SCIENTIFIC LETTER

Does adenosine prevent myocardial micronecrosis following percutaneous coronary intervention? The ADELINE pilot trial

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After successful percutaneous coronary intervention (PCI), 24–44% of patients suffer some myocardial damage as indicated by a significant change in the concentrations of cardiospecific troponin or the MB isoenzyme of creatine kinase (CK-MB).[1 2] Patients with minor increases of these cardiac markers after PCI constitute a population with a worse long term prognosis.[3] Preconditioning of human myocardium can be obtained by intracoronary administration of adenosine, as indicated by attenuation of ischaemia and chest pain in patients undergoing PCI.[4] In the present trial (ADELINE, does ADEnosine Limit myocardial Necrosis), we investigated the effect of intracoronary administration on chest pain and ischaemia during a 90 second balloon inflation during PCI. In addition, we evaluated the release of cardiac markers after angiographically successful coronary intervention.

METHODS

Patients were eligible when a PCI was planned of a lesion in a primary or secondary branch of either coronary artery, supplying a sizeable area of myocardium.

Exclusion criteria were: myocardial infarction during the previous two weeks; use of theophylline preparations, dipyridamole or glibenclamide; bronchial asthma; second or third degree atrioventricular block, and recanalisation of a total occlusion. This study was approved by the institutional review board, and written informed consent was obtained from all patients.

In this single centre, single blind study, 32 patients were randomly allocated to a control or an adenosine treated group. One patient was excluded because of occlusion of a major branch during PCI, and three patients were excluded because of missing data (no blood sample after 24 hours). The resulting study population involved 12 patients in the adenosine group and 16 patients in the placebo group (table 1). In the case of planned PCI of the right coronary artery (RCA), an external pacemaker was kept on standby, to allow for pacing via the guide wire in case of significant bradycardia.

Adenosine concentrations of 0.25 mg/ml and 0.50 mg/ml were used for PCI of the RCA and left coronary artery (LCA), respectively. Intracoronary infusion was performed at a rate of 4 ml/min (that is, 1 mg/min in the RCA or 2 mg/min in the LCA) over a 10 minute period. The control group received an equivalent volume of normal saline. Thereafter, a drug-free waiting period of exactly 10 minutes was maintained. During the last minute of this waiting period, an intracoronary ECG was recorded at 50 mm/s and 10 mm/mV for 10 seconds. The first balloon inflation was initiated exactly 10 minutes after the end of infusion of the study drug, and maintained for 90 seconds. During the last 10 seconds of this balloon inflation, the intracoronary ECG was recorded again. Thereafter, the procedure was completed at the discretion of the operator.

The intracoronary ECG recordings were analysed by a cardiologist unaware of the treatment allocation. ST segment shift was measured 80 ms after the J point, and expressed in millimeters.

At the end of the study drug infusion and at the end of the first balloon inflation, the intensity of chest pain was assessed with a 200 mm visual analogue scale.[5]

At the beginning of the procedure and 24 hours after the procedure, a serum sample was taken for determination of CK-MB and troponin I.

All data are presented as mean (SD). Comparisons within one group were performed using Student's *t* test, and proportions between groups were compared using the Fisher exact test.

RESULTS

Coronary angioplasty was successfully performed in all 28 patients. Heart rate and arterial blood pressure did not differ between the two study groups before and after drug infusion (table 1).

The mean ST elevation during balloon inflation was 7.3 (7.7) mm in the adenosine group and 12.4 (10.5) mm in the control group. The ST segment shift was higher in the control group (12.4 (11.1) mm) than in the adenosine treated group (6.1 (5.5) mm) ($p = 0.085$). The ST segment shift was greater than 10 mm in one of 12 adenosine treated patients and in eight of 16 control patients ($p = 0.119$).

The severity of chest pain during infusion of study drug was 50 (46) mm in the adenosine treated group and 3 (10) mm in the control group ($p < 0.001$). During balloon inflation, there was no difference in severity of chest pain between the two treatment groups (table 1).

In the adenosine treated group, CK-MB rose from 2.08 (1.29) µg/l before the procedure to 3.23 (2.02) µg/l 24 hours later ($p = 0.06$), and in the control group from 2.04 (1.05) µg/l to 9.41 (9.86) µg/l ($p = 0.011$). There was a significant difference in CK-MB increase between the adenosine treated and the control group (1.15 (1.90) *v* 7.36 (10.12) µg/l, $p = 0.047$).

A rise in CK-MB to > 5 µg/l occurred in two of the 12 patients in the adenosine treated group and in eight of the 16 patients in the control group ($p = 0.16$).

Troponin I increased from 0.86 (2.05) µg/l to 1.94 (2.48) µg/l ($p = 0.189$) in the adenosine treated group, and from 0.23 (0.50) µg/l to 3.09 (4.92) µg/l ($p = 0.037$) in the control group.

Nine out of the 12 patients receiving adenosine developed transient chest pain during the infusion of the nucleoside, which resolved promptly after the end of the infusion.

In one patient with a dominant left circumflex artery and a chronically occluded RCA undergoing PCI of an intermediate

Abbreviations: ADELINE, does adenosine limit myocardial necrosis; CK-MB, MB isoenzyme of creatine kinase; LCA, left coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery

Table 1 Clinical, anatomic and haemodynamic features, and serum cardiac markers in adenosine treated and control groups

	Control group (n=16)	Adenosine treated (n=12)	p Value
Clinical features			
Age (years)	66 (11)	59 (9)	
Sex (male/female)	10/6	12/0	
Anginal syndrome on admission (n)			
CSS class 1–2	11	5	
CSS class 3–4	5	7	
Antianginal medications (n)			
β Blocking agents	11	9	
Calcium channel blocking agents	7	5	
Long acting nitrates	7	4	
Anatomic and haemodynamic features			
Vessel undergoing PTCA (n)			
LAD	5	8	NS
LCx	6	3	
RCA	5	1	
Maximal balloon diameter (mm)	3.0 (0.3)	3.0 (0.5)	NS
Maximal balloon pressure (atm)	9.7 (3.8)	8.1 (3.1)	NS
Stent implantation (n)	8	5	NS
Systolic blood pressure (mm Hg)			
Before study drug infusion	151 (36)	128 (18)	NS
After study drug infusion	154 (40)	132 (22)	NS
Diastolic blood pressure (mm Hg)			
Before study drug infusion	76 (12)	77 (9)	NS
After study drug infusion	78 (13)	77 (9)	NS
Heart rate (beats/min)			
Before study drug infusion	71 (14)	70 (9)	NS
After study drug infusion	71 (12)	74 (9)	NS
Chest pain score			
During study drug infusion	3 (10)	50 (46)	<0.001
During balloon inflation	75 (59)	82 (53)	NS
ST segment shift (mm)	12.4 (11.1)	6.1 (5.5)	0.085
Serum cardiac markers			
Before PTCA			
CK-MB (µg/l)	2.04 (1.05)	2.08 (1.29)	NS
Troponin I (µg/l)	0.23 (0.50)	0.86 (2.05)	NS
24 hours after PTCA			
CK-MB (µg/l)	9.41 (9.86)	3.23 (2.02)	0.043
Troponin I (µg/l)	3.09 (4.92)	1.94 (2.48)	NS
Difference between before and 24 hours after PTCA			
CK-MB (µg/l)	7.36 (10.12)	1.15 (1.90)	0.047
Troponin I (µg/l)	2.85 (5.00)	1.09 (2.69)	NS

CCS, Canadian Cardiovascular Society; CK-MB, MB isoenzyme of creatine kinase; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery.

branch, second degree atrioventricular block developed during infusion of adenosine, for which pacing by means of the guidewire was necessary. Atrioventricular conduction recovered promptly after discontinuation of adenosine. In the only patient with infusion of adenosine in the RCA, extreme lengthening of the P–R interval developed.

The infusion of adenosine did not produce any changes in heart rate or blood pressure.

DISCUSSION

Intracoronary infusion of adenosine resulted in considerable chest pain in the majority of our patients. This may be explained by the non-selective infusion through the guiding catheter.

The reduction in ST segment shift during balloon inflation after adenosine infusion in the present study was less pronounced than in a previous study,[4] and chest pain during balloon inflation was similar in the two treatment groups. These observations suggest a less profound preconditioning effect. Although we used the same infusion rate and total dose as in that study, because of the non-selective infusion, a significant proportion of the drug is certain to go to non-target coronary artery branches. Consequently, the amount of adenosine reaching the myocardial territory that is subsequently being rendered ischaemic by balloon inflation could be insufficient to obtain maximal potential preconditioning effect.

The most important finding of this study is a reduced release of serum cardiac markers 24 hours after the procedure, reaching borderline significance.

Our findings foster hope that by further optimisation of the route of administration and dosage, prevention of myocardial necrosis by means of adenosine or other cardioprotective agents may enter clinical practice.

Preconditioning using intracoronary administration of adenosine resulted in a limitation of myocardial damage caused by coronary intervention. Clinical implications and applicability and efficacy of a simplified protocol merit further investigation in a larger trial.

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IMAGES IN CARDIOLOGY

Supernormal conduction mimicking a supraventricular capture beat during wide complex tachycardia

A 64 year old women was admitted because of palpitations and a rapid pulse rate. She had a history of coronary heart disease, diabetes, and arterial hypertension. Her medication comprised ramipril, aspirin, amitriptyline, and insulin. This ECG was taken upon admission and shows a tachycardia (136 beats/min) with a left bundle branch block and left axis morphology. A premature, more narrow complex was recorded (arrow) during the tachycardia. It was classified as a supraventricular capture beat, consistent with a diagnosis of ventricular tachycardia. However, the QRS morphology during tachycardia and the right axis vector of the presumed capture beat cast doubt on the diagnosis. Carotid sinus massage had no effect. A 12 mg dose of intravenous adenosine was administered that led to complete atrioventricular block, cessation of the tachycardia, disclosure of atrial flutter, and persistence of the left bundle branch block morphology of the QRS complex, as seen during tachycardia.

The most likely explanation for the "pseudocapture beat" is supernormal conduction of an atrial flutter beat along the left anterior bundle, with persistence of block along the left posterior bundle. Supernormal excitability and conduction are observed during a short period at the end of the recovery phase of the action potential, when an otherwise subthreshold stimulus can depolarise the membrane and be propagated faster than during normal resting potential.

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