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Muscular and Cardiac Adenosine-Induced Pain Is Mediated by A_1 Receptors

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Objectives. **This study attempted to establish whether bamiphylline, a selective antagonist of A_1 adenosine receptors, prevents the algogenic effects of adenosine in humans.**

Background. **Experimental findings indicate that the sympathoexcitatory response elicited by adenosine is mediated by A_1 receptors.**

Methods. **An intrailiac infusion of increasing doses (from 125 to 2,000 μg/min) of adenosine was given to 20 patients. Adenosine infusion was then repeated after intrailiac infusion of either bamiphylline or saline solution. In 14 other patients with angina, increasing doses of adenosine (from 108 to 1,728 μg/min) were infused into the left coronary artery. Adenosine infusion was then repeated after the intravenous infusion of either bamiphylline or placebo. Coronary blood flow velocity was monitored by a Doppler catheter. Data relative to pain severity are expressed as median and all other data as mean value ± 1 SD.**

Results. **Bamiphylline prolonged the time to pain onset caused by the intrailiac adenosine infusion from 444 ± 96 to 749 ± 120 s ($p < 0.001$) and reduced pain severity from 45 to 24 mm ($p < 0.01$). After placebo infusion, the time to pain onset and pain severity were similar to that of baseline (428 ± 112 vs. 430 ± 104 s, $p = 0.87$ and 44 vs. 43 mm, $p = 0.67$, respectively). Bamiphylline prolonged the time to pain onset caused by intracoronary adenosine infusion from 519 ± 128 to 603 ± 146 s ($p < 0.01$) and reduced pain severity from 58 to 28 mm ($p < 0.02$). After placebo infusion, the time to pain onset and pain severity were similar to that at baseline (542 ± 87 vs. 551 ± 79 s, $p = 0.14$ and 55 vs. 50 mm, $p = 0.61$). Maximal coronary blood flow velocities before and after bamiphylline administration were similar (47 ± 22 vs. 49 ± 24 cm/s, $p = 0.36$) as well as before and after placebo administration (40 ± 20 vs. 41 ± 20 cm/s, $p = 0.07$).**

Conclusions. **Bamiphylline reduces adenosine-induced muscular and cardiac pain but does not affect adenosine-induced coronary vasodilation. These findings indicate that at the dose used in this study, bamiphylline does not detectably block vascular A_2-receptor–mediated adenosine effects in humans, which suggests that the muscular and cardiac algogenic effects of adenosine are mediated mainly by A_1 receptors.**

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Adenosine is a mediator of ischemic pain in humans (1–3). Local muscular ischemic-like pain can be provoked by adenosine injection into the brachial (4) or iliac (5) artery. Furthermore, in patients with ischemic heart disease, intracoronary administration of adenosine elicits angina pectoris-like pain indistinguishable from their habitual anginal pain in the absence of ischemic electrocardiographic (ECG) changes (2,3,5). The cardiac effects of adenosine are due to the stimulation of two classes of extracellular receptors, subtypes A_1 and A_2 (6–8). The stimulation of A_1 receptors, present in cardiomyocytes and perivascular sympathetic nerves (8,9), causes electrophysiologic effects (10) and inhibits the neuronal release of catecholamines (8). The stimulation of A_2 receptors, present in endothelial and vascular smooth muscle cells, causes coronary vasodilation (11–14). Recent experimental investigations (15) suggest that adenosine-induced pain may be modulated by the stimulation of A_1 adenosine receptors because selective A_1 but not A_2 agonists elicit the sympathoexcitatory response caused by the intracoronary infusion of adenosine. In humans, bamiphylline, a selective antagonist of A_1 adenosine receptors (16), reduces the pain induced by intradermal injection of adenosine but not the A_2-receptor–mediated cutaneous hyperemia, thus suggesting that A_1 receptors are involved in cutaneous nociception (17).

To establish the role played by A_1 adenosine receptors in mediating the muscular pain caused by adenosine, we studied the effects of bamiphylline on pain induced by the intrailiac

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infusion of adenosine. After this preliminary study we then studied the effects of bamiphylline on cardiac pain and coronary vasodilation caused by the intracoronary infusion of adenosine.

Methods

Intrailiac study. *Patients.* A total of 20 consecutive patients (17 men, 3 women; mean age 61 ± 10 years, range 43 to 75 y) with uncomplicated stable angina who did not show any evidence of peripheral vascular disease (ankle–brachial index >1 assessed by vascular Doppler echocardiography) participated in this study. During the hospital period, calcium channel blocking and beta-adrenergic blocking agents were withdrawn 48 h before the study. Patients were also requested to abstain from xanthine-containing drugs and food and drink for at least 48 h before study. Patients with a history of glucose intolerance were excluded from the study. All patients gave written informed consent for participation in the study, which was approved by the Institutional Ethics Committee in March 1992.

Study protocol. At the end of routine cardiac catheterization, patients underwent heparinization (5,000 IU intravenously) and a randomized study of the algogenic effects of the intrailiac infusion of adenosine. In all patients adenosine was initially infused at increasing doses of 125, 250, 500, 1,000, 2,000 μg/min for periods of 3 min each into the right external iliac artery through a 5F catheter, advanced through a 7F sheath positioned in the right femoral artery. At the onset of pain, adenosine infusion was continued to complete the infusion period of that particular dose and was then stopped. After 10 min, patients were randomized to receive adenosine infusion at the same doses as those for the initial infusion after the intrailiac infusion of either injectable bamiphylline (bamiphylline hydrochloridum, 300 mg dissolved in 5 ml of 0.9% sodium chloride, Christiaens s.a., Brussels, Belgium) at a dose of 450 mg in 20 min (10 patients) or vehicle (10 patients). The time to onset of pain (in seconds from the beginning of the infusion) and maximal pain severity, assessed by using a visual analog scale, were recorded after each adenosine infusion. Arterial blood pressure, obtained through the side port of the femoral sheath, and the standard 12 ECG leads were recorded continuously throughout the study.

Intracoronary study. Fourteen patients (11 men, 3 women; mean age 55 ± 12 years) with uncomplicated stable angina pectoris and significant left coronary atherosclerosis (internal diameter reduction ≥50% by visual assessment in the proximal two-thirds of at least one major epicardial vessel) participated in this study. No patient had a previous myocardial infarction. All patients had positive exercise test results for myocardial ischemia, with horizontal or downsloping ST segment depression ≥1.0 mm, and anginal pain. Four patients had a stenosis in the left anterior descending coronary artery, eight in the proximal circumflex artery and two in both arteries. All patients were normotensive, in sinus rhythm and without evidence of heart failure, cardiomyopathy or valvular disease. Patients with a history of glucose intolerance were excluded from the study. No patient had evidence of left ventricular hypertrophy or conduction defects that could interfere with interpretation of ST segment changes, and no patient was taking digitalis. During the hospital period, calcium channel blocking and beta-blockers were withdrawn 48 h before the study. Only sublingual nitroglycerin was permitted, and a minimum of 12 h were allowed to elapse before the procedure was begun if this drug was used. All patients were also requested to abstain from xanthine-containing drugs and food and drink for at least 48 h before study. All patients gave written informed consent for participation in the study, which was approved by the Institutional Ethics Committee in January 1993.

Study protocol. On completion of the diagnostic angiograms for both coronary arteries, patients underwent heparinization (5,000 IU intravenously), and the left coronary artery ostium was recannulated with an 8F left Judkins-style Doppler-tipped angiographic catheter (Kern technique) of the appropriate size (Cordis Corporation) for continuous monitoring of coronary blood flow velocity (20-MHz pulsed Doppler velocimeter, MDV-20, Millar Instruments, Inc.). The Judkins-style Doppler-tipped catheter is an 8F polyvinylchloride catheter with a 20-MHz ultrasound crystal positioned on the inferior edge of the distal tip (18). For accurate measurements the Judkins tip angle was positioned parallel to the left main coronary artery. Patients in whom it was not possible to obtain a satisfactory tip angle to record an appropriate flow signal were excluded from the study. After obtaining an adequate and stable Doppler signal, adenosine was infused into the left main coronary artery at increasing scalar doses of 108, 216, 432, 864, 1,728 μg/min for periods of 2 min each until the appearance of pain. At the onset of pain, adenosine infusion was continued to complete the infusion period of that particular dose and was then stopped. After 10 min, patients were randomized to receive adenosine infusion at the same doses as those for the initial adenosine infusion 5 min after intravenous infusion of either injectable bamiphylline (300 mg in 20 min) (7 patients) or vehicle (7 patients). The time to pain onset (in seconds from the beginning of the infusion) and maximal pain severity assessed by using a visual analog scale were recorded after each adenosine infusion. Arterial blood pressure, obtained through the side port of the 8F femoral sheath, and the standard 12 ECG leads were continuously recorded throughout the study. The study was always completed within 60 min.

Assessment of pain. At the beginning of each adenosine infusion, patients were informed that they might develop pain or other unpleasant symptoms. This information was not repeated during adenosine infusions to avoid any potential bias. Patients were also instructed to report promptly the onset of pain and to record the maximal severity of the pain. Immediately after the test, while the patients were still in the catheterization laboratory, they were asked to report the maximal severity of pain experienced during both adenosine infusions on the same visual analog scale (19). To this end, the

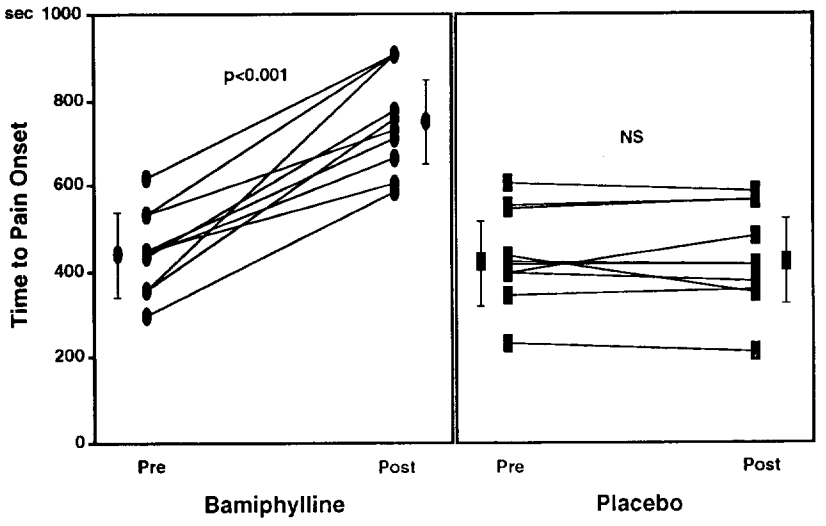

Figure 1. Effects of bamiphylline and placebo on the time to pain onset during intrailiac infusion of adenosine. Individual values and mean value ± 1 SD are shown.

100-mm scale was marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject's mark in millimeters. All subjects, but not the testing personnel, had no knowledge of the substances infused.

Statistical analysis. Statistical analysis of the hemodynamic data was performed using the Student *t* test for paired data. The Student *t* test for paired data was used also to compare the time to pain onset. Pain severity was analyzed using the Wilcoxon signed rank test because this variable does not follow a normal distribution (19). Visual analog scale data are expressed as median and interquartile ranges. The remaining data are presented as mean value ± 1 SD. For the purpose of this study, $p < 0.05$ was considered statistically significant.

Results

Intrailiac study. *Assessment of muscular pain.* All patients experienced pain localized to the right leg during the first adenosine infusion. Thirteen patients described the pain as a feeling of heaviness, three as a cramp and four as tingling. No patient reported any symptom during intrailiac bamiphylline or placebo infusion. The highest dose of adenosine given before bamiphylline was 250 μg/min in three patients, 500 μg/min in six and 1,000 μg/min in one. The highest dose of adenosine given after bamiphylline was 1,000 μg/min in four patients and 2,000 μg/min in six. After bamiphylline administration, three patients did not experience any pain at all, even during the infusion of the highest dose of adenosine. On average, bamiphylline prolonged time to pain onset from 444 ± 96 to 749 ± 120 s ($p < 0.001$); pain severity was reduced from 45 to 24 mm ($p < 0.01$). Conversely, after vehicle administration, the time to pain onset and pain severity did not change (428 ± 112 vs. 430 ± 104 s, $p = 0.87$ and 44 vs. 43 mm, $p = 0.67$, respectively) (Fig. 1 and 2). The highest dose of adenosine given before placebo was 250 μg/min in two patients, 500 μg/min in seven and 1,000 μg/min in one. The highest dose of adenosine given

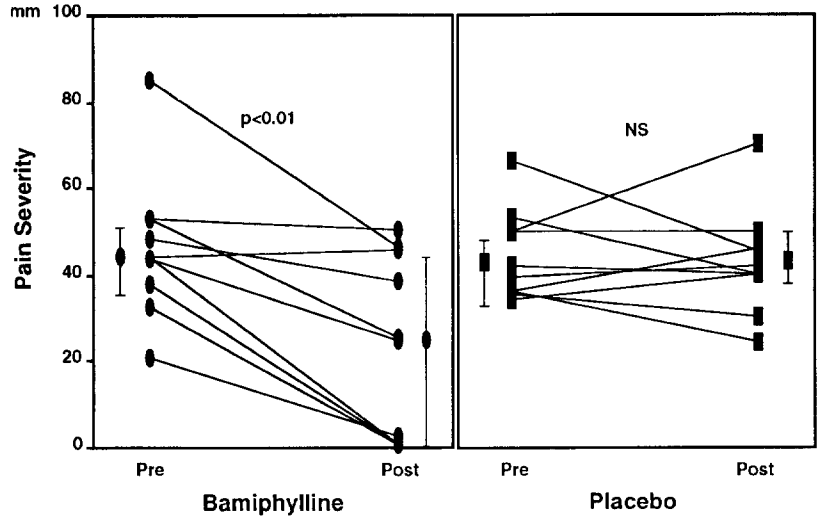

Figure 2. Effects of bamiphylline and placebo on severity of pain during intrailiac infusion of adenosine. Individual values and median value with interquartile range are shown.

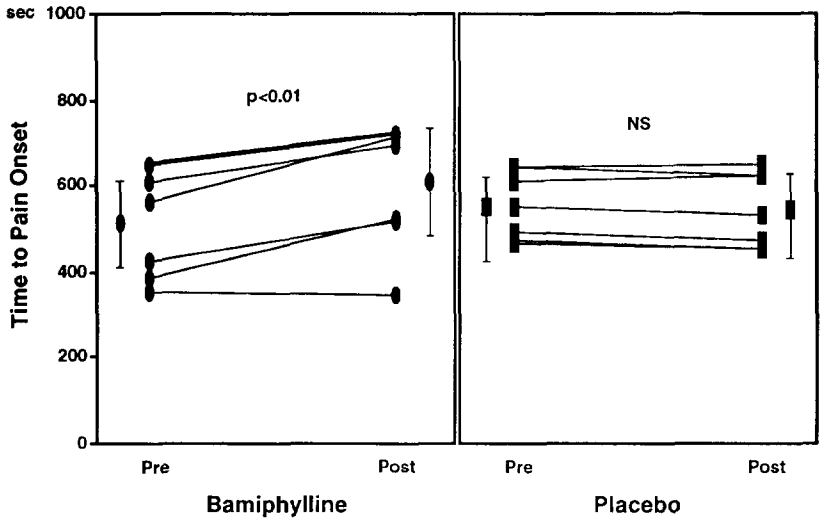

Figure 3. Effects of bamiphylline and placebo on the time to pain onset during intracoronary infusion of adenosine. Individual values and mean value ± 1 SD are shown.

after placebo was 250 μg/min in three patients, 500 μg/min in four and 1,000 μg/min in three.

Hemodynamic and ECG findings. Compared with baseline values, intraarterial infusion of bamiphylline or placebo did not produce any significant change in heart rate (70 ± 9 vs. 69 ± 10 beats/min, p = 0.20 and 68 ± 8 vs. 70 ± 7 beats/min, p = 0.17, respectively) or in mean aortic pressure (103 ± 15 vs. 99 ± 16 mm Hg, p = 0.06 and 102 ± 10 vs. 103 ± 12 mmHg, p = 0.76, respectively) compared with baseline values.

Intracoronary study. *Assessment of anginal pain.* During adenosine infusion before bamiphylline or placebo administration, all patients experienced pain similar to their habitual anginal pain. During intravenous infusion of bamiphylline, two patients complained of transient dizziness not associated to hemodynamic changes. No patient reported any symptom during placebo infusion. The highest dose of adenosine given before bamiphylline was 216 μg/min in one patient, 432 μg/min in two, 864 μg/min in one and 1,728 in three. The highest dose of adenosine given after bamiphylline was 216 μg/min in one, 864 μg/min in two and 1,728 μg/min in four. After bamiphylline administration, two patients did not experience any pain at all, even when the maximal dose of adenosine was infused. On average, bamiphylline prolonged time to pain onset from 519 ± 128 to 603 ± 146 s ($p < 0.01$); pain severity was reduced from 58 to 28 mm ($p < 0.02$). By contrast, placebo administration did not affect either time to pain onset (542 ± 87 vs. 551 ± 79 s, p = 0.14) or pain severity (55 vs. 50 mm, p = 0.61) (Fig. 3 and 4). The highest dose of adenosine given before placebo was 432 μg/min in two patients, 864 μg/min in two and 1,728 μg/min in three. The highest dose of adenosine given after placebo was 432 μg/min in three patients, 864 μg/min in one and 1,728 μg/min in three.

Coronary flow velocity findings. Compared with baseline values, intravenous infusion of bamiphylline or placebo did not produce any significant change in mean baseline coronary blood flow velocities (10 ± 7 vs. 9.5 ± 6 cm/s, p = 0.32 and

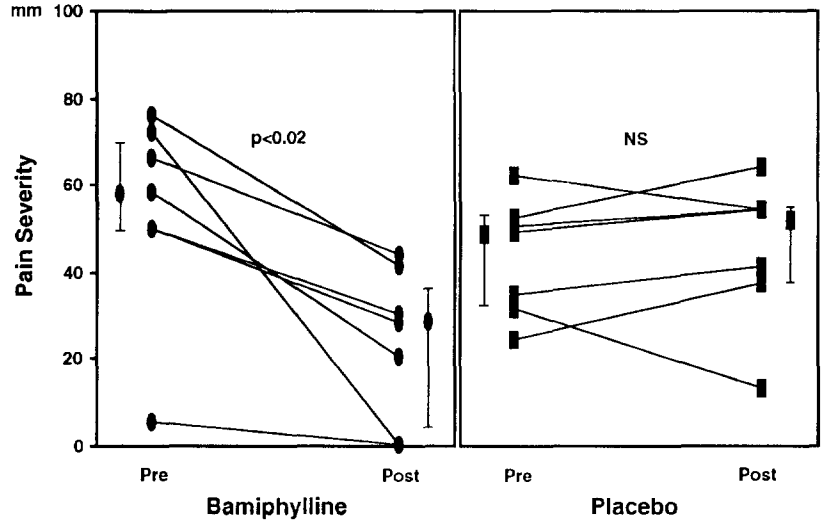

Figure 4. Effects of bamiphylline and placebo on severity of pain during intracoronary infusion of adenosine. Individual values and median value with interquartile range are shown.

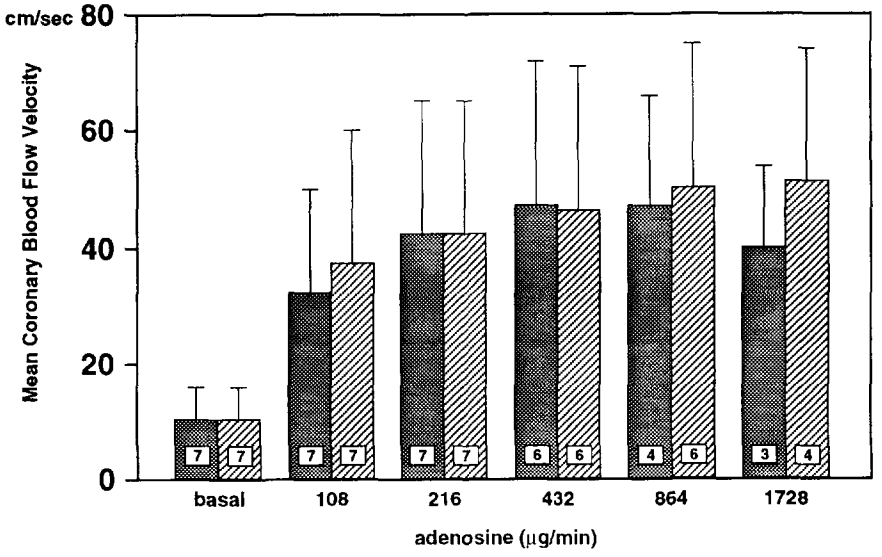

Figure 5. Effects of bamiphylline on coronary blood flow velocity during intracoronary infusion of adenosine. **Crosshatched bars** = before bamiphylline; **hatched bars** = after bamiphylline. **Numbers in boxes** at the **bottom of bars** indicate number of patients who achieved that particular adenosine dose. **Lines** = SD.

10 ± 6 vs. 9.2 ± 6 cm/s, p = 0.36, respectively). Administration of bamiphylline and placebo did not affect the increase in mean coronary blood flow velocities when increasing doses of intracoronary adenosine were infused (Fig. 5 and 6). Coronary blood flow velocities at the maximal adenosine dose that was tolerated both before and after bamiphylline were similar (47 ± 22 vs. 49 ± 24 cm/s, p = 0.36). Coronary blood flow velocities at the maximal adenosine dose that was tolerated both before and after placebo were also similar (40 ± 20 vs. 41 ± 20 cm/s, p = 0.07).

Hemodynamic and ECG findings. Intravenous infusion of bamiphylline or placebo did not produce any significant change in heart rate (68 ± 7 vs. 68 ± 8 beats/min, p = 0.21 and 68 ± 5 vs. 65 ± 7 beats/min, p = 0.14, respectively) or in systolic aortic pressure (135 ± 18 vs. 132 ± 10 mm Hg, p = 0.18 and 131 ± 12 vs. 132 ± 8 mm Hg, p = 0.22, respectively) or diastolic aortic pressure (77 ± 6 vs. 74 ± 4 mm Hg, p = 0.17 and 81 ± 9 vs. 80 ± 5 mm Hg, p = 0.24, respectively) compared with baseline values. During adenosine infusion, no patient developed ECG signs of myocardial ischemia.

Discussion

Present study. This study shows that in humans, bamiphylline, a selective antagonist of A_1 adenosine receptors, reduces both the muscular pain provoked by intrailiac adenosine infusion and the cardiac pain provoked by intracoronary adenosine infusion; yet, it does not affect adenosine-induced coronary vasodilation. These findings indicate that in humans, bamiphylline, at the dose used in this study, does not detectably block A_2 adenosine receptors and strongly suggest that the

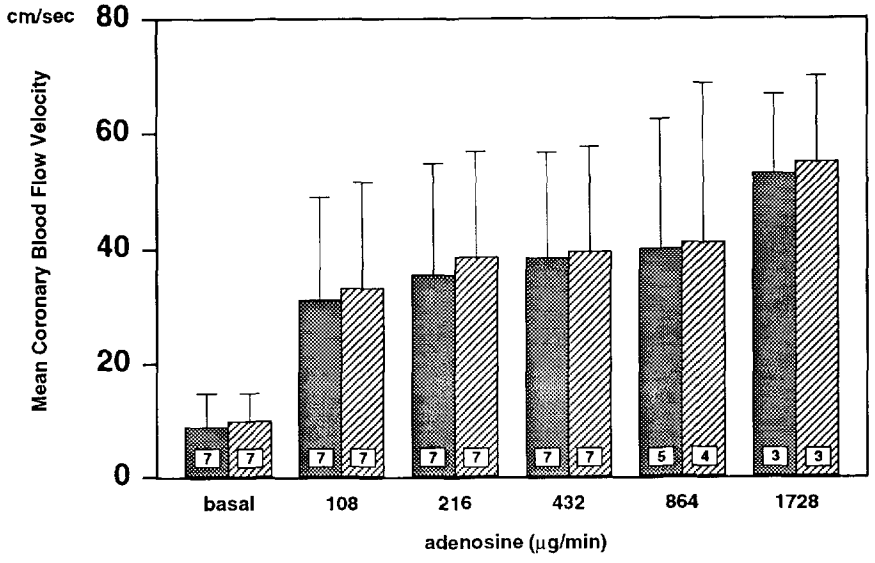

Figure 6. Effects of placebo on coronary blood flow velocity during intracoronary infusion of adenosine. **Crosshatched bars** = before placebo; **hatched bars** = after placebo. **Numbers in boxes** at the **botton of bars** indicate number of patients who achieved that particular adenosine dose. **Lines** = SD.

muscular and cardiac algogenic effects of adenosine are mainly mediated by A_1 receptors.

Bamiphylline is the most selective A_1-adenosine receptor antagonist clinically available in Europe. In crude synaptic membranes prepared from rat brain, it displaces radioligands from A_1 adenosine receptors with a potency similar to that of 8-phenil-theophylline, whereas it has a much lower potency on A_2 adenosine receptors (16). This results in a high degree of A_1-receptor selectivity, indicated by a A_2/A_1 ratio of 596. At the dose used in the present study, the mean plasma concentration of bamiphylline ($\sim 0.5 \cdot 10^{-5}$ mol/liter) displaces 80% of H-3 diethyl-8-phenilxanthine (an antagonist of A_1 adenosine receptors), 50% of H-3 cyclohexyladenosine (an agonist of A_1 adenosine receptors) but only 5% of H-3 *N*-ethylcarboxamidoadenosine (an agonist of A_2 adenosine receptors). Thus, at the dose used in this study, bamiphylline results in a rather selective blockade of A_1 adenosine receptors. To our knowledge the A_1-receptor bamiphylline selectivity has never been directly compared with that of some of the newest xanthine A_1 antagonists that have been developed in recent years. However, the previous observation that bamiphylline does not suppress adenosine-induced cutaneous vasodilation, which is known to be mediated by vascular A_2 receptors, and the present observation that bamiphylline does not inhibit adenosine-induced coronary vasodilation, suggest that the selectivity of bamiphylline for A_1 receptors, at the dose used in these investigations, is preserved.

Previous studies. Experimental studies (15,20–22) have indicated that adenosine activates afferent nerves, and several clinical studies (1–5) have shown that adenosine is an important mediator of muscular and ischemic pain. In patients with coronary artery disease, theophylline, a nonselective antagonist of adenosine receptors, reduces the severity of the anginal pain induced by intracoronary infusion of adenosine (2). Theophylline also completely abolishes adenosine-induced leg pain (23). However, theophylline is a competitive nonselective antagonist of both A_1 and A_2 adenosine receptors (24), and therefore which receptor subtype mediates the algogenic effects of adenosine cannot be determined. Previous studies have suggested that the vascular and algogenic effects of adenosine might be mediated by different receptors. Indeed, monitoring of coronary sinus blood oxygen saturation, during intracoronary infusion of adenosine, showed that the doses that cause chest pain are higher than those that cause maximal coronary dilation (2,25). More recent experimental investigations suggest that adenosine-induced pain might be mediated by the A_1-adenosine receptor subtype because in dogs with sinoaortic denervation and vagotomy, adenosine has been shown to activate cardiac sympathetic afferent fibers; this sympathoexcitatory reflex is elicited by selective A_1 but not A_2 adenosine agonists (15). Finally, in humans, bamiphylline reduces the pain induced by intradermal injection of adenosine but not the A_2-receptor–mediated adenosine-induced cutaneous hyperemia, thus suggesting that A_1 receptors are involved in cutaneous nociception (17). The present study confirms and expands these observations by showing that in humans, the muscular and cardiac algogenic effects of adenosine also are mediated by A_1 adenosine receptors.

Study limitations. Critical to our study was the evaluation of cardiac pain. The assessment of pain using a visual analog scale represents a well established and accepted method for evaluation of pain perception (19). The reliability of this method in assessing pain severity is supported by the observation that in this study adenosine-induced pain severity was similar before and after placebo administration, similar to results reported in a previous study (5). In the present study, the testing personnel had knowledge of the infused materials. However, the greatest care was taken to follow a very rigid protocol to avoid any potential bias. To this end, all patients were reminded that they could develop symptoms at the beginning of each infusion only, and this information was not repeated during the infusion. Furthermore, the patients themselves, who had no knowledge of the infused substances, marked the visual analog scale. Finally, we failed to find any effect of bamiphylline on the response of coronary blood flow to adenosine. The power of the study in the assessment of this effect of bamiphylline was low mainly because of the small number of patients. However, even if an increased number of patients proved that the observed small difference is statistically significant, it would not be relevant from a biologic and clinical standpoint. Furthermore, in the same patient bamiphylline significantly reduced the algogenic effects of adenosine, thus suggesting that antagonism by bamiphylline of the algogenic effects of adenosine is more relevant than the possible antagonism of the effects of adenosine on the coronary circulation.

Conclusions. In patients with angina pectoris, bamiphylline, a selective antagonist of A_1 adenosine receptors, reduces both muscular pain caused by intrailiac adenosine infusion and cardiac pain induced by intracoronary adenosine infusion. These findings indicate that in humans, bamiphylline, at the dose used in this study, does not detectably block vascular A_2-receptor–mediated adenosine effects and suggest that the muscular and cardiac algogenic effects of adenosine are mainly mediated by A_1 receptors.

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