Adenosine as an adjunct to reperfusion in myocardial infarction

Gerald Maurer

Department of Cardiology, AKH, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria

Online publish-ahead-of-print 22 September 2006

This editorial refers to 'Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial' by R.A. Kloner et al., on page 2400

Myocardial reperfusion, be it by thrombolysis or by PCI, is the only intervention that has been shown to reliably decrease both infarct size and mortality. Decreasing the time to initiation of reperfusion treatment and improving the efficacy of recanalizing the occluded coronary artery have had major impact on both myocardial salvage and clinical outcome. In spite of the success of reperfusion therapy, myocardial infarction continues to be associated with substantial morbidity and mortality. The search for additional means of myocardial salvage therefore continues and a multitude of approaches have been tried. One concern is that reperfusion may actually also have deleterious effects, including microvascular injury, myocardial stunning, and arrhythmias; reperfusion in and of itself has been postulated to even cause myocyte death, although this remains a matter of controversy.

Experimental evidence has suggested a number of possible treatments to diminish the effects of reperfusion injury, including antioxidants, agents to decrease blood viscosity, to improve perfusion, anti-inflammatory drugs, and strategies to reduce deleterious intracellular ion shifts, such as insulin–glucose–potassium, magnesium, or sodium hydrogen exchange inhibitors. Clinical trials have not consistently confirmed the usefulness of these approaches, and outcomes have overall been disappointing.

The agent that stands out as the most promising is adenosine, which appears to confer protection from ischemic injury not only in experimental animal models, but also in preliminary clinical studies of myocardial infarction, myocardial ischemia, and bypass surgery. A promising alternative approach to adenosine itself may be the use of adenosine-regulating agents, such as acadesine. This substance is believed to selectively increase interstitial adenosine concentration in ischemic tissue, thereby avoiding some of the potential side effects of adenosine, which include bradycardia and hypotension. In a large trial that included 2698 patients who underwent coronary artery bypass surgery, acadesine was recently shown to dramatically decrease mortality from perioperative myocardial infarction. A stimulation of the ischemic pre-conditioning pathways via adenosine was believed to be the principal mechanism of action in this study.

A number of possible protective mechanisms of adenosine have been reported. These include anti-inflammatory effects that may inhibit neutrophil adhesion to the endothelium and their migration into the myocardium, cytokine release from mononuclear cells, release of oxygen radicals and myocyte apoptosis, as well as an antiplatelet effect and vasodilatory properties. Reduction of the no-reflow phenomenon by adenosine has been suggested as one important mechanism by which adenosine is conferring its beneficial effects. Other explanations have included that adenosine may not only mimic ischemic pre-conditioning, but also post-conditioning.

Although the exact protective mechanisms of adenosine remain unclear, numerous experimental and clinical studies point to its beneficial effects and have provided the impetus for initiating larger prospective randomized clinical trials in the setting of myocardial infarction.

The first, the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial, was an open-label study designed to prospectively test the hypothesis that adenosine (infused at 70 μg/kg/min) as an adjunct to thrombolysis would reduce myocardial infarct size, as measured by SPECT imaging. In the 236 enrolled patients, there was an overall 33% relative reduction in infarct size when compared with placebo. Interestingly, the benefit was limited to patients with anterior infarction, where relative reduction in infarct size was 67%, with little evidence of benefit for infarcts located elsewhere. There was actually a tendency towards more clinical adverse events in the adenosine group, although the trial was not powered to evaluate clinical outcome.

The follow-up AMISTAD-II trial was a double-blinded placebo-controlled multicentre trial of 2118 patients with anterior ST-elevation myocardial infarction undergoing reperfusion therapy within 6 h of onset of symptoms, using either thrombolysis or primary angioplasty. Patients were randomized to a 3 h infusion of either adenosine 50 μg/kg/min, adenosine 70 μg/kg/min, or placebo.

© The European Society of Cardiology 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
A dose-response relationship with final infarct size was seen (11% at high dose, 23% at low dose vs. 27% with placebo). There was only a weak trend towards improvement in clinical outcomes, but the difference in primary endpoints (new onset congestive heart failure or death from any cause) between the pooled adenosine and placebo groups was not statistically significant; nevertheless, a significant relationship between infarct size and occurrence of primary endpoints was seen.

The current publication is a post hoc analysis of the patients included in the AMISTAD II trial. Its aim was to determine whether the efficacy of adenosine, when compared with placebo, was dependent on the timing of reperfusion therapy. This subanalysis did demonstrate that adenosine infusion administered as an adjunct to reperfusion within the first 3.17 h of onset of anterior ST-elevation myocardial infarction enhanced 1-month and 6-month survival and reduced the composite clinical endpoint of death or congestive heart failure. The benefit of adenosine was observed primarily in patients receiving thrombolysis, with a non-significant trend towards a benefit in patients undergoing PCI.

Although this post hoc analysis appears to point towards timing being an important factor not only for reperfusion, but also for adenosine therapy, it also raises a number of questions. It is not clear why a beneficial effect of adenosine should be seen with thrombolysis, but not with PCI and information on coronary artery patency rates and on microvascular perfusion is not available. Even more puzzling is the fact that in patients treated early, both the low- and the high-dose adenosine improved outcomes, even though only the high-dose adenosine reduced infarct size. As pointed out in the discussion section of this substudy publication, the dissociation between reduction of infarct size and clinical benefit raises questions about the mechanism leading to the clinical benefit, and the authors suggest that part of it may not be related to the degree of myocardial necrosis alone. This interpretation stands in contrast to the findings of the main AMISTAD II publication, where a significant relationship between infarct size and occurrence of primary endpoints was observed (as mentioned earlier), illustrating the difficulty of analysis that extends beyond the primary goals of the study.

Finally, we have to keep in mind that the currently published substudy is a post hoc analysis and not a prospectively designed trial. Although post hoc analyses can provide important insights and new ideas, they are also fraught with dangers. Such analyses should mainly be considered as means of generating a new hypothesis and cannot replace a proper prospective clinical trial.

Thus, although available evidence strongly points towards the beneficial role of adenosine for treating myocardial infarction, many open questions remain, including the optimal clinical indication, mode and timing of application, influence of patency rates, and the exact mechanisms leading to a benefit. Clarifying these issues will depend on further prospectively designed and adequately powered clinical trials, which can be expected to provide us with many answers but undoubtedly stand to also raise new questions.

Conflict of interest: none declared.

References

6. Yang X-M, Philipp S, Downey JM, Cohen MV. Postconditioning’s protection is not dependent on circulating blood factors or cells but involves adenosine receptors and requires P13-kinase and guanylyl cyclase activation. Basic Res Cardiol 2005;100:57–63.