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Effects of Intravenous Theophylline on Exercise-Induced Myocardial Ischemia: II. A Concentration-Dependent Phenomenon

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Objectives. **The effects of varying concentrations of theophylline on exercise-induced myocardial ischemia were evaluated in patients with stable coronary artery disease.**

Background. **Theophylline is a competitive antagonist of adenosine and may have potential as an anti-ischemic medication. It is not known whether these effects on myocardial ischemia are concentration dependent.**

Methods. **In a double-blind, randomized, crossover manner, 11 patients received, at 1-week intervals, placebo and each of three theophylline doses by intravenous infusion for 45 min. Graded exercise testing was performed before randomization and immediately after each infusion. Concurrent anti-ischemic medications were withheld for 24 h before each exercise test. Serum theophylline concentrations achieved were 3.9 ± 1.0 mg/liter (low), 8.2 ± 1.8 mg/liter (medium) and 13.2 ± 2.3 mg/liter (high).**

Results. **Compared with placebo, none of the three theophylline infusions produced a significant alteration in rest heart rate, blood pressure, mean frequency or severity of ventricular ectopic activity or noncardiac symptoms. The time to onset of ischemia was progressively increased, with medium and high concentrations achieving statistical significance. Similar patterns were observed for oxygen uptake and the heart rate–systolic blood pressure product at the onset of ischemia. Total exercise duration was significantly prolonged with the medium and high concentrations.**

Conclusions. **It is concluded that administration of varying doses of theophylline before exercise produces a clinically significant and concentration-dependent improvement in the indicators of myocardial ischemia in patients with chronic stable coronary artery disease.**

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Pharmacologic management of myocardial ischemia has traditionally focused on vasodilation of epicardial arteries or a reduction in myocardial oxygen demand, or both. Recently, an alternative approach to the treatment of ischemia was proposed wherein benefit may be derived from an improvement in the maldistribution of coronary blood flow caused by endogenous adenosine (1). The adenosine antagonist theophylline has been shown to delay the onset of ischemia and to increase the threshold for its occurrence (2–6).

To date, most studies of the short-term effects of intravenous theophylline have used one dose, based on body weight and without measured blood concentrations (2–5). Blood levels reported in a single study by Heller et al. (6) were approximately 8 mg/liter, lower than the 10- to 20-mg/liter concentration range typically associated with theophylline use in reactive airways disease (7). Although these studies have shown that an anti-ischemic benefit with theophylline may exist, no systematic concentration-response comparisons have been made of the agent. Such an approach may be useful in determining an optimal dosing regimen to maximize therapeutic effects while minimizing adverse reactions. The purpose of the present study was to determine the effects of three serum concentrations of theophylline on exercise-induced myocardial ischemia and to evaluate the potential of this agent for cardiac and noncardiac adverse effects.

Methods

Patient selection. Clinically stable patients with ischemic coronary artery disease were evaluated for inclusion in the study on the basis of results of exercise testing with radionuclide imaging administered at the Memorial Hospital of Rhode Island. Male and female patients were eligible for study entry if they completed at least stage I of a Bruce protocol and the exercise test resulted in horizontal ST segment depression ≥0.1 mV, with accompanying ischemia by radionuclide myocardial scintigraphy.

Exclusionary criteria included the following: 1) concurrent methylxanthine, dipyridamole or digoxin therapy; 2) known

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JACC Vol. 22, No. 4
October 1993:1155–8

allergy to theophylline, required use of bronchodilator therapy or history of pulmonary disease; 3) clinical instability; 4) left ventricular hypertrophy, left bundle branch block or other baseline ST segment abnormalities preventing interpretation of the exercise electrocardiogram (ECG); or 5) recent myocardial infarction (within 30 days), coronary artery bypass surgery (within 3 months) or percutaneous transluminal coronary angioplasty (within 3 months).

The study was approved by the Committee for the Use of Human Subjects in Research at the Memorial Hospital of Rhode Island. All subjects gave written informed consent before study participation.

Experimental design and medication protocol. The study was a double-blind, placebo-controlled crossover trial using a randomized block factorial design. After medical screening and baseline testing, patients received, in random order, a saline placebo and each of three theophylline doses at weekly intervals. The theophylline doses were administered as a bolus infusion for 45 min using the ethylenediamine salt aminophylline, and were estimated to achieve mean concentrations of 3.5, 7.5 and 12.5 mg/liter (8). During each infusion, patients were placed in the supine position, and frequent evaluations of blood pressure, symptoms and 12-lead ECGs were made. Three ECG leads were monitored continuously throughout the infusion period.

Procedures and analysis. *Exercise testing.* Five symptom-limited Bruce protocol exercise tests were performed in the fasting state at the same time of day by each patient at weekly intervals: at baseline and immediately after each of the four study medication infusions. All anti-ischemic medications (with the exception of sublingual nitroglycerin) were discontinued 24 h before exercise testing and reinstated immediately after each test. Three ECG leads were monitored continuously throughout the tests, and all spontaneous ectopic activity was recorded. Twelve-lead ECGs were recorded at the end of each minute of exercise, at the onset of ST segment depression and angina (if present) and until resolution of ECG changes during recovery. Blood pressure measurements were obtained during each stage of exercise and during recovery until return to baseline. Standard exercise test termination criteria, as described by Ellestadt (9) were used.

Oxygen uptake methods. Oxygen uptake was measured during each exercise test by open-circuit indirect calorimetry with an Ametek S-3A oxygen analyzer, a Beckman LB-2 carbon dioxide analyzer and a Hewlett-Packard heated digital pneumotach (model 77303A). Measurements were made using a Douglas bag method, with collection of 30-s mixed expired air samples during the last 30 s of each minute of exercise (10). Calibrations were performed before each exercise test (11).

Data analysis and interpretation. The ECGs were analyzed by consensus by two experienced cardiologists without knowledge of patient identity or treatment. The tests were analyzed in random order. For each subject, the lead showing the greatest ST segment depression was determined with the first test read and was utilized on all subsequent tests. Data extracted from the ECGs included the time of onset of 0.1-mV horizontal ST segment depression, the magnitude of ST segment depression at peak exercise, total exercise duration and the time to onset of angina pectoris.

Theophylline assays. Whole-blood samples were collected at the end of exercise, in a tube without additive and spun at 1,200 × *g* for 15 min. The supernatant was extracted and immediately frozen. Duplicate serum samples (10 μl) were assayed for theophylline using the theophylline two-part rate test with a Kodak Ektachem clinical analyzer (model 400, publication MP2-46). The coefficient of variation for this assay ranges from 2.5% to 4.9%, whereas accuracy has been reported to correlate highly with high performance liquid chromatographic methodology ($r = 0.99$).

Statistical analyses. Statistical analyses of the exercise data were performed using a repeated-measures analysis of variance with the Systat statistical package (Systat, Inc., Evanston, IL) (12). The Tukey Honestly Significant Difference (HSD) test was used for post hoc testing whenever there were significant main effects (13). The statistical significance level was set at $p < 0.05$. Data are reported as mean value ± SD.

Results

Study patients. The study group consisted of 11 men, with a mean age of 65 ± 8 years. All patients were receiving at least one anti-ischemic medication. Medications included long-acting nitrates (five patients), beta-adrenergic antagonists (four patients) and calcium channel blocking agents (five patients). In addition to positive responses on exercise scintigraphy, all patients had further evidence of coronary artery disease documented by a history of angina pectoris (10 patients), previous myocardial infarction (4 patients), and previous cardiac catheterization (7 patients).

Comparison of theophylline concentrations with placebo. Pretreatment with intravenous theophylline was completed in all patients without complications. The mean serum theophylline concentrations achieved were 3.9 ± 1.0 mg/liter (termed "low"), 8.2 ± 1.8 mg/liter (termed "medium") and 13.2 ± 2.3 mg/liter (termed "high"). Each theophylline concentration was significantly different from the other two ($p < 0.05$). Cardiac and noncardiac effects during the infusions are shown in Table 1. When compared with placebo, none of the three theophylline concentrations produced a significant alteration in heart rate or systolic or diastolic blood pressure. In addition, there was no change in the mean rate or severity of ventricular premature complexes or noncardiac symptoms, such as transient light-headedness or headaches. Finally, the frequency and severity of ventricular ectopic activity observed during exercise after placebo and theophylline infusions were similar.

Effects of theophylline on ischemia. The effects of varying concentrations of theophylline on the onset of exercise-induced ischemia were evaluated (Table 2). All patients demonstrated ECG evidence of ischemia during each exer-

Table 1. Effect of Varying Doses of Intravenous Theophylline Before Exercise

	Theophylline Concentration							
	Placebo		Low		Medium		High	
	Before	After	Before	After	Before	After	Before	After
Heart rate (beats/min)	65 ± 11	64 ± 10	65 ± 12	64 ± 10	62 ± 7	61 ± 7	68 ± 10	70 ± 14
Systolic blood pressure (mm Hg)	141 ± 20	147 ± 22	142 ± 23	149 ± 22	147 ± 16	149 ± 17	145 ± 16	146 ± 22
Diastolic blood pressure (mm Hg)	84 ± 9	83 ± 11	83 ± 5	83 ± 5	83 ± 7	83 ± 9	83 ± 9	85 ± 10
VPBs/h	4.7 ± 8.2		11.5 ± 29.2		7.0 ± 13.0		4.1 ± 7.9	
Total ADR	1		2		5		3	

There was no statistically significant difference in any of the variables between placebo and the low, medium or high concentration of theophylline. Values presented are mean value ± SD or number. ADR = adverse drug reaction (positional light-headedness, headache); After = after theophylline infusion; Before = before infusion; VPBs = ventricular premature beats.

cise test. After each theophylline infusion, the time to onset of ECG changes was progressively delayed, with the medium and high concentrations achieving statistical significance (Fig. 1). A similar pattern was shown with the uptake of oxygen at the onset of ischemia. The heart rate–systolic blood pressure product at the onset of ischemia also increased in a stepwise fashion, and all three concentrations of theophylline were significantly different from placebo (Table 2). Only five patients experienced angina during the baseline exercise protocol. In this subset of patients, no differentiation could be made among study treatments with regard to the onset of angina pectoris. The effects of varying concentrations of theophylline on peak exercise conditions were also evaluated, with results analogous to those at the onset of ischemia (Table 3).

Discussion

It has been proposed that in coronary artery disease, increased myocardial oxygen demand results in vasodilation and altered distribution of transmural myocardial blood flow from endocardium to epicardium (1,14). Endogenous adenosine may play an important role in the mediation of this vasodilation. Theophylline has been shown in vitro to be a moderately potent adenosine antagonist (15). Although previous studies have associated short-term theophylline administration with reduced myocardial ischemia, the outcomes have not been evaluated for concentration dependency (2–6). The present study demonstrates that in patients with coronary artery disease, the factors related to myocardial ischemia are altered in a concentration-dependent manner by theophylline.

Rationale for theophylline concentrations. The concentration range used in the present study was chosen to represent a wide variation for determining potential drug effect. The midrange concentration of 8 mg/liter was previously shown to improve exercise tolerance, but it was unknown whether a concentration within the traditional "therapeutic range" of theophylline (10 to 20 mg/liter) would produce added benefit (6). The lowest concentration tested, approximately 4 mg/liter, was chosen to parallel the dose of theophylline used to reverse the clinical and ECG effects of dipyridamole given during pharmacologic stress testing (16–18). Typically, the dosage ranges from 75 to 150 mg of aminophylline and would be expected to result in serum concentrations of <5 mg/liter.

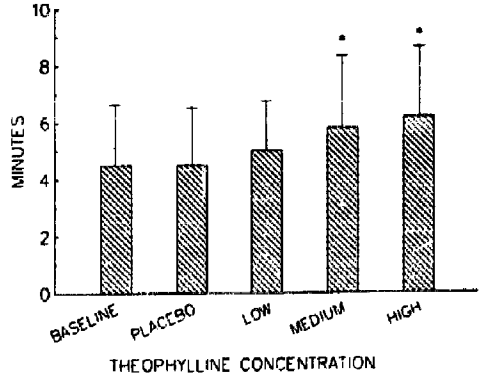
In the present study, theophylline at the lowest concentration produced a statistically significant 30-s increase in the time to ischemia and exercise duration, a result that may reflect the small number of subjects tested. However, the

Table 2. Effect of Varying Doses of Intravenous Theophylline on the Onset of Myocardial Ischemia in 11 Study Patients

	Time (min)	Oxygen Uptake (mg/kg per min)	HR × SBP
Baseline	4.5 ± 2.1	15.2 ± 2.7	19.7 ± 3.2
Placebo	4.5 ± 2.0	14.0 ± 3.1	18.6 ± 2.6
Low	5.0 ± 1.8	15.3 ± 3.0	21.1 ± 3.5*
Medium	5.8 ± 2.6*	16.4 ± 4.1†	21.6 ± 3.6*
High	6.2 ± 2.5*	17.0 ± 3.8*	22.8 ± 4.9*
p value (ANOVA)	< 0.0001	< 0.0001	< 0.0001

*$p < 0.05$ compared with baseline and placebo. †$p < 0.05$ compared with placebo. Values presented are mean value ± SD or p value. ANOVA = analysis of variance; HR × SBP = heart rate–systolic blood pressure product ($\times 10^3$).

Figure 1. Effects of increasing theophylline concentrations on the time to onset of significant ST segment depression. Data are presented as mean value ± SD. *$p < 0.05$ compared with baseline and placebo.



JACC Vol. 22, No. 4
October 1993:1155–8

Table 3. Effect of Varying Doses of Intravenous Theophylline at Peak Exercise in 11 Study Patients

	Time (min)	Oxygen Uptake (mg/kg per min)	HR × SBP	Max ST Depression (mV)
Baseline	6.9 ± 2.6	17.4 ± 3.0	22.8 ± 3.4	0.20 ± 0.08
Placebo	7.3 ± 2.5	17.4 ± 4.0	22.0 ± 3.5	0.24 ± 0.08
Low	7.8 ± 2.4*	18.8 ± 4.1	24.4 ± 4.3	0.24 ± 0.09
Medium	8.0 ± 2.4†	18.9 ± 4.1	25.1 ± 4.1†	0.21 ± 0.09
High	8.3 ± 2.2†	19.4 ± 3.5†	25.8 ± 4.3†	0.19 ± 0.07‡
p value (ANOVA)	< 0.0001	< 0.003	< 0.0001	< 0.03

*$p < 0.05$ compared with baseline. †$p < 0.05$ compared with baseline and placebo. ‡$p < 0.05$ compared with placebo and low concentration. Values presented are mean value ± SD or p value. Max = maximal; other abbreviations as in Table 2.

heart rate–systolic blood pressure product at the onset of ischemia was increased with theophylline, a finding that suggests that the drug can increase the threshold for myocardial ischemia, even at low concentrations. Although not part of this study, isolated improvement of the ischemic threshold may correspond to a therapeutic benefit in patients with ambulatory ischemia (19,20). Increasing serum concentrations of theophylline were mirrored by further improvements in exercise tolerance. The highest concentration appeared to add a slight additional anti-ischemic benefit over the moderate level and was without significant adverse effect.

Competitive antagonism. With in vitro models, the antagonism of adenosine by theophylline appears to be competitive (21), a result that may explain the concentration-response gradient of theophylline found in the present study. It is unknown whether still higher concentrations would produce a greater effect on the outcomes of exercise. However, caution would be warranted in light of potential theophylline toxicity at higher blood levels (22). The onset of angina pectoris was not affected by theophylline in the present study. However, the presence of angina with exercise was not a study entry criterion and occurred in only 40% of patients, an inadequate number for evaluation. In previous studies (2–6) with a greater number of patients demonstrating angina, theophylline was shown to delay the onset of exercise-induced angina.

Conclusions. Administration of varying concentrations of theophylline before exercise testing resulted in a concentration-dependent decrease in myocardial ischemia. The magnitude of anti-ischemic benefit created by intravenous theophylline in this study was substantial, producing an 11% to 38% increase in the time to onset of myocardial ischemia over the concentration range tested. This improvement compares favorably with maximized therapeutic regimens with traditional anti-ischemic medications (23). These beneficial effects were not associated with serious side effects; thus, theophylline is a promising addition and alternative to traditional agents for the management of myocardial ischemia.

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