Effect of N-0861, a Selective Adenosine A1 Receptor Antagonist, on Pharmacologic Stress Imaging with Adenosine

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N6-endonorborman-2-yl-9-methyladenine (N-0861) is a drug which inhibits the A1 adenosine receptor subtype. One proposed use for N-0861 is to eliminate A1 receptor-mediated side effects such as A-V heart block and possibly angina in patients undergoing pharmacologic stress with adenosine. The goal of this study was to determine whether N-0861 has any crossover effect on the A2 vasodilatory action of adenosine or on ^{201}Tl uptake which would adversely affect imaging of coronary stenoses. **Methods:** In eight dogs with critical left anterior descending (LAD) stenoses, we compared the hemodynamic response to intravenous adenosine (250 μg/kg/min) before and after N-0861 administration. LAD and left circumflex (LCx) coronary flows were measured ultrasonically and regional blood flow was assessed using microspheres. Thallium-201 (18.5–37.0 MBq) was injected during adenosine hyperemia while N-0861 was present. Imaging of heart slices was performed and defect magnitude was calculated as LAD:LCx count ratios from regions of interest (ROIs) on images. Regional ^{201}Tl activity and microsphere flow were determined by gamma well counting. **Results:** There was no change in mean heart rate, arterial and left atrial pressures, +dP/dt, and ultrasonically measured LAD and LCx coronary flows upon N-0861 administration. In addition, adenosine evoked a similar hemodynamic response after N-0861. There was also no change in coronary flow in the critically stenotic LAD but LCx flow tripled to 106 ± 14 ml/min ($p < 0.01$). **Conclusion:** These data indicate that N-0861 pretreatment does not adversely affect adenosine A2 receptor-mediated vasodilation and has no effect on the detection of a critical coronary stenosis by ^{201}Tl imaging. Thus, the pretreatment strategy may prove useful for the elimination of A1 receptor-mediated side effects during pharmacologic stress imaging with adenosine.

Key Words: adenosine; adenosine receptors; pharmacologic stress imaging

J Nucl Med 1995; 36:270–275

Received Apr. 6, 1994; revision accepted Sept. 7, 1994.

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Pharmacologic stress imaging has become an important tool for detecting coronary artery disease in patients unable to exercise. The most common pharmacologic stress agent used in this setting is dipyridamole. Dipyridamole exerts its vasodilatory effect indirectly by blocking the uptake of endogenous adenosine, a potent coronary vasodilator. However, because dipyridamole has a relatively long biologic half-life, reversal of side effects often requires the administration of aminophylline, a nonselective adenosine receptor antagonist.

Recently, adenosine has been administered directly in patients to achieve pharmacologic vasodilation (*1–4*). The major advantage of adenosine in this setting is its rapid biological half-life of less than 2 sec (*5*). If severe side effects develop during adenosine administration, the infusion can be stopped and the side effects will usually disappear rapidly. Two common side effects reported during adenosine administration are atrioventricular (A-V) block and chest pain (*1–4*). Although second or third degree A-V block is infrequent and usually transitory, the possibility of complete A-V block, albeit rare, cannot be discounted. Whereas the vasodilatory action of adenosine is due to its stimulation of an A2 receptor subtype, the negative inotropic, chronotropic and dromotropic effects of adenosine are due to the stimulation of an A1 receptor subtype (*6*). One of the more severe side effects experienced by approximately one third of patients during adenosine infusion is chest pain (*4*). The mechanism for pain induction is probably not adenosine-induced ischemia, since chest pain is also common in patients with normal coronary arteries during adenosine administration (*7,8*).

N6-endonorbornan-2-yl-9-methyladenine (N-0861) is a new selective antagonist of the A1 adenosine receptor subtype, the pharmacokinetics of which have been previously described in detail (*9,10,12*). Several preclinical studies determined that N-0861 selectively antagonized adenosine A1 receptor-mediated negative inotropism, dromotropism and chronotropism without affecting adenosine A2 receptor-mediated vasodilation (*9–11*). N-0861 also selectively antagonized adenosine A1 receptors in humans (*12,13*). In a recent trial, N-0861 (250 μg/kg, intravenously) prevented the A-V conduction delay and the chest pain, but had no

effect on the coronary vasodilation induced by adenosine infusion (*13*). These results suggest that N-0861 may be a clinically useful adjunctive therapy to prevent these undesirable A1 receptor-mediated actions in patients undergoing pharmacologic stress with adenosine. However, the effect of N-0861 on ^{201}Tl imaging of abnormal perfusion distal to a coronary stenosis during pharmacologic stress has not been determined. In addition, although aminophylline, a nonspecific adenosine receptor antagonist, is frequently administered to reverse side effects of dipyridamole vasodilation, and is occasionally used with adenosine vasodilation, it is unknown whether there might be an adverse hemodynamic interaction between N-0861 and aminophylline.

Thus, the goals of the current study were to determine if N-0861 has any direct or indirect effect on adenosine stress ^{201}Tl imaging which might affect the detection of a coronary stenosis and whether there is any adverse interaction between N-0861 and aminophylline. If pretreatment with N-0861 had no effect on the extent and severity of adenosine-induced ^{201}Tl perfusion abnormalities, then perhaps the drug would be clinically useful to administer prior to adenosine infusion to prevent undesirable A1 mediated effects of adenosine such as A-V block or chest pain (*1–4,13*).

METHODS

Eight fasted adult mongrel dogs (mean weight = 27.8 kg) were anesthetized with Innovar (0.08 ml/kg) and sodium pentobarbital (6.6 mg/kg), intubated and ventilated on a respirator (Harvard Apparatus, South Natick, MA) with 4 cm of positive end-expiratory pressure. Arterial blood gases were monitored throughout each experiment (model 158, Ciba-Corning, Medfield, MA) and pH, PO_2, PCO_2 and HCO_3 levels were maintained at physiologic levels. Both femoral veins were cannulated with 8F polyethylene catheters for the administration of N-0861, adenosine, ^{201}Tl and aminophylline. Additional Innovar anesthetic was also administered intravenously as needed. The right and left femoral arteries were then isolated and cannulated with similar 8F catheters to serve as sites for the collection of arterial blood for blood gas determinations and microsphere reference samples and to monitor systemic arterial pressure. Next, the left main carotid artery was isolated and cannulated with a Millar high-fidelity pressure recording catheter. While observing the pressure waveform, the Millar catheter was advanced into the left ventricle.

The heart was then exposed through a left lateral thoracotomy and suspended in a pericardial cradle. A flare-tipped polyethylene catheter was inserted into the left atrial appendage for continuous monitoring of left atrial pressure and for the injection of radiolabeled microspheres. A 1-cm section of the left anterior descending (LAD) coronary artery was isolated and encircled with an ultrasonic flow probe and snare ligature. A similar flow probe was placed on the left circumflex (LCx) artery.

The electrocardiogram, heart rate, arterial and left atrial pressures, LAD and LCx coronary flows and left ventricular pressure and its first derivative (dP/dt) were continuously monitored on an eight-channel stripchart recorder (Model 7758D, Hewlett Packard Co., Lexington, MA).

All experiments were performed in accordance with the University of Virginia Animal Research Committee in compliance with the position of the American Heart Association on use of research animals.

Experimental Protocol

The protocol is summarized in Figure 1. After collecting baseline hemodynamic measurements of heart rate, arterial and left atrial pressures, left anterior descending and left circumflex coronary flows and dP/dt, the snare ligature was tightened to produce a critical LAD stenosis. A critical stenosis was defined as no change in resting coronary flow, but with complete abolition of the reactive hyperemic response to a 10-sec total occlusion. After a brief stabilization period, a left atrial injection of radioactive microspheres was given to assess regional myocardial blood flow. Microspheres have been used extensively in our laboratory and their use has been previously described (*14*). Five minutes later, an intravenous infusion of adenosine (250 μg/kg/min) was begun and continued until ultrasonically measured LCx flow was maximal, at which time a second microsphere injection was made and the adenosine infusion was terminated. Approximately 5–10 min later, when the monitored hemodynamic parameters had returned to baseline, an intravenous infusion of N-0861 was begun. N-0861 (1 mg/ml solution in pH 4.0 acetate buffer) maintenance was administered as a slow infusion (250 μg/kg over 3 min), followed by a continuous infusion (22.0 μg/kg/min). Similar doses of N-0861 selectively antagonize A1 adenosine receptor-mediated responses in pigs, dogs and humans (*11–13,15*). Two minutes after beginning the maintenance infusion, a third microsphere injection was made and 8 min after that; the intravenous adenosine infusion was resumed at the previous rate (250 μg/kg/min). At the peak LCx flow response, 18.5–37.0 MBq (0.5–1.0 mCi) ^{201}Tl and microspheres were simultaneously administered. One minute later, the adenosine infusion was abruptly terminated and aminophylline (5 mg/kg) was intravenously injected. Within 2 min after injection of aminophylline, a final microsphere blood flow determination was made.

At the end of the protocol, the dogs were killed with an overdose of sodium pentobarbital and their hearts removed and sliced into four rings of equal thickness. The slices were trimmed of excess fat and adventitia and placed on a thin piece of cardboard and covered with cellophane wrap. The slices were imaged directly on the collimator of a conventional gamma camera (Model 420, Ohio Nuclear, Cincinnati, OH) for maximal count time using a 25% window centered on the ^{201}Tl photopeak. To quantitate the magnitude of the defects on the uncorrected myocardial slice images, regions of interest (ROIs) were drawn on the defect area visible in the antero-apical region of the left ventricular wall and on the normal posterior wall of the ^{201}Tl images. A defect count ratio was then obtained by dividing the average counts in the LAD ROI by the average counts in the normal LCx ROI. Quantification

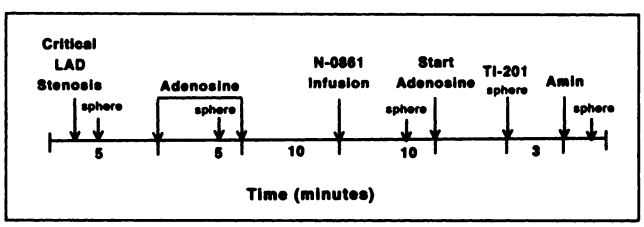

FIGURE 1. Experimental protocol. LAD = left anterior descending coronary artery and Amino = aminophylline.

TABLE 1
Hemodynamic Parameters (mean ± s.e.m.)

Parameter	Base	Sten	Pre Ado	N0861	Post Ado	Amin
HR (bpm)	101 ± 7	107 ± 8	123 ± 6*	113 ± 5	129 ± 4*	133 ± 6
AP (mmHg)	88 ± 3	95 ± 4	75 ± 6*	94 ± 5	80 ± 5*	95 ± 7
LAP (mmHg)	7 ± 1	9 ± 1	8 ± 1	8 ± 1	8 ± 1	7 ± 1
DPDT (mmHg/sec)	1660 ± 129	1881 ± 94†	1766 ± 154	1868 ± 129	1909 ± 122	2239 ± 141

*$p < 0.019$ versus Sten or N0861.
†$p < 0.05$ versus baseline.
Base = baseline; Sten = LAD critical stenosis; Pre Ado = pre N0861 adenosine; Post Ado = post N0861 adenosine; Amin = aminophylline; HR = heart rate; AP = mean arterial pressure; and LAP = left atrial pressure.

was performed only on the two center slices since the basal slice was above the stenosis and hence was always normal, whereas the apical slice lacked a quantifiable normal region. The defect magnitude was determined as the average count ratio of the two center slices.

After imaging, the heart slices were divided into 96 endocardial, midwall and epicardial segments and counted in a gamma well counter (Model 5550, Packard Instruments, Downers Grove, IL). The tissue samples were counted within 24 hr for 5 min each using ^{201}Tl window settings (50–100 keV). Three weeks later, when the ^{201}Tl had decayed, the tissue samples were recounted for microsphere blood flow. The window settings used were ^{141}Ce:120–175; ^{113}Sn:340–440; ^{103}Ru:450–550; ^{95}Nb:680–840; and ^{46}Sc:842–1300. The tissue counts were corrected for background, decay and isotope spillover and regional myocardial blood flow was calculated using specialized computer software (PCGERDA, Packard Instruments, Downers Grove, IL). Transmural activity and flow values were calculated as the average of the corresponding epicardial, midwall and endocardial samples.

Data Analysis

All statistical computations were made using SYSTAT software (Systat Inc., Evanston, IL). The results were expressed as the mean ± s.e.m. Differences between means within a group were assessed using ANOVA with posthoc multiple contrasts ($p < 0.05$ were considered significant).

RESULTS

Effect of N-0861 on Hemodynamic Parameters at Rest and During Adenosine Stress

As shown in Table 1, setting the critical LAD stenosis had no significant effect on heart rate, arterial or left atrial pressures. However, there was a slight increase in peak dP/dt from 1660 ± 129 to 1881 ± 94 after setting the stenosis ($p = 0.03$). During adenosine administration, arterial pressure decreased from 95 ± 4 to 75 ± 6 ($p = 0.001$) and there was a reflex rise in heart rate from 107 ± 8 to 123 ± 6 ($p = 0.016$).

N-0861 treatment resulted in no change in the resting values of heart rate, arterial and left atrial pressures, or on dP/dt, since the value of these hemodynamic parameters after N-0861 administration was similar to those obtained at rest after setting the coronary stenosis. In addition, N-0861 had no effect on these hemodynamic parameters during adenosine infusion since the peak adenosine stress parameters were not significantly different from those obtained at a similar time point during adenosine infusion prior to N-0861 administration. Finally, Table 1 shows that injection of aminophylline with N-0861 pretreatment increased mean arterial pressure from 80 ± 5 to 95 ± 7 ($p = 0.029$) concomittant with the reversal of systemic vasodilation and the resulting hypotension.

Coronary Response to Adenosine Before and After N-0861

The graph in Figure 2 depicts serial measurements of mean (±s.e.m.) ultrasonically measured coronary flow in both the LAD and LCx arteries. As shown, coronary flow in the critically stenotic LAD artery remained unchanged throughout the experiment, even during adenosine stress. However, as depicted in the figure, coronary flow in the nonstenotic LCx tripled from 36 ± 3 to 106 ± 14 ml/min with adenosine stress ($p = 0.003$). In addition, the magnitude of the adenosine-induced increase in LCx flow after N-0861 treatment (106 ± 14) was not significantly different from the increase evoked prior to N-0861 (101 ± 17).

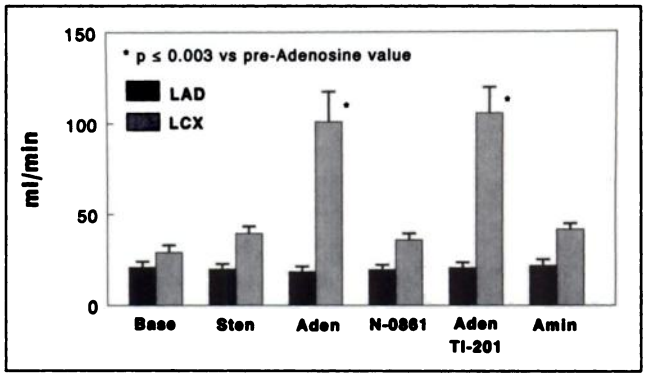

FIGURE 2. Ultrasonically measured flow in the left anterior descending and left circumflex (LCx) coronary arteries at serial time points. Base = baseline, Sten = stenosis, Aden = adenosine, Amin = aminophylline.

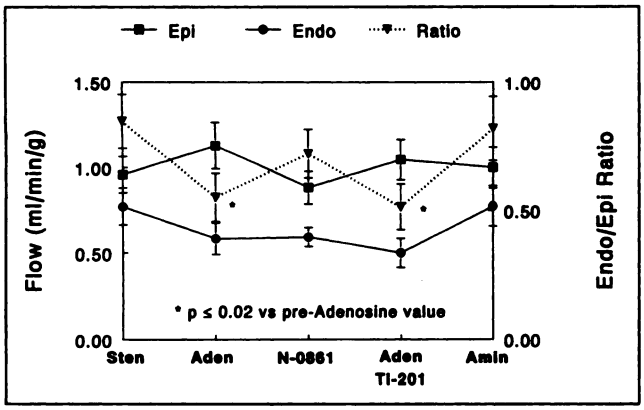

FIGURE 3. Regional microsphere-determined blood flow in the LAD stenotic zone. Epi = epicardial tissue segments, Endo = endocardial tissue segments. Time points are the same as described above. Note that the degree of coronary steal was equivalent before and after N-0861 administration. Also note that aminophylline completely reversed the coronary steal.

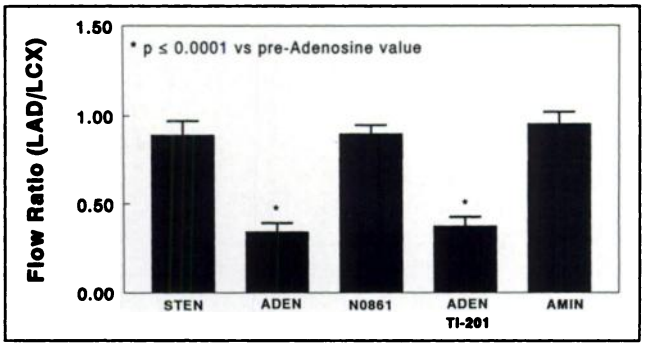

FIGURE 4. Regional transmural flow expressed as the ratio between the LAD and LCx myocardial segments. Note that adenosine induced an equivalent disparity in flow before and after N-0861 treatment.

Microsphere Determined Regional Myocardial Blood Flow and Endocardial/Epicardial Flow Ratios

The graph in Figure 3 displays mean regional myocardial blood flow from the critically stenotic LAD region measured serially with radioactive microspheres at the time points shown. The graph depicts flow in the endocardial and epicardial layers of myocardium, as well as the calculated ratio between these layers (endo/epi). During adenosine infusion, there was a significant decrease in the endocardial to epicardial ratio from 0.85 ± 0.11 to 0.55 ± 0.09 ml/min/g ($p = 0.02$) indicative of transmural coronary steal. With N-0861 pretreatment, the endo/epi ratio during adenosine stress (0.51 ± 0.09) was similar to that obtained prior to N-0861, demonstrating a similar amount of endocardial to epicardial steal. With aminophylline administration, the disparity in flow between the epicardial and endocardial myocardial layers was reversed resulting in an endo/epi ratio (0.82 ± 0.13), similar to what was seen in the ratio after initially setting the coronary stenosis (0.85 ± 0.11).

Transmural Regional Myocardial Blood Flow

Figure 4 displays the transmural myocardial blood flow ratio between the LAD and LCx regions of the myocardium at the same time points as in the previous figure. With adenosine administration, the flow ratio fell from 0.89 ± 0.08 at rest to 0.34 ± 0.05 ($p \leq 0.0001$). Treatment with N-0861 had no significant effect on the resting flow ratio (0.90 ± 0.04), or on the ratio during adenosine stress (0.38 ± 0.05), at the time point when ^{201}Tl was administered. Injection of aminophylline rapidly reversed the disparity in flow resulting in a transmural flow ratio of 0.96 ± 0.06 ($p \leq 0.0001$ versus adenosine stress).

Comparison Between Transmural Blood Flow, ^{201}Tl Activity and Image Defect Magnitude During Maximal Adenosine Vasodilation

The bargraph in Figure 5 compares the mean transmural blood flow ratio at peak adenosine vasodilation with the ^{201}Tl activity ratios determined by gamma well counting and by LAD/LCx defect magnitude quantification of defects on gamma camera images of myocardial slices. As shown, the ^{201}Tl activity ratio (0.55 ± 0.05) by gamma well counting was similar to the image defect ratio (0.61 ± 0.03) quantified from ex vivo images of myocardial slices. The microsphere flow ratio between LAD and LCx beds (0.38 ± 0.05) was lower than the ^{201}Tl activity or defect ratios ($p = 0.001$).

DISCUSSION

Atrioventricular conduction abnormalities and other side effects mediated by stimulation of A1 adenosine receptors are common in patients undergoing adenosine stress ^{201}Tl imaging (*1–4*). The negative dromotropic effect of adenosine is due to the direct stimulation of the A1 adenosine receptor subtype in the myocardium, whereas the desired vasodilatory effect for pharmacologic stress perfusion imaging is due to stimulation of the A2 receptor subtype in the vascular endothelium (*6*). The clinically

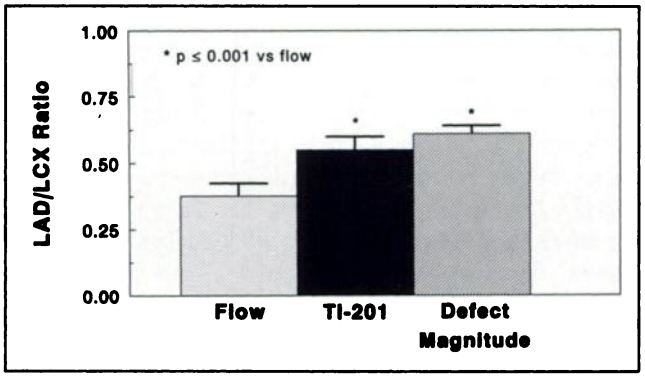

FIGURE 5. Comparison between transmural blood flow (solid bar), gamma well counter ^{201}Tl activity (narrow hatch), and image defect magnitude (wide hatch). Thallium-201 significantly underestimated the size of the flow disparity, but there was good accordance between the gamma well counter and imaging assessments of ^{201}Tl activity.

available adenosine antagonists such as the xanthine derivatives are nonselective and effectively block both the A1 and A2 receptor subtypes. Aminophylline cannot be given prophylactically to prevent side effects of adenosine since the drug will also prevent vasodilation precluding stress imaging.

It has been well-established that N-0861 selectively antagonizes the A1 adenosine receptor subtype and prevents the negative dromotropic and chronotropic effects of either endogenous or exogenous adenosine without affecting the A2 vasodilatory response (*10–13,15,16*). These findings would suggest that patients undergoing pharmacologic stress imaging with adenosine could be pretreated with N-0861 to prevent conduction abnormalities and other A1-mediated side effects, such as chest pain in the absence of CAD, without affecting the vasodilatory action of adenosine. By blocking the direct negative effect of adenosine on the sinoatrial and A-V nodes, as well as by blocking the indirect antiadrenergic effect of adenosine, N-0861 pretreatment might also allow a higher heart rate and double product response and a greater incidence of ST segment depression during adenosine administration. Ischemic ST segment depression has been shown to provide additional information to scintigraphic data with respect to the extent of myocardium at risk and may have diagnostic and prognostic value (*17*). However, before conducting clinical research studies with N-0861 in the setting of pharmacologic stress imaging, experimental data are necessary to ensure that this A1 receptor antagonist does not affect regional flow and ^{201}Tl uptake.

In the current study, we used anesthetized dogs to examine the effect of N-0861 on adenosine stress ^{201}Tl imaging results. We chose a canine model due to our extensive past experience with it, and to facilitate comparisons with our previous work (*18*). Although Martin (*19*) found a markedly reduced potency of A1 agonists in canine left atrial tissue, and concluded that the A1 receptors in dogs may not be typical, the goals of our study were limited to examining the effect of N-0861 on regional flow (A2 receptor mediated) and ^{201}Tl imaging. We did not analyze A1 receptor responses in these experiments. Nevertheless, Pelleg and Hurt (*15*) were able to demonstrate increases in sinus cycle length (delayed conduction) after adenosine administration in anesthetized dogs that were attenuated by N-0861. Yet, even with the feedback control mechanisms ablated by performing a bilateral stellectomy and cervical vagotomy, the changes these investigators observed in dogs were of a lesser magnitude than that seen in pigs (*11,16*).

Effect of N-0861 on Hemodynamics and Regional Myocardial Blood Flow

The administration of N-0861 had no significant effect on baseline heart rate, arterial and left atrial pressures, coronary flow or dP/dt compared with the pretreatment values. The mean baseline value of heart rate (101 ± 7) was lower than in other studies from our laboratory (*18,20*), since in the present study Innovar was used adjunctively with sodium pentobarbital as an anesthetic rather than sodium pentobarbital alone. We chose Innovar in these studies to maintain the heart rate near the normal range of a resting, unanesthetized dog (80–100 BPM) to attempt to avoid masking any A1 effects that may be present.

After administration of N-0861, we found that the hemodynamic response to adenosine was similar to that found prior to N-0861 pretreatment. There was a similar fall in mean systemic arterial pressure with a concomittant reflex rise in heart rate. In addition, coronary flow in the normal circumflex artery increased to a similar extent while flow in the stenotic LAD remained fixed. Thus, hemodynamically, N-0861 did not alter the adenosine-induced disparity in flow between the normal LCx and critically stenotic LAD vessels.

Furthermore, measurements of regional myocardial blood flow by the microsphere technique were not different before and after N-0861 treatment. N-0861 did not significantly change the endocardial to epicardial flow ratios at rest or during peak adenosine stress, indicating a similar level of transmural coronary steal. The transmural distribution of flow between the LAD and LCx regions was also unchanged with N-0861, suggesting that N-0861 should not affect the assessment of coronary flow reserve with ^{201}Tl imaging.

Finally, administration of aminophylline resulted in an increase in systemic arterial pressure, a decrease in LCx flow and a normalization of the endocardial-to-epicardial flow ratio. This finding is in accordance with our previous data in dogs (*20*), and indicates that there is no adverse hemodynamic interaction between N-0861 and aminophylline.

Effect of N-0861 on Thallium-201 Distribution During Adenosine Stress

In the current study, ^{201}Tl activity significantly underestimated the size of the true flow disparity as measured by microspheres. The roll-off in extraction of ^{201}Tl at high flow is characteristic of all diffusible flow tracers and has been previously reported by our laboratory and others (*18,21*). Despite the underestimation of the flow disparity, the mean magnitude of the ^{201}Tl defect (0.61) was large and well within clinically detectable limits. In addition, the mean defect magnitude was not significantly different from our previously reported findings in a similar canine model without N-0861 pretreatment (0.59 ± 0.05) (*18*). Thus, N-0861 treatment did not alter the size of the myocardial perfusion defect.

Study Limitations

There are several possible limitations to this study. One limitation is that we did not measure any A1 receptor parameters that would be affected by an A1 antagonist such as the P-R interval on the electrocardiogram. Secondly, although adenosine A2 receptor-mediated coronary vasodilatory responses are similar in dogs and humans

(*18*), A1 receptor-mediated responses are less easily evoked in dog hearts (*15,19*). It is unclear whether the decreased sensitivity of the canine A1 receptor results from a lower affinity of adenosine for the receptor, reduced receptor density or differences in the amino acid sequences in the binding domain (*19,22*). A third potential limitation pertains to the use of anesthesia. Anesthesia affects neural control mechanisms which could possibly mask out A1-mediated chronotropic and dromotropic effects. In this study, adjunctive Innovar allowed us to use a lower dose of sodium pentobarbital, thereby minimizing the increase in heart rate due to the vagolytic effect of the barbiturate. The primary result of these first three limitations is that we were unable to ascertain the effectiveness of N-0861 at blocking the A1 adenosine receptor. However, as previously mentioned, N-0861 has been shown to be a potent antagonist of the A1 adenosine receptor in several species; the dose that we chose was similar to those that attenuated A1 receptor-mediated responses in pigs and in humans (*11–13,16*). Our goal was to determine whether there was any "crossover" A2 receptor antagonism which would affect pharmacologic stress imaging. A final limitation of this study was the inability to use the same animals as their own controls when comparing defect magnitude with or without N-0861 pretreatment since we were only able to give one dose of ^{201}Tl during each experiment. However, as noted, the defect magnitude in this study was similar to our previous experimental work using a similar protocol but without N-0861 pretreatment.

Clinical Implications

In summary, there are a number of side effects reported in patients undergoing adenosine stress ^{201}Tl imaging. Two of the more common side effects are A-V block and chest pain (*1–4*). In the recent study by Hill et al. (*13*), N-0861 eliminated both of these undesired effects during adenosine infusion without affecting coronary flow velocity. The current study demonstrated that N-0861 has no adverse hemodynamic effects which would limit the assessment of coronary flow reserve by ^{201}Tl imaging. The degree of vasodilation produced by adenosine is unaltered as is the magnitude of coronary steal distal to a critical stenosis. It was also shown that N-0861 has no negative effect on the assessment of coronary flow reserve by ^{201}Tl imaging and there was no adverse hemodynamic interaction between N-0861 and aminophylline. Thus, a pretreatment strategy with N-0861 prior to adenosine infusion may indeed be feasible. However, further clinical investigative studies appear warranted to determine the effectiveness of N-0861 for eliminating undesirable A1 receptor-mediated side effects of adenosine. The results from this study indicate that N-0861 pretreatment will not detract from perfusion defect detectability.

ACKNOWLEDGMENT

Supported by a research grant from Whitby Research, Inc.

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