ORIGINAL CONTRIBUTION
esmolol, use in theophylline toxicity;
theophylline, toxicity

The Effects of Esmolol on the Hemodynamics of Acute Theophylline Toxicity

The effects of esmolol, a beta$_1$-selective adrenergic receptor antagonist with a short duration of action, were studied in a canine model of the hemodynamics of theophylline toxicity. Animals were anesthetized, then given 50 mg/kg aminophylline IV over 20 minutes followed by a continuous infusion of 1.75 mg/kg/hr. Hemodynamic parameters, including heart rate, cardiac output, systemic blood pressure, pulmonary arterial pressure, and pulmonary artery wedge pressure, were measured every 30 minutes along with plasma catecholamines and theophylline levels. Marked tachycardia was seen in the intoxicated state, with heart rate rising from a baseline of 128.0 ± 8.3 beats per minute (BPM) to 179.0 ± 7.4 BPM (P = .012). This was associated with increases in catecholamines (baseline norepinephrine .04 ± .04 ng/mL plasma rose to .42 ± .21 ng/mL plasma after intoxication, P = .048). The average serum theophylline level during the experiment was 44.0 ± 1.1 μg/mL serum. Esmolol then was given by IV infusion in these animals in doses of 25, 50, and 100 μg/kg/min. It returned the heart rate to the preintoxication baseline in a dose-related manner. Esmolol did not decrease cardiac output or lower blood pressure. [Gaar GG, Banner W Jr, Laddu AR: The effects of esmolol on the hemodynamics of acute theophylline toxicity. Ann Emerg Med December 1987;16:1334-1339.]

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INTRODUCTION

Acute theophylline toxicity is often manifest, with signs of cardiac dysfunction including tachycardia, arrhythmias, and changes in blood pressure.[1-7] This cardiotoxicity may, in part, be catecholamine mediated, as theophylline infusion increases circulating plasma catecholamine levels.[8-10]

We studied the hemodynamic parameters and circulating catecholamine levels in dogs intoxicated with theophylline in an attempt to determine possible catecholamine mediation of the hemodynamic changes. The effects of esmolol (Brevibloc®), a rapidly metabolized, cardio-selective, beta-adrenergic receptor antagonist then were studied in this model.

MATERIALS AND METHODS

All experiments were done under the supervision of a laboratory animal care committee in accordance with the guidelines of the American Physiological Society. Mongrel dogs with a mean weight of 19 kg (range, 16 to 23 kg) were used for the study. Three dogs were used in initially establishing an animal model of theophylline intoxication, and then five animals were used in the treatment phase of the study.

Model

Anesthesia was induced with IV sodium thiopental at a dose of 25 mg/kg, then maintained by 100 mg/kg of IV alpha-chloralose. A triple-lumen, thermodilution Swan-Ganz catheter and femoral arterial line were placed for hemodynamic monitoring. A multichannel physiograph recorder (Electronics for Medicine, Inc, Pleasantville, New York) was used to continuously display ECG and both pulmonary and systemic arterial blood pressure. Intermittent measurements of pulmonary artery wedge pressure were obtained. Determinations of cardiac output by thermodilution[11] and body core temperature were performed using an Edwards cardiac output computer (Edwards Labora-

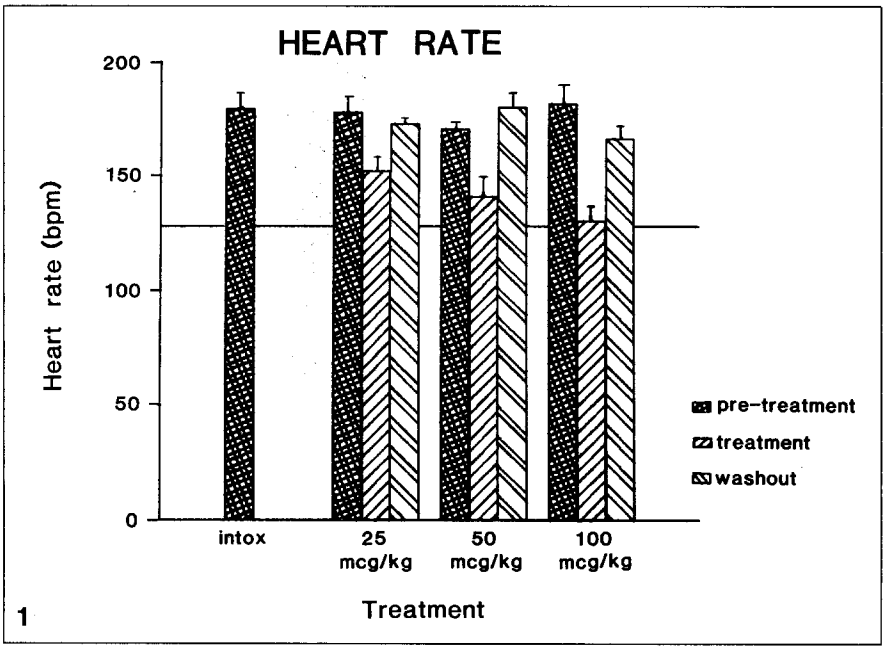


FIGURE 1. *Heart rate data presented as mean ± SEM. Average of values at the initiation of the 25 μg/kg/min dose is labeled the "pre-treatment-25" value; at the end of the infusion, the "treatment-25" value; and at the end of the period with no therapeutic intervention immediately following the dose of 25 μg/kg/min, the "washout-25" value. Likewise for the other two dosages. Actual values (mean ± SEM): baseline (horizontal reference bar), 128 ± 8.3; intoxicated, baseline 179 ± 7.4; pretreatment 25, 178 ± 6.5; treatment 25, 152 ± 6.1; washout 25, 173 ± 2.0; pretreatment 50, 170 ± 2.0; treatment 50, 141 ± 8.1; washout 50, 180 ± 6.7; pretreatment 100, 182 ± 8.0; treatment 100, 130 ± 5.7; and washout 100, 166 ± 4.1. All treatment values differed significantly from pretreatment values with* $P < .05$.

tories, Santa Ana, California). Arterial blood gases were obtained every ten minutes (or as necessary) until ventilator settings were optimal. They then were checked each time hemodynamic parameters were measured. Artificial ventilation with a pressure ventilator was used to maintain $PaCO_2$ levels within the range 35 to 45 mm Hg when necessary. Arterial oxygen tension was maintained above 70 mm Hg.

Following induction of anesthesia, the preparation was considered stable when systemic blood pressure was maintained within a range of ± 10% systolic for 30 minutes. Measurements of all hemodynamic parameters were taken at the beginning and end of this stabilization period. The average of these values defined the preintoxication baseline. Peripheral vascular resistance values were calculated using the standard equation.[12]

Aminophylline then was administered as an IV infusion at a dose of 50 mg/kg body weight over 20 minutes. This was followed by a continuous infusion of 1.75 mg/kg/hr for the duration of each experiment. This dosage was designed, based on pilot animals and knowledge of volume of distribution and elimination characteristics, to achieve serum theophylline levels > 35 μg/mL, which are considered to be in the toxic range. Hemodynamic parameters were measured every 15 minutes, and stabilization in the intoxicated state was defined as systemic systolic blood pressure that remained at ± 10% variation over a 30-minute period. The measurements of each parameter taken at the beginning, middle, and end of this 30-minute period were averaged and were denoted the intoxication baseline value.

Cardiovascular parameters then were measured every 30 minutes for four hours to determine stability of the model over time. Each time cardiovascular parameters were measured blood was obtained for determination of arterial blood gases, plasma catecholamines, and serum theophylline concentrations. Animals received IV

TABLE 1. *Hemodynamic changes in intoxication model*

	Post-Anesthetic, Pre-Intoxication (Mean ± SEM)	Post-Intoxication (Mean ± SEM)	P
Heart rate (BPM)	137 ± 17	189 ± 14	.026
Pulmonary pressure (mm Hg)			
Systolic	36 ± 6	32 ± 4	NS
Diastolic	25 ± 5	18 ± 3	.044
Systemic pressure (mm Hg)			
Systolic	191 ± 7	170 ± 13	NS
Diastolic	142 ± 6	125 ± 9	.028
Cardiac output (L/min)	3.6 ± 0.3	3.1 ± 0.1	NS
Stroke volume (mL/min)	26.9 ± 4.3	16.7 ± 1.0	NS
Systemic vascular resistance (resistance units)	44.9 ± 2.3	44.7 ± 3.1	NS
Norepinephrine (ng/mL plasma)	.12 ± .12	.96 ± .12	NS

TABLE 2. *Hemodynamic changes following theophylline intoxication in animals in the treatment group*

	Pre-Intoxication (Mean ± SEM)	Post-Intoxication (Mean ± SEM)	P	100 μg/kg/min Esmolol (Mean ± SEM)	P (Compared to Intoxicated Value)
Heart rate	128 ± 8	179 ± 7	.012	130 ± 6	.010
Pulmonary pressure (mm Hg)					
Systolic	18 ± 4	20 ± 4	NS	24 ± 5	NS
Diastolic	8 ± 3	6 ± 2	NS	10 ± 2	.037
Pulmonary capillary wedge pressure (mm Hg)	11 ± 4	5 ± 2	NS	7 ± 1	NS
Systemic blood pressure (mm Hg)					
Systolic	140 ± 19	128 ± 8	NS	142 ± 9	NS
Diastolic	104 ± 12	92 ± 8	NS	97 ± 6	NS
Cardiac output (L/min)	2.6 ± 0.4	3.4 ± 0.7	NS	2.7 ± 0.3	NS
Stroke volume (mL/min)	20.7 ± 3.2	18.4 ± 3.0	NS	20.4 ± 2.2	NS
Systemic vascular resistance (resistance units)	44.9 ± 3.3	36.3 ± 2.8	NS	43.9 ± 5.2	.023
Norepinephrine (ng/mL plasma)	.04 ± .04	.42 ± .21	.048	.28 ± .08	NS

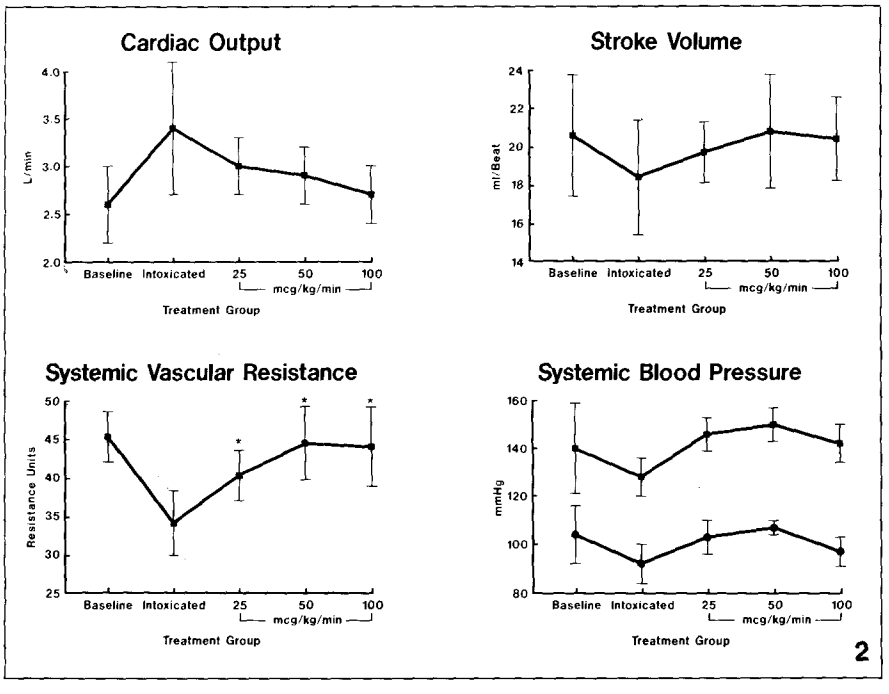


FIGURE 2. *Cardiac output (L/min), stroke volume (mL/beat), systemic vascular resistance (resistance units), and systemic blood pressure, both systolic and diastolic (mm Hg), expressed graphically for the treatment group of animals. All values expressed as mean ± SEM. Baseline values refer to the period after anesthesia yet prior to aminophylline infusion; intoxicated values are those following the initial aminophylline infusion; and values marked 25, 50, and 100 μg/kg/min represent those measured following those dosages of esmolol by continuous infusion for 30 minutes.*
**Denotes that these treatment values differed from the intoxicated values with a P < .05.*

crystalloid therapy to replace volume lost through blood sampling.

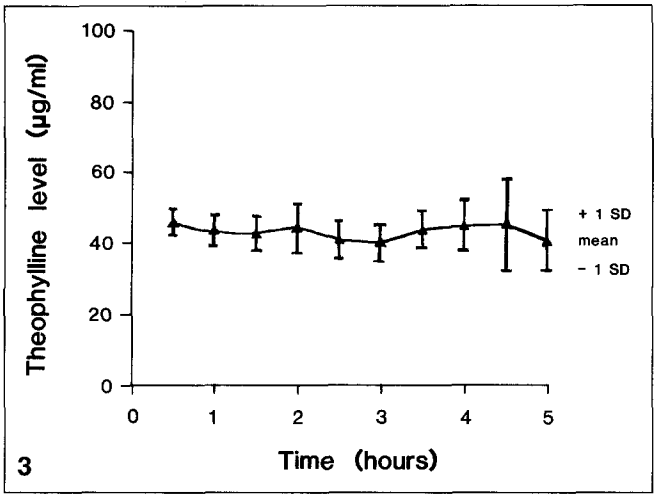
Treatment

Using this animal model of intoxication, the effects of esmolol on the cardiovascular system were studied.

Three dosages of esmolol, 25 μg/kg/min, 50 μg/kg/min, and 100 μg/kg/min continuously infused for 30-minute periods were evaluated in random order in each animal. [These dosages were chosen based on previous animal data.][13,14] These treatment periods were each followed by 30 minutes without esmolol to allow the animal to return to the intoxicated state prior to evaluating another dosage. Hemodynamic determinations were made at the initiation and end of each infusion, and at the end of the period with no therapeutic intervention immediately following the dose.

Plasma theophylline concentrations were measured by enzyme multiplied immunoassay technique [Syva, Palo Alto, California].[15] Plasma concentrations of norepinephrine were determined after alumina extraction using high-pressure liquid chromatography with electrochemical detection, a method adapted from Eriksson.[16]

Analysis of data was performed using the Statistical Package for the Social Sciences.[17] Student's paired t test was used in comparing the means



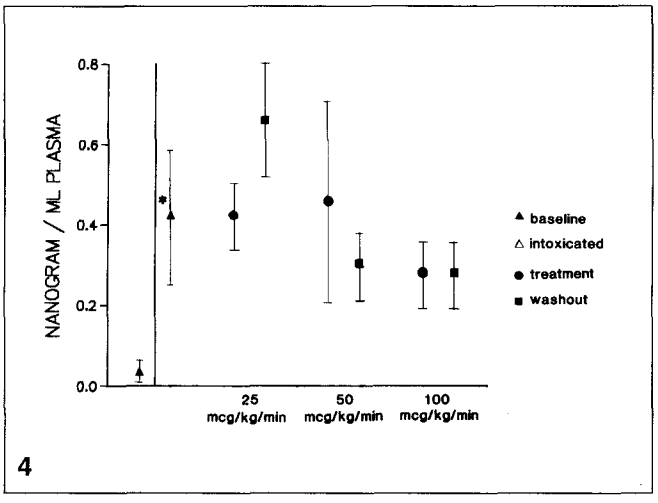


FIGURE 3. *Serum theophylline levels for the treatment group of experiments. Mean ± 1 standard deviation expressed for all time points following intoxication. Levels were very stable during the course of the experiments, indicating that correction of tachycardia was due to therapy, not to decreasing intoxication.*

FIGURE 4. *Plasma norepinephrine concentration expressed as mean ± standard deviation. Vertical reference bar denotes beginning of aminophylline infusion. Treatment and washout values are denoted at each dosage of esmolol, 25 µg/kg/min, 50 µg/kg/min, and 100 µg/kg/min.*

**Denotes* P < *.05.*

of the hemodynamic parameters at different time points: intoxication baseline with pre-intoxication baseline; intoxicated, pretreatment values versus treatment values at each dosage; and washout values versus treatment values at each dosage. (Student's paired t test was chosen as the large numbers of repeated measurements made on relatively few experimental animals made the usage of the repeated measures tests invalid. The usage of paired t tests allowed each animal to serve as its own control).

Values are expressed as means ± standard error of the mean (SEM). Linear regression statistics were performed where appropriate. A *P* value of .05 was considered maximal for statistical significance.

RESULTS

Model

Initially, experiments were done on three animals to test the validity of this model in the study of the hemodynamics of theophylline toxicity. Of the parameters measured, the most striking change was noted in the heart rate, with the animals becoming tachycardic after infusion of theophylline in toxic doses (Table 1). The pre-intoxication heart rate was 136.7 ± 17.7 beats per minute (BPM); after intoxication the heart rate increased to 188.7 ± 13.6 BPM (P = .026). No arrhythmias were noted during the period of intoxication. Cardiac output was not changed by intoxication. The systolic arterial blood pressure in both the pulmonary and systemic circuits was not statistically different after intoxication, but the diastolic pressure in both vascular beds was significantly decreased (Table 1). These hemodynamic changes persisted for the duration of the continuous infusion of aminophylline.

In animals used in establishing the model, theophylline levels during intoxication were all greater than 35 µg/mL plasma. The mean theophylline level, 47.3 ± 3.8 µg/mL (mean ± SD), was consistently elevated throughout the study.

Treatment

Changes in hemodynamic parameters associated with theophylline intoxication for the five animals in the treatment phase of the study are shown (Table 2). Tachycardia was seen in the intoxicated state, with an increase in heart rate from 128 ± 8.3 BPM, prior to administration of theophylline, to 179 ± 7.4 BPM in the intoxicated state (P = .012). Cardiac output, pulmonary arterial blood pressure, pulmonary artery wedge pressure, and systemic arterial blood pressure were not statistically different when comparisons between pre-intoxication and intoxication values were made using Student's paired t test. Calculated values of systemic vascular resistance showed no statistically significant change following intoxication. Neither body core temperature nor arterial blood gases changed following intoxication.

Esmolol infusion of 25 µg/kg/min for 30 minutes reduced the heart rate to 152 ± 6.1 BPM (P = .005). Increasing doses of esmolol produced a progressive decrease in heart rate. Between esmolol infusions heart rate returned to pre-treatment tachycardic values (Figure 1).

Treatment with esmolol did not significantly change cardiac output or pulmonary arterial systolic pressure. Left ventricular end diastolic pressure, as estimated by pulmonary artery wedge pressure, was not affected by treatment with esmolol. Arterial blood pressure, both systolic and diastolic, was unchanged. Changes in systemic vascular resistance, stroke volume, cardiac output, and systemic blood pressure with esmolol treatment are shown (Figure 2).

Theophylline levels remained in the toxic range for the duration of the experiments in which esmolol was tested (mean level, 44.0 ± 1.1 µg/mL plasma) (Figure 3). Heart rate in the intoxicated state correlated with the theophylline level (r^2 = 0.33; F = 14.11; P = .0008).

Circulating plasma norepinephrine concentrations increased following the infusion of aminophylline. Prior to intoxication, the norepinephrine concentration was .04 ± .04 ng/mL

plasma. This rose to .42 ± .21 ng/mL after the aminophylline infusion (P = .048). This circulating catecholamine level remained elevated during the course of the experiments, including the periods of intervention with esmolol (Figure 4).

DISCUSSION

Marked tachycardia is often associated with theophylline toxicity.[1,2,5,6] The animal model presented in this study reproduced this tachycardia. The response of systemic blood pressure to theophylline intoxication has been reported as both hypo- and hypertension, but hypotension has been reported in severe poisoning in human beings.[3-5] In our study, both pulmonary and systemic blood pressures decreased with intoxication (Table 2). Although no statistically significant difference was demonstrated in either instance, this decrease would correlate with the hypotension reported in cases of severe human intoxication.[3-5]

In our study, cardiac output was measured directly and was unchanged; therefore the decrease in arterial blood pressure was due to a decrease in vascular resistance. Although the changes in calculated vascular resistance were not statistically significantly different between the intoxicated and baseline states, the change was of clinical significance considering that blood pressure decreased despite an increase in cardiac output.

Elevated levels of plasma norepinephrine were seen in this model following administration of toxic doses of aminophylline. This is direct evidence that theophylline in some manner stimulates release of norepinephrine or inhibits its destruction/metabolism. These findings are consistent with those of previously published reports.[8-10,18] IV aminophylline infusion in therapeutic concentrations in human beings increases urinary excretion of epinephrine and norepinephrine.[8] Vestal demonstrated significant increases in circulating plasma levels of epinephrine (262%) and norepinephrine (64%) when subjects received dosages that achieved concentrations of 20 μg/mL plasma.[9] These increases correlated with the dose-related increases in heart rate observed during the study, supporting the hypothesis that the cardiac effects associated with theophylline are in part catecholamine mediated.[9] This increase is likely due to increased synthesis/release of norepinephrine, as an increase in circulating dopamine-β-hydroxylase has been reported following theophylline administration.[18]

Our study provides further evidence to support catecholamine mediation of the tachycardia in theophylline intoxication by demonstrating that a beta-adrenergic receptor antagonist, esmolol, can decrease the tachycardia. This is consistent with data from human beings, in whom metoprolol and propranolol partially attenuated the cardiovascular effects of therapeutic doses of theophylline.[19]

Esmolol is a beta-adrenergic receptor antagonist synthesized specifically to be metabolized by plasma esterase. This compound has an elimination $t_{1/2}$ of nine minutes and a duration of action of less than 15 minutes in dogs.[13,20] The relative β_1-selectivity of this compound has been demonstrated in preparations of isolated guinea pig cardiac and tracheal tissues. In isolated canine hindlimb perfusion studies, dosages of 320 μg/kg/min demonstrated β_1-selectivity.[14] Human pharmacokinetic data demonstrate a terminal $t_{1/2}$ of 9.2 ± 3.5 minutes, with no significant drug effects evident 30 minutes after discontinuation of continuous infusions in eight male volunteers.[21] Clinical studies have demonstrated that esmolol is effective in controlling ventricular rate in adults with supraventricular tachyarrhythmias.[22]

Esmolol proved efficacious in reversing the tachycardia associated with theophylline toxicity in a dose-related manner. This reduction in heart rate was not accompanied by a decrease in cardiac output, and blood pressure was maintained. The fact that the tachycardia was again seen 30 minutes after discontinuation of esmolol therapy confirms its short duration of action in canines. This property is very beneficial in treatment of an acute, severe poisoning, as the dosage of esmolol can be titrated to effect and rapidly reversed. Its property of cardioselectivity is important in that patients who are poisoned with theophylline often have reactive airway disease and may have an increased acute risk of bronchospasm after administration of a non-selective beta-adrenergic receptor antagonist.

Until recently, the only accepted modes of therapy for treatment of acute theophylline intoxication were decontamination of the gastrointestinal tract, prevention of further absorption by the use of activated charcoal, and good supportive symptomatic care. More recently, multiple doses of activated charcoal in the gastrointestinal tract have been demonstrated to lower theophylline levels more rapidly than can be explained by the patient's intrinsic theophylline clearance.[23] Charcoal column hemoperfusion also has been used successfully.[5-7,24,25] In a published case series, two adults with severe intentional theophylline poisoning were treated with IV propranolol hydrochloride and charcoal hemoperfusion with reported good results.[26]

CONCLUSION

We have demonstrated in an animal model that circulating norepinephrine levels increase with theophylline toxicity. Esmolol, a beta$_1$-adrenergic receptor antagonist, was very effective in reversing the tachycardia seen in this experimental model. Two properties of this compound make it a potentially useful agent for the treatment of the hemodynamic abnormalities of acute theophylline intoxication: its cardioselectivity, which lessens the risk of bronchospasm, and rapid metabolism, which leads to a short duration of action.

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