

## COMMENTARY

## Role of acadesine in clinical myocardial protection

Acadesine (AICA riboside, 5-amino-1- $\beta$ -D-ribofuranosyl-imidazole-4-carboxamide) is the prototype of a new class of compounds termed adenosine regulating agents. Acadesine is a purine nucleoside analogue that enters the myocyte and is immediately phosphorylated to ZMP (AICA ribotide), which is further metabolised to inosine monophosphate (an intermediate in the synthesis of adenosine triphosphate (ATP) and guanosine triphosphate).<sup>1-3</sup> Claims that acadesine may serve as a substrate for ATP synthesis and result in repletion of myocardial ATP were supported by some studies<sup>4</sup> and refuted by others.<sup>5-8</sup> Because acadesine may be a precursor in the synthesis of myocardial ATP it was proposed as a possible agent of myocardial protection during ischaemia, particularly because myocardial ATP depletion has been linked to cell death.<sup>9,10</sup> Initial studies suggested that acadesine can accelerate repletion of the adenine nucleotide pool during reperfusion<sup>4</sup> but subsequent reports did not.<sup>5-7</sup>

The myocardial protective properties of acadesine were shown in several in vivo models of myocardial ischaemia. Acadesine maintained contractile function and lessened the ST segment changes of the intramyocardial electrogram in dogs with pacing induced ischaemia.<sup>11</sup> It also suppressed ischaemia and reperfusion induced arrhythmias.<sup>12,13</sup> In various models of ischaemia acadesine improved blood flow to the ischaemic region causing preferential redistribution towards the subendocardium<sup>11,13</sup> and reducing the size of the evolving myocardial infarct.<sup>14</sup>

It has been suggested that the cardioprotective properties of acadesine may be mediated, at least in part, by increased release of adenosine in regions of ischaemia<sup>13,15,16</sup> because such regulation of the cardioprotective properties of acadesine was shown to be brought about by inhibition of endogenous adenosine formation<sup>16</sup> or rapid breakdown of newly formed adenosine.<sup>17</sup> It has been argued that because both acadesine<sup>13,18</sup> and adenosine<sup>19,20</sup> inhibit neutrophil activation, the adenosine-mediated protective effects of acadesine are attributable to attenuation of neutrophil activation which prevents neutrophil-dependent tissue injury.

Ely *et al* first suggested that adenosine has cardioprotective properties.<sup>21</sup> These protective properties are well established,<sup>19-25</sup> and they seem to mirror those of acadesine,<sup>5,13,14,26</sup> which suggests that the cardioprotection afforded by acadesine may be mediated by increased release of local adenosine.

Because acadesine does not influence basal adenosine concentrations in non-ischaemic regions or have cardiac or haemodynamic effects in the absence of ischaemia, its actions have been defined as "event specific and site specific". This implies that acadesine works only in regions of ischaemia that are undergoing net ATP breakdown, thus providing protection where it is most needed. The search for a reliable therapeutic agent designed to reduce the consequences of irreversible ischaemia continues, and it is not surprising that acadesine, with its unique protective properties, is considered to be such an agent. Though these unique properties of acadesine (event

specific and site specific) theoretically make it an attractive treatment in patients with acute myocardial infarction or unstable angina, its application in these conditions has not yet been tested. One argument against this potentially beneficial use is that acadesine must be present in the tissues before ischaemia and before irreversible myocardial injury has ensued. This may not be possible in patients who present hours after the initial symptoms. The same argument may not apply in those with unstable angina, because there is blood flow, albeit limited, to regions of ischaemia during episodes of angina and, in addition, collateral blood flow may also increase penetration of the drug into ischaemic zones. Because of its event and site specificity, acadesine administration does not produce systemic haemodynamic effects.<sup>11,13</sup> The haemodynamic effects associated with adenosine, such as hypotension and chronotropia<sup>23</sup>, are all but eliminated except when large doses of acadesine are given.<sup>27</sup>

Acadesine has been tried and tested in the setting of coronary artery bypass grafting (CABG) where both the onset and the duration of ischaemia can be predicted with a high degree of certainty. At least two clinical trials have attempted to evaluate the safety and the efficacy of acadesine in patients undergoing routine CABG. Initially Leung *et al* evaluated the effects of acadesine in a group of patients undergoing CABG.<sup>28</sup> Two treatment groups received high or low dose acadesine (intravenous infusion) as well as St Thomas's cardioplegia solution with added acadesine. Acadesine offered no added protection against ischaemia in either treatment group as judged by electrocardiography, creatine kinase MB fraction (CK MB), and transoesophageal Doppler criteria.

In a multicentre double blind prospective randomised study (unpublished data) acadesine (intravenous infusion of 0.1 mg/kg/min for seven hours and 5 mg/l of cardioplegia solution) was compared with a placebo. Patients were further stratified into high risk group (unstable angina, age > 70 years, previous CABG, ejection fraction < 30%, and acutely failed angioplasty), and a group not at high risk. The incidence of myocardial infarction defined by Q wave, necropsy, and CK MB criteria was not significantly different between the treatment and placebo groups. The incidence of myocardial infarction (Q wave or necropsy criteria) was significantly lower in the high risk group (10%) than in the group not at high risk (19.7%,  $P = 0.03$ ). Analysis of the CK MB data showed no difference in the incidence of myocardial infarction. The inconsistency in the reported CK MB concentrations could reflect differences in the timing of sample collection at the various centres in the study.

Acadesine remains an interesting investigative tool for the evaluation of ischaemia and reperfusion injury that has yet to realise its potential as a therapeutic agent in clinical practice.

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