EDITORIAL COMMENT

Adenosine as Adjunctive Therapy for Acute Myocardial Infarction

Is It Time for Another Clinical Trial?*

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In the current era of translational research and evidence-based medicine, the published data abounds with examples of promising therapeutic strategies on the basis of brilliant theories that succeed in the laboratory and in pilot studies but fail in large-scale clinical trials. This has been particularly true for adjunctive therapies designed to reduce infarction in acute myocardial infarction (MI). Over the past several decades, numerous clever ideas have been proposed and tested. They succeeded primarily in enhancing the academic careers of basic scientists and cardiologists rather than the outcomes of patients with MI. Strategies such as therapeutic hypothermia, hyperbaric oxygen, stem cell injection, distal protection devices, aspiration thrombectomy, prophylactic intra-aortic balloon pumps, nitrates, magnesium, pexelizumab (an anti-C5 complement inhibitor), glucose/insulin/potassium infusion, and other drugs have been studied as methods to reduce infarction size or no-reflow. They were all on the basis of sound physiological principles and promising preliminary data, yet the expensive clinical trials that followed did not find clinical benefit.

In theory, adenosine is one of the most promising of these adjuncts. Several biological properties of adenosine could prove beneficial in patients with acute MI such as augmentation and preservation of microvascular flow, inhibition of oxidative stress, and inhibition of neutrophil-mediated reperfusion injury (1). Animal models demonstrated reductions in infarct size with adenosine, and small pilot studies in humans showed promising results (1); however, randomized clinical trials were mostly unsupportive. In a trial of 236 patients within 6 h of MI treated with lysis and randomized to a 3-h intravenous infusion of 70 µg/kg/min of adenosine versus placebo (AMISTAD [Acute Myocardial Infarction STudy of ADenosine]), only the subgroup with anterior MI had a reduction in infarct size compared with placebo (2). AMISTAD II, a larger trial enrolling >2,000 patients within 6 h of an anterior MI randomized to a 3-h infusion of either low-dose (50 µg/kg/min) or high-dose (70 µg/kg/min) adenosine or placebo, found no difference in the primary endpoint of the study (new heart failure or death within 6 months). A substudy consisting of 243 patients designed to measure infarct size observed no effect on infarct size in the pooled adenosine groups; however, the high-dose adenosine group had a significant reduction in infarct size versus placebo (3). Post-hoc analysis of AMISTAD II observed improved outcomes in the subset of patients undergoing reperfusion within the first 3 h of infarction (4). Other randomized clinical trials using an intracoronary bolus of adenosine found no benefit (5,6). Thus, despite some "positive" findings, these clinical trials were essentially negative. Adenosine is not used routinely for this purpose nor is it recommended by current practice guidelines.

So why not abandon adenosine to the trash heap of other good ideas that failed in clinical trials? The answer to this question is complex, and many critics consider the studies flawed and the question of adenosine's benefit in MI unresolved. Studies designed to test whether a drug reduces reperfusion injury and infarction size must consider many variables. With such a very short half-life, the optimal

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dose, rate, duration, and route of adenosine administration are critical to get right. In addition, it is important to deliver the drug at the optimal time relative to the onset of infarction and reperfusion. It is very possible that the existing clinical trials simply got these parts wrong.

To add further complexity, the optimal window during which a therapy may reduce reperfusion injury and limit infarct size is likely very small. If reperfusion is accomplished very early, say within the first hour or 2 of symptom onset, the area at risk is mostly salvaged and the resulting infarction and area at risk of reperfusion injury will likely be very small. In such cases, a drug cannot be expected to show an improvement. Alternatively, if reperfusion is delayed, say 6 to 8 h after symptom onset, then the risk area is mostly infarcted. In such cases, there will be little additional injury from reperfusion and subsequently little benefit from agents that reduce reperfusion injury. Thus, agents such as adenosine may only prove effective during a very narrow time frame of only a few hours after symptom onset.

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In this issue of *JACC: Cardiovascular Interventions*, Yetgin et al. (7) persevered in the face of negative trials and provide valuable insight into the role of adenosine in limiting infarct size. Their study design differed importantly from other work. They measured the size of infarction and no-reflow in pigs subject to 45 min of coronary occlusion followed by 2 h of reperfusion and compared the effect of 2 strategies of adenosine with control subjects: an intracoronary bolus of 3 mg adenosine administered over 1 min and a 2-h intracoronary infusion of 50 μg/kg/min of adenosine. The intracoronary bolus of adenosine had no effect. There was no increase in blood flow (beyond the expected reactive hyperemia caused by the infarction) and no reduction in infarction size, no-reflow area, or attenuation of neutrophil influx. In contrast, intracoronary infusion of high-dose adenosine increased blood flow and caused an absolute 13% reduction of infarct size and a 23% reduction in no-reflow along with a nonsignificant trend toward reduced neutrophil infiltration into the no-reflow area. They concluded that only high-dose, prolonged, intracoronary administration of adenosine is effective at reducing infarct size and no-reflow and that adenosine as an adjunctive therapy should be reconsidered.

Is it time then for another expensive trial? I believe that this would be very challenging and require extensive additional work to justify. The interesting work by Yetgin et al. (7) created more questions than answers. What is the optimal adenosine dose? Instead of using the same dose for all, should the dose be on the basis of the amount of adenosine needed to achieve a certain blood flow? Should we use a Doppler FloWire to dose adenosine and, if so, what is the optimal blood flow needed for benefit? Is a 3- to 4-fold increase needed or is 2-fold adequate? Is even higher better? For what duration should the infusion be administered? Is 2 h necessary or is 1 h enough? Clinicians will be faced with logistic problems to accomplish a prolonged intracoronary infusion. Infusion through the guide catheter is problematic as there is the potential to dislodge the catheter during a prolonged infusion or there may be reflux of drug into the aorta or noninfarct vessel during infusion, thus diminishing the amount of drug entering the infarct-related artery. This can be overcome by positioning a microcatheter, allowing selective infusion into the infarct-related artery, but there may be additional risk during a prolonged infusion. Prolonged infusion will also occupy the cardiac catheterization laboratory for many hours; it is unlikely that it will be safe to do this outside of the lab for fear of catheter dislodgment or vessel injury. Finally, the timing of adenosine administration relative to symptom onset and reperfusion remains to be determined. As alluded to earlier, there may be only a very narrow window of benefit limited to patients undergoing successful reperfusion 2 to 6 h after symptom onset, but this needs additional careful study. So, although I applaud the perseverance and excellent work of Yetgin et al. (7), I doubt that intracoronary adenosine will become routine therapy after successful reperfusion therapy during acute MI any time soon.

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REFERENCES

1. Forman MB, Stone GW, Jackson EK. Role of adenosine as adjunctive therapy in acute myocardial infarction. Cardiovasc Drug Rev 2006;24:116–47.

2. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–20.

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3. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 2005;45: 1775–80.

4. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J 2006;27:2400–5.

5. Desmet W, Bogaert J, Dubois C, et al. High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction. Eur Heart J 2011;32: 867–77.

6. Fokkema ML, Vlaar PJ, Vogelzang M, et al. Effect of high-dose intracoronary adenosine administration during primary percutaneous coronary intervention in acute myocardial infarction: a randomized controlled trial. Circ Cardiovasc Interv 2009;2:323–9.

7. Yetgin T, Uitterdijk A, te Lintel Hekkert M, et al. Limitation of infarct size and no-reflow by intracoronary adenosine depends critically on dose and duration. J Am Coll Cardiol Intv 2015;8:1990–9.