Editorial Comment

Adenosine
Renewed Interest in an Old Drug

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In 1929, A.N. Drury and A. Szent-Györgyi wrote, "As adenylic acid has been found to be a constituent of many and different types of animal cells, an investigation into its general physiological properties in addition to its detailed action upon the mammalian heart seems to us very desirable." The authors then noted that adenosine and adenylic acid "slow the rate of beating, impair conduction from auricle to ventricle . . . ," and "lower general arterial pressure and . . . dilate the coronary vessels. . . ." An additional important role for adenosine as the mediator of metabolically regulated coronary flow was proposed by Berne in 1963, although more of adenosine are rapid in onset (5–30 seconds) and transient; adenosine’s half-life is 10–30 seconds because it is quickly taken up and metabolized by adenosine deaminase in erythrocytes and by endothelial cells.

These differing regional cardiac effects and short half-life have led to the use of adenosine in the treatment of cardiac arrhythmias. Adenosine can terminate supraventricular arrhythmias in 86–100% of cases if the AV node is involved in the genesis of the arrhythmia; for example, in AV and AV-nodal reentry arrhythmias. However, the arrhythmia may recur quickly in up to one third of cases after the effects of adenosine dissipate. Adenosine will rarely terminate tachyarrhythmia of atrial origin. Rather, adenosine may be of diagnostic value because it slows the ventricular rate by causing block at the AV node and reveals the unaffected atrial arrhythmia, as in automatic atrial tachycardia, atrial flutter, and atrial fibrillation. Although adenosine is not effective in terminating ventricular tachycardia, it has been safely and effectively used to help differentiate ventricular tachycardia from supraventricular tachycardia with a wide QRS complex. It appears to be a safer choice for this procedure than verapamil, which often has deleterious hemodynamic effects in patients with ventricular tachycardia.

In an interesting case report aminophylline, an adenosine antagonist, reversed atropine-resistant AV block following acute inferior myocardial infarction. This suggests that persistent ischemia or hypoxia may cause high tissue levels of adenosine leading to bradycardia or AV block. It also suggests a possible therapeutic role for adenosine antagonists in atropine-resistant AV block. The possible role of adenosine in sick sinus syndrome or profound bradycardia has not been adequately investigated.

Side effects have been reported to occur in 24–64% of the patients given adenosine. These include dyspnea (perhaps due to bronchospasm), chest pain, flushing, hypotension, nausea, vomiting, and headache. Although transient (usually lasting less than 1 minute), patients often judged the symptoms as moderate to severe. Major adverse hemodynamic changes have rarely been noted. However, high degrees of AV block with prolonged pauses (2–6 seconds) have occurred. Aminophylline, caffeine, and other methylxanthines antagonize the

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actions of adenosine, and dipyridamole and denervation of the heart potentiate the sino-atrial (SA) and AV node effect of adenosine three- to sevenfold. Thus, the use of adenosine in patients with underlying conduction disease, or in those receiving other drugs that impair AV conduction or that may interact with adenosine, is not recommended or, if judged important, should be done with a reduced dosage and with extreme care. Adenosine also has some proarrhythmic effects. The development of atrial fibrillation and ventricular extrasystoles has been infrequently noted.

Role of Adenosine in Myocardial Ischemia

Adenosine may play a role in causing pain. An anginalike chest pain has been reported in patients without known coronary artery disease who have received intravenous adenosine. A recent study found that in patients with chronic stable angina, intracoronary adenosine provoked chest pain with a character, location, and radiation similar to their typical anginal pain, but without any electrocardiographic changes of ischemia. Aminophylline reduced both adenosine- and exercise-induced anginal pain, suggesting that adenosine could be partially responsible for anginal pain during myocardial ischemia. In patients with coronary disease and a positive exercise test without chest pain (silent ischemia), the chest pain provoked by adenosine infusion was milder than that induced in patients who developed exercise-induced angina. These intriguing findings suggest that abnormalities of adenosine feedback or metabolism might play a role in the syndrome of anginalike pain in individuals with normal coronary arteries, silent ischemia, or classic angina pectoris, but these possibilities have not yet been thoroughly investigated. If adenosine does play a role in causing chest pain, then adenosine antagonists may offer new therapeutic options.

Adenosine (or agents that increase adenosine concentration) given during ischemia or reperfusion in dogs has been reported to decrease arrhythmias, improve collateral flow to ischemic myocardium, improve regional function, and reduce infarct size. The mechanisms for these benefits are not clearly understood, but may be increased blood flow, prevention of microvascular obstruction or endothelial cell injury due to granulocyte adherence, or inhibition of superoxide anion formation. The value of adenosine administration during myocardial ischemia or reperfusion is another area that needs further investigation.

Adenosine as a Vasodilator

Important information about the adequacy of coronary flow can be obtained during pharmacologically induced maximum or near-maximum increases in flow. This enables measurement of coronary flow reserve and the detection of inadequate flow to a region of the myocardium by thallium-201 scintigraphy and by echocardiographic imaging to detect wall motion abnormalities. Papaverine and dipyridamole, the two most commonly used coronary vasodilator agents in humans, are not ideal for this purpose because of their long half-lives and duration of action and the prolongation of the QT interval and induction of arrhythmias that they cause. Adenosine could be a more suitable agent for repeatedly inducing maximum coronary vasodilation because of its rapid onset and offset of action. Its use in humans has been limited mainly because of side effects reported by patients and the AV node block produced. In addition, only a mild vasodilator effect had been previously noted with bolus injections.

Renewed interest in adenosine as a coronary vasodilator occurred with reports that maximum and sustained vasodilation could be achieved without the adverse effects on the conduction system when it was given as a continuous low-dose infusion. In this issue of Circulation, Wilson and colleagues provide detailed and helpful information about the use, efficacy, and safety of intravenous and intracoronary adenosine in humans.

The strengths of this study are 1) the administration of adenosine by three modes (intracoronary bolus, continuous intracoronary infusion, and continuous intravenous infusion), 2) a careful description of the dose–response kinetics for each mode of adenosine administration, and 3) comparison of the vasodilatory responses to intracoronary and intravenous adenosine with those to intracoronary papaverine (the gold standard). They found that intracoronary adenosine induces coronary vasodilation equivalent to that generated by papaverine without causing important changes in systemic hemodynamics or the electrocardiogram. Intravenous adenosine at as much as 140 μg/kg/min for at least 2 minutes caused coronary vasodilation similar to that caused by papaverine in 83% of patients. A mild dose-dependent fall in mean arterial pressure and a rise in heart rate occurred during the intravenous administration. Adverse symptoms or effects on the conduction system were uncommon. A finding not well described was that intravenous adenosine infusion at dosages just below that required to achieve maximum vasodilation (70–100 μg/kg/min) frequently caused a pattern of fluctuating flow. This pattern disappeared when the infusion rate was increased.

These results clearly establish that intracoronary and intravenous infusions of adenosine effectively induce coronary vasodilation to the same degree as does intracoronary papaverine. The safety and effectiveness of the intravenous infusion of adenosine is important because this route of administration would greatly simplify its clinical use as a coronary vasodilator.

The authors are appropriately cautious in interpreting and generalizing their results. Although the data are encouraging, it must be remembered that they studied only 36 individuals who had normal coronary arteries and normal left ventricular function. The highest intravenous dosage (140 μg/kg/min) was given for approximately 2 minutes. The
safety of longer infusions, which would likely be necessary in clinical studies, was not determined. The effectiveness and safety of adenosine in people with significant coronary obstructions, left ventricular dysfunction, ventricular hypertrophy, predisposition to arrhythmias, or SA or AV node disease needs to be established. Interactions between adenosine and other drugs need to be better defined. Additional information might be desirable regarding the frequency, significance, and mechanism of the fluctuations noted in coronary flow at the lower infusion rates of adenosine.

Conclusions

After a long history of use in experimental animal studies, adenosine now appears to have real and potential uses in humans. The safety and efficacy of adenosine in the diagnosis and treatment of supraventricular tachyarrhythmias are now established. The role adenosine plays in myocardial ischemia is being explored, including its part in causing anginalike chest pain and also in counteracting ischemia or reperfusion-induced myocardial injury. Finally, adenosine holds promise as a safe and effective coronary vasodilator that could be useful in studying the normal and abnormal coronary circulation in humans.29–31

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