Dromotropic effects of adenosine and adenosine antagonists in the treatment of cardiac arrhythmias involving the atrioventricular node

ROBERT M. BERNE, M.D., JOHN P. DIMARCO, M.D., PH.D., AND LUIZ BELARDINELLI, M.D.

THE ELECTROPHYSIOLOGIC EFFECTS of adenosine and other adenine derivatives were first described by Drury and Szent-Györgyi in 1929.1 These investigators clearly demonstrated that intravenous administration of adenosine produced a decrease in sinus rate and transient atrioventricular (AV) block. Adenosine is a mediator of many physiologic phenomena and most of the interest in its effects on the cardiovascular system have, until recently, been centered on its ability to regulate regional blood flow in the heart and other organs.

During the last several years, we and several other investigators have reexamined the electrophysiologic effects of adenosine.2 6 In our initial experiments, we showed that adenosine produced variable degrees of dose-related reversible AV block in guinea pig and rabbit hearts perfused by the Langendorff technique. The negative dromotropic effect was localized to AV nodal tissue.5,6 In the anesthetized dog, perfusion of the sinus and AV nodal arteries with solutions containing adenosine produced a decrease in sinus nodal discharge and an increase in AV nodal conduction time, respectively.3,4,7,8 Studies in isolated segments of the AV node and the isolated perfused mammalian heart have confirmed the earlier observations that adenosine impairs conduction through AV nodal tissue, and that its action is restricted to the proximal portion of the node, i.e., the slow channel-dependent tissue of the AV node.9 In addition to these effects on the sinoatrial and AV nodes, adenosine shortens the action potential duration and hyperpolarizes the membrane of atrial cells.10,11 In isolated atrial cells with intrinsic autonomic activity, spontaneous depolarization is inhibited. These effects of adenosine have been attributed to an increase in K+ conductance.11-13 Catecholamine-induced triggered automaticity is also prevented by the addition of adenosine to the media.14 Direct effects of adenosine on isolated ventricular myocytes are less marked, but the effects of isoproterenol on the action potential duration of these cells is antagonized by adenosine.14 In all of these systems, the effects of adenosine are potentiated by inhibitors of adenosine uptake (e.g., dipyridamole) and antagonized by methylxanthines. Less permeable analogues of adenosine retain electrophysiologic activity, suggesting that the effects of adenosine are mediated by a receptor located on the extracellular surface of the plasma membrane.6 Although significant interspecies differences in sensitivity to adenosine have been noted, qualitatively similar effects have been reported in all mammalian species studied, including man.

Of interest was the finding that when AV nodal conduction was impaired by interventions, such as hypoxia or ischemia, that caused increased release of adenosine from myocardial cells, the AV conduction delay and block was similar to that caused by exogenous adenosine.5,15 That is, hypoxia in the isolated perfused mammalian heart5 or ischemia of the AV node (ligation of the AV nodal artery) in the dog heart in situ8,16,17 caused a prolongation of the AH interval that often resulted in second-degree AV block. The fact that the hypoxia or ischemia-induced AV conduction block could be modified in a predictable manner by interventions known to antagonize and/or potentiate the actions of adenosine lends support to the concept that the dromotropic effects of hypoxia and ischemia are mediated by the adenosine released from oxygen-deprived myocardial cells.5,6,8,17 Dipyridamole (a drug that protects against adenosine degradation by blocking its uptake into cells and hence its deamination to inosine) potentiates and methylxanthines (competitive adenosine antagonists) attenuate the hypoxia and ischemia-induced AH prolongation and AV block.8,17

From the Departments of Physiology/Medicine and Division of Cardiology, University of Virginia, Charlottesville.

The studies cited in this review were supported in part by grant-in-aid 81-911 from the American Heart Association, AHA-Virginia Affiliate, and from NHLBI (HL10384 and HL-3111).

Address for correspondence: Robert M. Berne, M.D., Department of Physiology, Box 449 Jordan Hall, University of Virginia School of Medicine, Charlottesville, VA 22908.

Dr. Belardinelli is the recipient of NIH Research Career Development Award No. 1K04-HL00969-01.
Similarly, it was recently shown that reperfusion-induced bradycardia (in a preparation of canine atrium) is enhanced by dipyridamole and attenuated by aminophylline but not by atropine, suggesting that adenosine may be involved in the genesis of this type of bradycardia. Thus, adenosine may be an important participant in the regulation of the function of both the sinus and AV nodes.

Further investigation is necessary before the relative significance of the contribution of adenosine to normal and pathologic physiology can be defined, but recent experiments have demonstrated potential applications of the experimental findings described above in two clinical situations: in patients with bradyarrhythmias during acute myocardial ischemia and in those with episodes of reentrant arrhythmias involving the AV node.

Myocardial cells release adenosine into the intracellular space during hypoxia or ischemia. Millimolar concentrations of adenosine have been measured under these circumstances. Since inferior myocardial ischemia is often associated with sinus bradycardia and/or AV nodal block, we postulate that local increases in adenosine concentration might be responsible for these arrhythmias. Thus, in bradyarrhythmias associated with ischemic disease of the AV node (e.g., inferior myocardial infarction or spasm of the right coronary artery), which are sometimes not responsive to treatment with atropine, adenosine antagonists may prove to be useful.

Adenosine is rapidly taken up by the cellular elements of the blood and the effects seen after intravenous bolus injections dissipate within seconds. Therefore, it seemed possible that adenosine could be used to terminate episodes of reentrant supraventricular arrhythmias in which the AV node is involved in the reentrant pathway. We have recently shown this to be feasible and have found administration of adenosine to be a reliable method for terminating paroxysmal supraventricular tachycardia due to both AV nodal reentry and reciprocating tachycardias in which the AV node is the antegrade pathway. In patients with other forms of atrial arrhythmia, the transient high-grade AV block produced by the injection of adenosine may unmask underlying atrial activity on the electrocardiogram, and thus may help in the diagnostic evaluation of the arrhythmia. Only minor side effects, including transient dyspnea and occasional facial flushing, have been reported in patients in whom episodes of supraventricular tachycardia were successfully treated with adenosine. The dose of adenosine required to terminate the tachycardia was small and did not reduce systemic blood pressure; in fact, arterial pressure rose as a result of the greater ventricular filling that occurred with termination of the tachycardia. Furthermore, since adenosine is very rapidly inactivated by deamination to inosine and tachyphylaxis to adenosine does not occur, successive doses can be safely given after very brief periods of time. Hence, adenosine, a natural product of the body, has both diagnostic and therapeutic value with respect to supraventricular tachycardias.

Finally, since the mid-1950s adenosine triphosphate has been reported to be useful in the treatment of paroxysmal supraventricular tachycardia. However, only recently has its efficacy become well established and it is now used extensively in Europe for the short-term management of paroxysmal supraventricular tachycardia. However, the adenosine triphosphate currently used (Striadyne) contains adenosine and other nucleotides (adenosine diphosphate and monophosphate) and furthermore, adenosine triphosphate is rapidly hydrolyzed to the monophosphate which is dephosphorylated to adenosine. Although in some species (e.g., the dog) part of the effect of adenosine triphosphate seems to be vagally mediated (since atropine and/or vagotomy attenuate its action), in man atropine does not antagonize the effects of adenosine triphosphate. In the guinea pig heart the AV conduction delay and block caused by adenosine triphosphate is due to its degradative product, adenosine. Thus, it is probable that in humans, as in the case of the guinea pig, adenosine triphosphate must be hydrolyzed to adenosine to exert its effect. Hence, it is adenosine that is the active agent.

As we recognize new properties of adenosine and better understand its actions, additional therapeutic possibilities may be revealed for this interesting nucleoside and perhaps useful stable analogues and antagonists will be developed.

References
1. Druy AN, Szent-Györgyi A: The physiological action of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol (London) 68: 213, 1929
11. Belardinelli Johnson
13. Nawrath
16. James Watanabe
12.  
15.  

Vol. 69, No. 6, June 1984
1197
Dromotropic effects of adenosine and adenosine antagonists in the treatment of cardiac arrhythmias involving the atrioventricular node.

R M Berne, J P DiMarco and L Belardinelli

_Circulation._ 1984;69:1195-1197
doi: 10.1161/01.CIR.69.6.1195

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/69/6/1195.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/