Differential antagonism of cardiac actions of adenosine by theophylline


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Abstract

Objective: To determine the relative sensitivity of cardiac A₁ and A₂ adenosine receptor-mediated effects to antagonism by theophylline in man. Methods: Baseline measurements of the A-H interval (A₁-adenosine receptor-mediated effect) and coronary blood flow (A₂-adenosine receptor-mediated effect) were made in 10 patients with angiographically normal coronary arteries. Adenosine was then administered as a continuous intravenous infusion followed by a rapid intravenous bolus, and measurements repeated. Theophylline (5 mg/kg i.v.) was then administered, and the adenosine infusion repeated. To corroborate the results found in man, the cardiac A₁ and A₂ adenosine receptor-mediated effects were measured in guinea pig isolated hearts exposed to increasing concentrations of adenosine, in the absence and presence of theophylline (60 μM). Results: Compared to baseline, adenosine infusion and bolus caused significant prolongation of the A-H interval (109 ± 41 vs. 116 ± 44 vs. 168 ± 57 ms, respectively), and increase in coronary blood flow (46 ± 37 vs. 86 ± 71 vs. 172 ± 98 ml/min, respectively). Theophylline abolished the prolongation of the A-H interval during adenosine infusion and bolus (99 ± 36 and 107 ± 44 ms, respectively), yet had minimal effect on the increase in coronary blood flow (63 ± 51 and 136 ± 121 ml/min, respectively). In guinea pig isolated hearts, theophylline was shown to significantly antagonize the A₁-adenosine receptor-mediated effects only when the concentrations of adenosine were ≤ 1.0 μM. Conclusions: In man, theophylline completely antagonizes the A₁-adenosine receptor-mediated prolongation of the A-H interval, but has minimal effect on the A₂-receptor-mediated coronary vasodilation, particularly when adenosine concentrations exceed 1.0 μM.

Keywords: Adenosine; Adenosine receptor; Theophylline; Purinergic receptors; Atrioventricular node; Coronary circulation; Guinea pig; heart; Human

1. Introduction

Theophylline has been used clinically to reverse the undesirable cardiac effects of endogenous and exogenously-administered adenosine, such as AV block and chest pain. The cardiac effects of adenosine are mediated through at least two specific cell surface adenosine receptors, A₁ and A₂ [1]. A₁-adenosine receptors are present on cardiomyocytes and depress sinoatrial (SA) and atrioventricular (AV) nodal conduction, whereas A₂-adenosine receptors are present on vascular endothelial and smooth muscle cells and mediate coronary vasodilation [1]. In vitro animal studies have shown that theophylline is a competitive, non-selective adenosine antagonist [2]; however, the distribution of cardiac A₁ and A₂-adenosine receptors and their respective affinity for adenosine may impact on the selectivity of theophylline antagonism in vivo. The main objective of the present study was to determine the relative sensitivity of cardiac A₁- and A₂-adenosine receptor-mediated effects to antagonism by theophylline in man. Additionally, a series of animal experiments was performed in order to corroborate the observations made in man as well as to further define the mechanism of any differential action of theophylline on the cardiac A₁- and A₂-receptor-mediated adenosine effects.

2. Methods

2.1. Human studies

2.1.1. Patient population

Patients recruited for participation in this study were scheduled for cardiac catheterization for evaluation of...
chest pain, and determined during coronary angiography to have normal or minimally diseased (≤ 30% stenosis) coronary arteries. All patients gave informed consent for participation in this research prior to the diagnostic cardiac catheterization. The research protocol used was reviewed and approved by the University of Florida Institutional Review Board and Gainesville Veterans Affairs Hospital research review subcommittee, and conforms with the principles outlined in the Declaration of Helsinki.

2.1.2. Methods

After diagnostic catheterization and angiography, a 6-French quadripolar catheter was advanced through a 7-French introducer placed in the femoral vein and positioned across the tricuspid valve in the region of the His bundle. This catheter was then manipulated until a clearly identifiable His bundle deflection was recorded. The His bundle electrogram was recorded continuously throughout the study. An 8-French guiding catheter was advanced into the left coronary ostium. Through this catheter, a 3-French coronary velocity Doppler catheter (NuMed) was advanced into the left anterior descending coronary artery. 10,000 units of heparin was administered intravenously to prevent thrombus formation on the Doppler catheter. The Doppler catheter was then connected to a DC-101 velocimeter (Millar Instruments, Houston, TX) to obtain the mean and phasic velocity signals. Before beginning the protocol, the range gate was adjusted and catheter position manipulated until an optimal blood flow velocity signal was obtained. Doppler catheter position was then kept constant throughout the protocol. The reliability and use of this velocity catheter to measure coronary blood flow velocity in humans has been reported previously [3,4]. The electrophysiologic and hemodynamic parameters were monitored throughout the study. After all instrumentation was completed, baseline measurements of the atria-to-His bundle interval (A-H), His bundle-to-ventricle interval (H-V), sinus cycle length (SCL), arterial pressure, and coronary blood flow velocity (CBFV) measurements were made. After all baseline measurements were obtained, adenosine (Adenocard®, Fugisawa) was infused at a rate of 80 µg/kg/min and increased until an approximate two-fold increase in the mean coronary blood flow velocity was achieved. Following each dosing change of the continuous infusion of adenosine, a 3-min period was allowed in order to achieve the steady state. Measurements of the A-H and H-V intervals, sinus cycle length, coronary blood flow velocity and arterial pressure were then made. The patients were also questioned about the emergence of symptoms such as chest pain or shortness of breath. In order to produce a significant prolongation of the A-H interval and maximal coronary vasodilation, 3 mg of adenosine was given as a bolus injection via the femoral vein introducer, and the measurements and symptoms experienced at peak effect were recorded, after which the adenosine infusion was discontinued. Theophylline was then administered at 5 mg/kg i.v. over a 5-min period. The continuous infusion and bolus injection of adenosine were then repeated and measurements of the electrophysiologic and hemodynamic parameters made. The angiographic coronary artery diameter immediately distal to the Doppler catheter was measured using electronic calipers. Using the measured coronary artery diameter and the peak CBFV, coronary blood flow for each intervention was calculated and compared.

2.2. Animal studies

Experiments were performed in isolated hearts obtained from adult guinea pigs (Hartley) of either sex weighing 250–300 g. This animal species was chosen for experimentation due to a close analogy with man as regards cardiac adenosine receptor-mediated effects [5]. This part of the investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

2.2.1. Chemicals

Adenosine and theophylline were purchased from Sigma Chemical Co. (St. Louis, MO). Xanthine amine congener (XAC), a potent, non-selective adenosine receptor antagonist, was purchased from Research Biomedical Inc. (Natick, MA) A 10 mM stock solution of adenosine, XAC, and theophylline was prepared in dimethylsulfoxide (DMSO). The final concentration of DMSO in the perfusion fluid was 0.5% v/v or less which is known to have no effect on the stimulus-to-His bundle interval prolongation (unpublished data).

2.2.2. Experimental preparation

The animals were anesthetized with methoxyflurane and killed by cervical dislocation. The hearts were quickly removed and rinsed in ice-cold Krebs-Henseleit solution. After cannulating the aorta, the hearts were retrogradely perfused at a constant flow rate of 10 ml/min. The perfusate was an oxygenated Krebs-Henseleit solution with the following composition (mM): NaCl 117.9, KCl 4.5, CaCl2 2.5, MgSO4 1.18, KH2PO4 1.18, pyruvate 2.0, glucose 5.5, Na2EDTA 0.57, ascorbic acid 0.007, and NaIICO3 25.0. The solution was oxygenated with 95% O2/5% CO2 gas, temperature maintained at 35.0 ± 0.5°C, and pH maintained at 7.30–7.40. The sinoatrial nodal region and part of the right atrium were excised to facilitate pacing of the heart and exposure of the AV node region. An unipolar electrode was positioned in the AV node region to record the His bundle electrogram (HBE). The HBE was filtered and amplified using a differential amplifier (Tektronix, Beaverton, OR), and displayed on a dual beam storage oscilloscope (Tektronix). The hearts were electrically paced via a bipolar electrode placed on the left atrium at a constant cycle length of 300 ms. An interval generator (model 1830, WPI, New Haven, CT) was used to deliver square-wave pulses of 3 ms duration.
with an amplitude of at least twice the threshold intensity. As the negative dromotropic effect of adenosine is confined to the proximal part of the AV node, the stimulus-to-ES interval was used as a measure of the delay in AV nodal conduction. The S-H interval was measured directly from the oscilloscope display at a sweep speed of 10 ms/cm. The S-H interval was also measured using an on-line data acquisition program (Snapshot storage scope, HEM data, Southfield, MI). After completing the dissection and instrumentation, the hearts were allowed to equilibrate for 30 min before data collection.

The coronary perfusion pressure (CPP, mm Hg) was monitored throughout the experiment using an on-line Gould Statham P23 ID pressure transducer connected to the perfusion line using 3-way stopcocks. The mean pressure was recorded on a 4-channel Gould strip-chart recorder. Because the hearts were perfused at constant flow, the coronary conductance (ml/min/mmHg) was calculated as the ratio between the coronary perfusion rate (10 ml/min) and the perfusion pressure (mmHg).

All experimental interventions were preceded and followed by measurement of S-H interval and coronary perfusion pressure. If the pre- and post-intervention values differed by more than 15%, the data were discarded. Whenever the interventions caused second-degree AV block, the maximal stable S-H interval prior to the onset of the AV block was used for analysis. Effect of all interventions were determined during steady state, generally requiring a 5-min infusion time. Drug solutions were infused into the perfusion line at different flow rates via a Harvard syringe infusion pump to achieve desired perfusate concentrations.

2.2.3. Protocols

In 8 isolated perfused hearts, the effect of theophylline and XAC on the negative dromotropic and coronary vasodilatory effects of adenosine (A1- and A2-receptor-mediated effects, respectively) were studied. In each heart, the baseline S-H interval and coronary perfusion pressure were measured 30 min after the hearts had been instrumented. The measurements were then made continuously throughout the experiment. Adenosine (3 μM) was infused for a period of 5 min to achieve a steady-state effect. The S-H interval and coronary perfusion pressure were measured. A 60 μM solution of theophylline was then infused along with adenosine for a duration of 5 min. This was followed by infusion of 5 μM solution of XAC along with adenosine until a steady state was reached. The corresponding S-H intervals and coronary perfusion pressures were measured continuously throughout the experiment.

In 5 guinea pig isolated perfused hearts, the effect of theophylline on the negative dromotropic and coronary vasodilatory effects of adenosine (A1- and A2-receptor-mediated effects, respectively) were studied. In each heart, the baseline S-II and coronary perfusion pressure were measured after a 30-min period of equilibrium. After recording baseline coronary perfusion pressure and S-H interval, adenosine was infused at increasing rates to achieve perfusate concentrations of 0.005, 0.05, 0.5, 1.0, 2.0, and 3 μM in that order. The corresponding S-H intervals and coronary perfusion pressures were measured continuously and a control adenosine concentration-responses was established for both the A1- and A2-receptor-mediated effects of adenosine. After a 30-min washout of adenosine, theophylline (60 μM) was infused until a steady state was reached. Adenosine infusion was repeated in an identical manner in the presence of a continuous infusion of theophylline (60 μM) and the adenosine concentration-response was established in the presence of theophylline. In this isolated heart preparation, up to 3 concentration-response curves to adenosine can be obtained without noticeable evidence of deterioration or diminished responsiveness to adenosine.

2.3. Data analysis

All values are expressed as mean ± standard deviation. The Student's t-distribution for paired data was used for analysis of paired data, using the Bonferroni correction. Statistical analysis of multiple comparisons among control and interventions were made using a two-way analysis of variance (ANOVA). Scheffe's F-test was used when multiple post-hoc comparisons were performed. Differences between the group means, control versus intervention, were considered significant at P < 0.05.

3. Results

3.1. Human study

Ten patients (9 men, 1 woman), aged 31–68 (mean 54 years), were recruited for participation in this study. The protocol was successfully completed in all 10 patients, and no adverse events or complications were experienced by any patient during administration of adenosine or after theophylline.

3.1.1. Pre-theophylline

The steady-state effect of the continuous intravenous infusion of adenosine was achieved after a 5-min infusion at a mean dose of 88 ± 10 μg/kg/min. The continuous infusion of adenosine caused an increase in the coronary blood flow (46 ± 37 to 86 ± 71 ml/min, P ≤ 0.05), but had no significant effect on the A-H interval, systolic blood pressure, or sinus cycle length as compared to the baseline (Table 1). When additional adenosine (3 mg) was administered as an intravenous bolus, a significant prolongation of the A-H interval (116 ± 44 to 168 ± 57 ms, P ≤ 0.05) and a further increase in the coronary blood flow (86 ± 71 to 172 ± 98 ml/min, P ≤ 0.05) as compared to adenosine infusion alone was observed (Table 1). Like-
Table 1
Comparison between A1- and A2-receptor-mediated cardiovascular effects of adenosine and theophylline

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Infusion</td>
<td>Infusion + Bolus</td>
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<tr>
<td>Pre-theophylline</td>
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<tr>
<td>A-H (ms)</td>
<td>109 ± 41</td>
<td>116 ± 44</td>
<td>168 ± 57 *</td>
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<tr>
<td>CBF (ml/min)</td>
<td>46 ± 37</td>
<td>86 ± 71 *</td>
<td>172 ± 98 *</td>
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<tr>
<td>SBF (mmHg)</td>
<td>136 ± 33</td>
<td>130 ± 33</td>
<td>110 ± 30 **</td>
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<tr>
<td>SCL (ms)</td>
<td>846 ± 158</td>
<td>833 ± 156</td>
<td>965 ± 141</td>
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<td>Post-theophylline</td>
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<tr>
<td>A-H (ms)</td>
<td>98 ± 35</td>
<td>99 ± 36 1</td>
<td>107 ± 44 2</td>
</tr>
<tr>
<td>CBF (ml/min)</td>
<td>50 ± 33</td>
<td>63 ± 51</td>
<td>136 ± 121 **</td>
</tr>
<tr>
<td>SBF (mmHg)</td>
<td>129 ± 26</td>
<td>131 ± 28</td>
<td>114 ± 25 *</td>
</tr>
<tr>
<td>SCL (ms)</td>
<td>750 ± 291</td>
<td>871 ± 200</td>
<td>812 ± 179</td>
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Values are mean ± standard deviation. Continuous i.v. infusion of adenosine was at a mean rate of 88 μg/kg/min. The i.v. bolus of adenosine was 3 mg. Changes in A-H and SCL are A1-mediated effects, whereas changes in CBF and SBF are A2-mediated effects. A-H = atrial-His interval; CBF = coronary blood flow; SBF = systolic blood pressure; SCL = sinus cycle length.

A trend was noted toward prolongation of the sinus cycle length following the adenosine bolus, but did not reach statistical significance (Table 1).

A difference in receptor responsiveness to adenosine was observed. The A2-receptor-mediated effect was significantly greater than that of the A1-receptor-mediated effect during both the continuous infusion and infusion plus bolus injection of adenosine (Fig. 1, Panel A). Additionally, as summarized in Table 2, the duration of the adenosine-induced increase in the mean CBFV (23 ± 10 s) was significantly longer than the adenosine-induced prolongation of the A-H interval (9 ± 6 s).

3.1.2. Post-theophylline
Theophylline alone (5 mg/kg infused over 5 min i.v.) caused a small, but non-significant, decrease in the A-H interval (98 ± 35 vs. 109 ± 41 ms) and sinus cycle length (750 ± 291 vs. 846 ± 158 ms) when compared to baseline. Likewise, theophylline, of itself, caused no change in the coronary blood flow or systolic blood pressure. However, in the presence of adenosine, theophylline completely antagonized the prolongation of the A-H interval noted following bolus administration of adenosine (Table 1). In comparison, theophylline only blunted but did not completely antagonize the adenosine-mediated increase in coronary blood flow, and had no effect on the decline in systolic blood pressure following the adenosine bolus. These results are summarized in Table 1. This differential effect of theophylline to antagonize the adenosine receptor-mediated effects on A-H interval and coronary blood flow is illustrated in Fig. 1, Panel B.

This observation is further supported by comparing the effect of theophylline on the duration of both adenosine receptor-mediated effects following the 3 mg adenosine bolus (Table 2). As compared to baseline, the duration of the adenosine-induced A-H interval prolongation was essentially eliminated (89% reduction) by theophylline (9 ± 6 vs. 1 ± 2 s, P < 0.05); whereas the duration of increase in mean CBFV was reduced by only 35% (23 ± 10 vs. 15 ± 6 s, P < 0.05).

3.1.3. Allogenic effects of adenosine
Eight of the ten patients complained of some degree of chest discomfort during the continuous infusion and/or bolus administration of adenosine. No ST-segment changes were noted on the ECG to suggest myocardial ischemia. Theophylline prevented the sensation of this discomfort in 5 of the 8 patients (62%). The 3 patients who experienced...
Fig. 2. The $A_1$- and $A_2$-adenosine receptor-mediated effects of adenosine in the absence and presence of adenosine receptor antagonists in guinea pig hearts. The $A_2$-adenosine receptor-mediated effect (S-H interval prolongation) is shown in Panel A and the $A_2$-adenosine receptor-mediated effect (increase in coronary conductance) is depicted in Panel B. With the addition of a 3 μM concentration of adenosine (ADO), the S-H interval and coronary conductance both increased significantly. Theophylline (THEO, 60 μM) completely reversed the adenosine-induced S-H prolongation, denoted by the asterisk (•) in Panel A, but caused no change in the coronary conductance. In contrast, 5 μM of xanthine amine congener (XAC), a potent and non-selective adenosine antagonist, promptly and completely reversed the increase in coronary conductance caused by adenosine, denoted by the asterisk (•) in Panel B, but caused no further change in the S-H interval.

Chest discomfort following theophylline also had some measurable $A_2$-receptor-mediated effect (i.e., A-H interval prolongation) during the adenosine bolus. In the remaining 5 patients in whom theophylline prevented the adenosine-induced pain, there was complete abolition of any measurable $A_1$-effect (e.g., prolongation of the A-H interval or sinus cycle length). No relationship between chest discomfort and the $A_2$-response (e.g., coronary blood flow) was noted.

3.2. Isolated heart experiments

The results from the isolated heart preparation parallel those obtained from human subjects. Fig. 2 (Panels A and B) illustrates the results of the first series of experiments. When the guinea pig hearts were exposed to a 3 μM concentration of adenosine, a mean 29% increase in the S-H interval (adenosine $A_1$-receptor effect) and 86% increase in coronary conductance (adenosine $A_2$-receptor effect) was observed. Following the addition of a 60 μM concentration of theophylline $^1$ to the adenosine, the S-H interval prolongation was completely abolished, whereas no effect on the coronary conductance was observed. In order to demonstrate that the increase in coronary conductance was an adenosine $A_2$-receptor-mediated effect, a more potent than theophylline and non-selective adenosine receptor antagonist, xanthine amine congener (XAC) at 5 μM concentration, was added to the perfusate. The coronary conductance then returned to baseline levels. This finding confirms that when using clinically significant concentrations of theophylline, this xanthine functions as a 'selective' antagonist for the $A_2$-receptor-mediated responses.

Fig. 3 shows the changes in the S-H interval ($A_1$-adenosine receptor effect) and coronary conductance ($A_2$-adenosine receptor effect) when the guinea pig hearts were exposed to increasing concentrations of adenosine in the absence and presence of theophylline. Adenosine caused a concentration-dependent increase in the S-H interval and coronary conductance. Theophylline (60 μM) effectively antagonized (i.e., reversed) the increase in the S-H interval, but had no significant effect on the increases in

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$^1$ This concentration of theophylline is equivalent to a plasma level of 12 μg/ml, which is a therapeutic concentration.
coronary conductance when the concentration of adenosine was \( \geq 1.0 \, \mu M \).

The \( \text{EC}_{50} \) (concentration of adenosine required to cause 50\% of maximal effect) of the \( \text{A}_1 \)- and \( \text{A}_2 \)-adenosine receptor-mediated effects in the absence and presence of theophylline were determined. The \( \text{EC}_{50} \) of \( \text{A}_2 \)-adenosine receptor-mediated effect (increase in coronary conductance) at baseline was \( 0.23 \pm 0.21 \, \mu M \), and following theophylline administration the \( \text{EC}_{50} \) was \( 1.27 \pm 1.47 \, \mu M \). The \( \text{EC}_{50} \) for the \( \text{A}_1 \)-adenosine receptor-mediated effects could not be calculated because at the concentrations of adenosine tested no A-H interval prolongation (\( \text{A}_1 \)-adenosine-mediated effect), in the presence of theophylline, was observed (Fig. 3).

4. Discussion

In this study, we demonstrate that in man adenosine elicits a greater increase in the coronary blood flow (adenosine \( \text{A}_2 \)-receptor-mediated effect) than A-H interval prolongation (adenosine \( \text{A}_1 \)-receptor-mediated effect). This differential responsiveness was observed with either continuous or bolus infusions of adenosine. Identical results were obtained in guinea pig isolated heart preparations. These observations are fully consistent with reports that the concentration of adenosine which causes maximal or near-maximal coronary vasodilation (\( \text{A}_2 \)-response) is 10-fold less than that threshold concentration required to mediate the negative dromotropic effects (\( \text{A}_1 \)-response) [2,6]. This observation may be due to differences in adenosine receptor density and/or receptor affinity for adenosine. In addition, because adenosine is so avidly taken up and metabolized by the vascular endothelium, the adenosine receptor-mediated responses to intravenous infusions or boluses of adenosine are expected to be greater at the vascular site than at the AV node based solely on the difference in adenosine concentration at these sites [6].

Radioligand binding studies of adenosine receptors revealed that theophylline has a 9-fold greater affinity for the \( \text{A}_1 \)-receptor than the \( \text{A}_2 \) [7], yet is a non-selective adenosine receptor antagonist [2,6]. This study, in both man and guinea pig hearts, provides evidence that theophylline behaves as a non-selective adenosine receptor antagonist only at low concentrations of adenosine. In the presence of high concentrations of adenosine, theophylline completely antagonizes the \( \text{A}_1 \) adenosine receptor mediated effects but only partially antagonizes the \( \text{A}_2 \)-adenosine receptor-mediated effects. That is, as the concentration of adenosine rises to levels that cause near-maximal coronary vasodilation (\( \geq 1.0 \, \mu M \)), the antagonism of the \( \text{A}_2 \)-adenosine receptor-mediated coronary vasodilation is significantly reduced or lost. The implication is that under certain conditions (i.e., maximal activation of the \( \text{A}_2 \)-receptors), theophylline primarily inhibits \( \text{A}_1 \)-adenosine receptor-mediated responses.

Theophylline has the potential to have multiple modes of action: (1) adenosine receptor antagonism, (2) inhibition of phosphodiesterase, and (3) stimulate catecholamine release. Even though we cannot exclude these other actions of theophylline, evidence suggests that, in this study, adenosine receptor antagonism is the primary mode of action. Adenosine antagonism is the only action of theophylline within or below the 'therapeutic' level for theophylline [8].

The results of the guinea pig heart experiments are in keeping with and provide the explanation for the observed differential action of theophylline on the \( \text{A}_1 \)- and \( \text{A}_2 \)-adenosine receptor-mediated effects in man (Fig. 3). These findings help explain the observations of Nahser et al. [9] and Rossen et al. [10] in which the adenosine-induced coronary hyperemia in man was not significantly altered by aminophylline. Furthermore, Heller et al. [11] found that pretreatment with theophylline (6.5 mg/kg) ameliorated adenosine-induced chest pain and heart block (\( \text{A}_1 \)-receptor-mediated effects), but preserved coronary vasodilation (\( \text{A}_2 \)-receptor-mediated effect) to a degree that allowed effective 'stress' thallium imaging. These studies suggest that the \( \text{A}_2 \)-receptor-mediated effects of adenosine are not completely antagonized by theophylline in the doses used clinically. Our data provide a mechanistic explanation for these observations.

Adenosine induced chest discomfort in the majority of our patients (8/10). Theophylline abolished this discomfort in 5 patients, an effect that appeared related to the completeness of \( \text{A}_1 \)-receptor antagonism. This finding strongly suggests that the adenosine-mediated chest discomfort is mediated through the \( \text{A}_1 \)-receptor. Recent studies from our laboratory using the highly selective \( \text{A}_1 \)-adenosine receptor antagonist, N-0861, provide additional evidence that adenosine-induced chest pain is mediated through this adenosine receptor subtype [12]. Similar conclusions have been reached using the adenosine receptor antagonist, bambiphylline [13].

Potential limitations include that the human study was performed on patients with multiple cardiac risk factors. The cardiac responses to adenosine, particularly the change in coronary blood flow, may be somewhat altered in this population. Secondly, it took approximately 30 min to complete the study in each patient. Changes in the A-H interval and CBFV may be affected by other physiologic variables such as change in vagal tone or circulating catecholamines over time. However, it is improbable that these potentially confounding factors influenced the results of the human study because the findings from guinea pig hearts were identical to that obtained in the human patients.

In summary, adenosine, when administered at various dosages, elicits a greater increase in cardiac \( \text{A}_2 \)-receptor-mediated effects than \( \text{A}_1 \)-receptor-mediated effects. In the presence of low concentrations of adenosine, theophylline functions as a non-selective adenosine receptor antagonist.
However, in the presence of concentrations of adenosine that cause maximal or near-maximal coronary vasodilation, theophylline acts as a differential adenosine receptor antagonist, thereby completely antagonizing adenosine-induced prolongation of the A-H interval and chest discomfort (A₁-receptor-mediated effects), yet only minimally attenuating the A₂-receptor-mediated coronary vasodilation.

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