainly expect a decrease in 1-methyluric acid production and corresponding increases in the other end products of theophylline metabolism after allopurinol administration.

Studies of 3-methylxanthine (99), a major (36%) metabolite of theophylline, showed that it produces respiratory and cardiovascular effects similar to those produced by theophylline, but that it is 1 to 5 times less potent than theophylline. Nevertheless, 3-methylxanthine may contribute to the effects of theophylline during prolonged therapy and, by implication, so may the other metabolites. Thus, results of theophylline therapy in any given patient are likely to depend on the relative dominance of different degradative enzymes leading to formation of various breakdown products.

Another area of importance in theophylline elimination is its distribution into breast milk. On a relative body weight basis, a nursing infant receives as much as 10% to 15% of the mother’s dose (170). Infants who metabolize the drug very slowly could accumulate a significant body store of theophylline, enough to cause toxicity, as has been reported (170). Thus, nursing women needing theophylline should be given the drug just after nursing to avoid peak serum and milk concentrations at the time of feeding.

Placental transfer of maternally administered theophylline resulting in serum concentrations in the therapeutic range (10 to 20 mg/L) in the neonate after delivery has been reported (3). One neonate exhibited irritability, emesis, and tachycardia, evidence of theophylline toxicity, even though the peak neonatal serum level of theophylline was 14 mg/L. This concentration was 3 mg/L higher than peak maternal level, and possibly reflected a “deep” compartment with slow drug entry and elimination relative to the mother, perhaps due to incomplete neonatal development of the cytochrome P-450 monoxygenase system responsible for demethylation (3). Alternatively, reduced protein binding of theophylline noted in full-term infants could have resulted in increased free, pharmacologically active drug at a “safe” total serum concentration, producing toxicity (2).

**Toxicity**

The first deaths associated with aminophylline were reported in 1943 (83). Since that time numerous other reports of fatalities have appeared in the literature (11, 17, 19, 41, 82). In many of these cases overdose and/or rapid central administration was clearly the likely cause (11, 17, 19, 41). High local concentrations may result in precipitation of free alkaloids when theophylline salts are exposed to the pH of the blood (112). Inadequate distribution due to rapid intravenous administration exposes the heart and other vital organs to excessive drug concentrations (102). This is well documented by a report (17) that 36% of all catastrophic events leading to cardiac arrest in 39 patients in one intensive care unit consisted of aminophylline administration via central venous catheters.

As noted above, aminophylline is most effective when circulating serum theophylline levels range from 10 to 20 mg/L (102). Toxicity in unanesthetized man occurs with levels greater than 20 mg/L (15, 102). The highest level reported in man is 300 mg/L (165). The most prominent symptoms of early toxicity are anorexia, nausea, vomiting, insomnia, restlessness, and irritability (92, 102). Signs of severe toxicity include delirium, tachycardia, dehydration, fever, convulsions, hematemesis, stupor, and coma (82, 92, 102); cardiorespiratory arrest is not uncommon (17). Early and less severe signs of toxicity do not always precede more dangerous ones (58, 116, 168). The only safe way to administer aminophylline is in conjunction with measurement of serum theophylline levels.

Successful therapy of aminophylline-induced cardiac arrhythmias with lidocaine has been reported in both awake and halothane-anesthetized man (32, 113). In dogs, we observed rapid, spontaneous resolution of ventricular arrhythmias which occurred after administration of toxic doses of aminophylline during halothane anesthesia (135).

Seizure activity associated with aminophylline was first described in children in 1954 (117) and in adults in 1959 (5). Since that time numerous reports of seizure activity have appeared (31, 122, 168, 174). One study (174) found a striking correlation of seizure activity with theophylline level: eight patients with grand mal seizures had theophylline levels from 25 to
Aminophylline (theophylline ethylenediamine) has been in clinical use for more than 75 years. Its primary use today is in the treatment of asthma, although it is also a mainstay in the therapy of neonatal apnea and, primarily in Europe, acute cerebrovascular accidents.

The mechanism of action of aminophylline has not yet been precisely characterized, but seems to involve cAMP and phosphodiesterase inhibition. Strong evidence exists for a relationship to calcium flux and concentration. Aminophylline also causes increased synthesis and release of catecholamines by the adrenal medulla.

Use of aminophylline during anesthesia is controversial. Scattered reports of cardiac arrhythmias in man during anesthesia seem to indicate that high theophylline levels predispose to cardiotoxicity; animal studies confirm this. There is evidence that theophylline levels believed safe in conscious man are, in fact, arrhythmogenic when followed by halothane anesthesia induction in dogs.

Intravenous aminophylline will produce a serum theophylline level of approximately 2 mg/L for every 1 mg/kg given as a loading dose. Thus, to achieve a minimum effective blood level of 10 mg/L, a loading dose of aminophylline should be 5 mg/kg. This must be followed by infusion to maintain a therapeutic blood level. Therapeutic serum theophylline levels range from 10 to 20 mg/L. Monitoring of serum theophylline concentration is essential to avoid toxicity, especially in patients who are elderly or have heart or liver disease. Aminophylline should always be administered diluted in 25 to 50 ml of saline over 10 to 20 minutes via peripheral vein, never through a central venous or pulmonary artery catheter.

Toxicity from aminophylline therapy is not uncommon, and is always related to serum theophylline levels greater than 20 mg/L. Toxicity often manifests itself by gastrointestinal symptoms such as nausea and vomiting, and other signs and symptoms include irritability, insomnia, cardiac arrhythmias, convulsions, coma, and cardiorespiratory arrest. Less severe signs of toxicity do not always precede arrhythmias, seizures, and cardiorespiratory arrest.

Treatment of aminophylline toxicity consists first of immediately discontinuing aminophylline when clinical signs noted above appear. In the event of a serum theophylline level greater than 20 mg/L during aminophylline infusion without clinical signs or symptoms of toxicity, the infusion rate should be decreased.
Cardiac arrhythmias caused by aminophylline may be treated with lidocaine; high doses of anticonvulsants may be required to control seizure activity. As long as hemodynamic and pulmonary status is stable, such anticonvulsant therapy should be continued irrespective of dosage until control of seizures is achieved. Muscle relaxants are not indicated as part of the treatment of seizures. Aminophylline appears contraindicated in conjunction with anesthesia in patients susceptible to malignant hyperthermia.

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