EDITORIAL

New Directions in Pharmacologic Stress Imaging

In this issue of the *Journal*, Glover et al. examined the effects of a new selective adenosine A1 receptor antagonist (N-0861, N6-endonorbornan-2-yl-9-methyladenine) in a canine model with coronary stenosis (*1*). They concluded that N-0861 has no direct effect on coronary flow and systemic hemodynamics; it did not affect the adenosine changes in coronary blood flow such as the disparity of flow between the stenosed and normal regions and the endocardial and epicardial distribution of flow; and, finally, it did not have a detectable interaction with aminophylline. They concluded that pretreatment with N-0861 may prove useful for the elimination of A1 receptor-mediated side effects during pharmacologic stress testing with adenosine.

Adenosine is an endogenous substance that is generated from cellular ATP (adenosine triphosphate) and S-adenosyl-homocysteine via a bidirectional reaction pathway. Adenosine may also be metabolized with the help of the enzyme adenosine deaminase into inosine → hypoxanthine → xanthine → uric acid (*2–5*). The plasma half-life of adenosine is 0.6–1.5 sec but may be longer at higher concentrations (*5*). The mechanism of action of adenosine is through activation of specific receptors (A1, A2, A3 and A4). A1 and A2 receptors are found in many types of tissues and cells. In the heart, A2 receptors are located in the coronary vessels and A1 receptors in the myocytes. Stimulation of A2 receptors produces vasodilation probably through activation of guanylate cyclase which results in increased cyclic GMP concentration. Glover et al. used a selective A2a receptor agonist to produce coronary hyperemia that was comparable to adenosine (*6*). Adenosine increases most regional blood flows with the exception of renal and hepatic blood flow. The vasodilatory effect of adenosine has been utilized in the control of blood pressure during surgical (especially, neurosurgical) operations: in the study of reactivity of the pulmonary vascular resistance in patients with pulmonary hypertension and in pharmacologic stress testing in patients with ischemic heart disease (*3,7*). Also, numerous studies have shown that adenosine may limit myocardial infarct size and attenuate myocardial stunning (*8*). The availability of specific A1 and A2 receptor antagonists and agonists has shown that myocardial protection is due to A1 receptor activation, the exact mechanism of which is not clear but may be related to decreased catecholamine release, increased glucose uptake, increased ATP, decreased free radicals and decreased calcium overload (*8,9*).

In 1929, Drury and Szent-Gyorgyi first described the negative chronotropic, dromotropic and inotropic effects of adenosine in the guinea pig heart (*4*). The negative dromotropic effect is the basis of using adenosine in the treatment of supraventricular arrhythmias (*10*). The negative inotropic effect on ventricular myocardium has since been described in several species for both in vitro and in vivo experiments and in human hearts for in vitro experiments. In these experiments, the force of contraction is decreased by adenosine only if it was first stimulated by isoproterenol or catecholamines. This type of negative inotropic effect is referred to as an indirect or antiadrenergic effect (*3*). Since endogenous adenosine is increased during ischemia and during catecholamine stimulation, it is postulated that this indirect negative inotropic effect acts as a biofeedback inhibitor to protect the myocardium from excessive stimulation. The mechanism of action of adenosine on ventricular myocardium is via stimulation of A1 receptors which are coupled through G-proteins to adenylate cyclate, thereby reducing cyclic AMP (adenosine monophosphate) formation and the cyclic AMP-induced slow calcium ion inward current. In our human study (*11*), we found no evidence of a decrease in left ventricular function by adenosine, and in the study of Koglin et al. there was no evidence of depression of left ventricular contractility in the human ventricle, even during catecholamine stimulation (*12*). This difference between human and different animal species is an important observation that should be taken into consideration when extrapolating animal data into human data. For example, A1 receptor-mediated responses are less easily evoked in dog hearts. Such species differences may be related to fewer receptors or less effective receptor-effector coupling or both.

The basic mechanism for the use of adenosine in pharmacologic perfusion imaging is predicated on the variability in coronary hyperemia in normal and diseased vessels (*1,13,14*). Several studies have shown a high degree of accuracy in detecting coronary artery disease, in identifying patients with high-risk coronary anatomy (left, main or three-vessel disease) and in risk stratification using ^{201}Tl or technetium-labeled perfusion imaging agents. These results are not different from those obtained with dipyridamole. The mechanism of action of dipyridamole is indirect via inhibition of cellular re-uptake of endogenous adenosine, resulting in higher adenosine concentration at the receptor sites. McLaughlin et al. measured the coronary sinus adenosine concentrations in patients with and without coronary artery disease during dipyridamole infusion (*15*). They observed an increase in the level from 16 ± 4 to 35 ± 10 ng/ml in patients without disease and from 35 ± 13 to 69 ± 35

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ng/ml in patients with disease. These levels are probably several folds lower than those achieved with a standard infusion dose of adenosine (140 μg/kg/min).

The common side effects of adenosine include chest pain, dyspnea and flushing. In a recent report from the Multicenter Registry, flushing was observed in 37% of the patients, dyspnea in 35%, chest pain in 35% and high-degree A-V block in 4% of patients (*16*). These side effects can be controlled by xanthine-containing compounds such as aminophylline, a nonselective adenosine inhibitor (it inhibits both A1 and A2 receptors). There is a reason to believe that bronchospasm in patients with asthma is due to A1 or A3 receptor stimulation located in the mast cells. Therefore, it is possible that a selective A1 receptor antagonist may reduce the side effects due to A1 receptor stimulation (chest pain, A-V block and, possibly, dyspnea). This amelioration of side effects would not detract from the detection of perfusion defects during adenosine stimulation.

Should N-0861 be routinely used during adenosine or dipyridamole perfusion imaging? Although chest pains occur in one of three patients receiving adenosine infusion, it is a transient phenomena and is seldom severe enough to warrant discontinuation of the infusion. Parenthetically, the chest pain may be a useful indirect evidence of the hemodynamic effect of adenosine and it remains to be seen whether its elimination will be a desirable effect. It should be noted that chest pain may occur in patients with and without coronary artery disease. Thus, its presence does not necessarily imply the presence of myocardial ischemia (*17*). High-degree A-V block is a more serious complication, but it occurs infrequently and is, again, transient, intermittent and unpredictable. Although it seldom requires treatment, it nevertheless raises a certain degree of apprehension among some physicians working in nuclear cardiology laboratories (*18,19*). Severe chest pain and high-degree A-V block are less frequent complications during dipyridamole infusion, but such complications may increase if a higher dose is used (*20*). The routine use of the A1 antagonist will depend on the safety profile of the drug, the efficacy, the ease of administration (e.g., need for bolus injection or infusion) and the cost. The study Glover et al. expands our understanding of pharmacologic stress testing and opens the opportunity for clinical trials that examine the use of N-0861 in combination with adenosine and dipyridamole in humans.

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