Role of Adenosine in Acute Myocardial Infarction

The Acute Myocardial Infarction Study of ADenosine (AMISTAD II) is a pivotal trial having major clinical implications for the treatment of patients with acute myocardial infarction (AMI) (1). The AMISTAD II study corroborates the findings of the first AMISTAD study (2); it verifies that, as in animals (3), myocardial reperfusion injury significantly contributes to final infarct size in humans, and demonstrates that reperfusion injury accounts for >50% of the final infarct size after reperfusion.

Several issues regarding the design of the AMISTAD II study should be addressed. First, the study was severely underpowered. This was further compounded by having a second treatment arm with low-dose adenosine. The rationale for the second arm is unclear as the first AMISTAD study clearly shows that high-dose adenosine is efficacious with regard to reducing infarct size in patients with anterior AMI and does not cause serious adverse clinical events (2).

Second, because the beneficial effects of adenosine in experimental models occur only with reperfusion, adenosine should attenuate reperfusion injury only in reperfused patients. In the AMISTAD II study approximately 60% of the patients were treated with thrombolytic agents, with streptokinase used in almost 40% of these patients. This would result in only approximately 80% of patients undergoing successful reperfusion. A subset analysis of the primary clinical end points in the high-dose group who underwent successful reperfusion (placebo 15% vs. pooled adenosine 11%; p = 0.04), whereas no significant difference was found in patients who did not reperfuse (placebo 34% vs. pooled adenosine 33%; p = 0.7) (4).

Third, because animal studies demonstrate that adenosine’s beneficial effects are lost if myocardial ischemia occurs for more than 3 h (5), adenosine would prevent reperfusion injury only in patients receiving adenosine within the first 3 h after coronary occlusion. Therefore, a subset analysis of the high-dose group who were reperfused within 3 h may yield an even greater reduction in clinical end points. Indeed, data from the abstract presentation show strong trends in the combined end points in the pooled adenosine group treated within 2 h of symptoms (pooled adenosine 9% vs. placebo 13%) (4). This is further supported by the study of Marzilli et al. (6) in which patients undergoing mechanical reperfusion within 2 h of symptoms and who were treated with adenosine showed a significant improvement in ventricular function and a reduction in major adverse clinical end points.

Despite these shortcomings, the AMISTAD II study, taken in conjunction with other clinical studies with adenosine, has important implications for the treatment of AMI. Adenosine is the only agent that has been shown consistently to reduce infarct size and, in some studies, to improve clinical outcomes in AMI patients undergoing reperfusion therapy. Adenosine should therefore be added to the armamentarium of agents used to treat patients with AMI who are candidates for either pharmacologic or mechanical reperfusion strategies.

REFERENCES


hours of ischemia: effects on infarct size, ventricular function, and regional myocardial blood flow. Am Heart J 1990;120:808–18.

AMISTAD Trials: Possible Reasons for Lack of Success

Results of the Acute Myocardial Infarction STudy of ADenosine (AMISTAD II) trial were recently reported by Ross et al. (1). As in the AMISTAD I trial (2), most of the conclusions were at best equivocal, although subgroup analysis each time suggested adenosine might be useful as an adjunct to reperfusion therapy in certain patients with acute myocardial infarction. Thus the hope was raised that a more targeted trial might yield a significant difference between placebo and treatment groups. Although this possibility is real, we would like to offer an alternative hypothesis. Contrary to the twice-repeated assertion by the investigators that “adenosine...has consistently provided myocardial protection from ischemic injury in animal models,” the ability of adenosine administered at or shortly before reperfusion to provide cardioprotection against infarction is indeed quite controversial. There are certainly some studies which report that adenosine at reperfusion can decrease infarct size in various animal models, and some of these experimental investigations are acknowledged by Ross et al. (1). However, it is notable that two of the references cited by the researchers to justify their conclusion have been misquoted. Yao and Gross (3) and Thornton et al. (4) found protection when adenosine or an adenosine agonist was used as a preconditioning agent.

Furthermore, Thornton et al. (4) actually observed that when N6-(2-phenylisopropyl) adenosine (PIA) was infused at reperfusion, it had no cardioprotective effect despite its effectiveness when applied as a pretreatment. Also, numerous other preclinical studies have been unable to document an effect of authentic adenosine (5–8) at reperfusion on infarct size. Therefore, it is possible that both the inability to demonstrate a significant effect of adenosine at reperfusion in patients and the inconsistent preclinical results are because adenosine given at reperfusion simply does not protect the heart.

In the two AMISTAD trials it was reported that infarct size was significantly diminished in those patients with anterior wall myocardial infarction who were treated with adenosine. Although this observation is potentially important and noteworthy, a technical limitation diminishes the significance of the data. It has been recognized for many years that a major determinant of infarct size is the size of the region at risk. In fact, no experimental study of infarct size limitation would be accepted for publication if the size of the risk region were not quantitated and used to normalize the measurement of infarct size. It is recognized that it is difficult, but not impossible, to obtain these data in clinical studies because scans must be recorded both before and after the intervention. Reliance on absolute infarct size as a percentage of the left ventricle—despite the many reasonable correlations between this parameter and measures of ventricular function and clinical outcome, without normalization for the size of the region at risk — can yield incorrect conclusions. And this difficulty is perhaps best highlighted by the very different measurements of infarction in patients treated with placebo: 45% in the AMISTAD I study and 27% in the AMISTAD II study.

REFERENCES


REPLY

We thank Drs. Cohen and Downey for their interest in our report on treatment of anterior myocardial infarction with adenosine (1). We do not agree that we misquoted Yao and Gross (2) and Thornton et al. (3) with respect to the cardioprotective effects of adenosine. The Thornton et al. study was cited, with others, in stating that “adenosine has consistently provided myocardial protection from ischemic injury.” The Yao and Gross study (2) supports the statement that “adenosine and adenosine agonists are myocardial protectants.” We did not say that this protection was specifically related to the time of reperfusion, as implied. The reduction in infarct size may have been related also to other salutary effects of adenosine. In many patients the drug was on board during at least part of the time of coronary occlusion, and thus it might have a protective effect during ischemia. Certainly, in those receiving thrombolytic therapy, there was a time lag between administration of the lytic and when reperfusion was complete. Thus, it is possible that adenosine played a protective role during this time of continuing ischemia.

We do not agree that the difference in infarct size in the AMISTAD I and AMISTAD II studies somehow impugns the reliability of the single-photon emission computed tomography data in the AMISTAD II study. The validity of SPECT infarct