Lack of cardioprotective efficacy of allopurinol in coronary artery surgery

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Abstract

***Objective*—To examine the cardioprotective efficacy of allopurinol in patients undergoing elective coronary artery surgery.**

***Design*—Prospective randomised trial.**

***Setting*—London teaching hospital.**

***Patients*—Twenty patients with at least moderately good left ventricular function undergoing elective coronary artery surgery and requiring at least two bypass grafts.**

***Interventions*—Patients were randomised to receive allopurinol (1200 mg in two divided doses) or to act as controls.**

***Main outcome measure*—The primary determinant of the efficacy of myocardial protection was serial measurement (preoperatively and subsequently at one, six, 24, and 72 hours after the end of cardiopulmonary bypass) of cardiac troponin T (cTnT) a highly sensitive and specific marker of myocardial damage. Additional evidence was provided by serial measurement of the MB-isoenzyme of creatine kinase (CK-MB) and myoglobin, ECG changes, and clinical outcome.**

***Results*—There was no significant difference in age, ejection fraction, number of grafts, bypass times, or cross clamp times between the two groups. In both groups there was a highly significant ($p < 0.01$) rise in cTnT, CK-MB, and myoglobin. Peak concentrations were reached between one (CK-MB and myoglobin) and six hours (cTnT) after the end of cardiopulmonary bypass. At 72 hours cTnT concentrations were six times higher than baseline concentrations whereas CK-MB and myoglobin were approximately double baseline concentrations. There was no significant difference in cTnT, CK-MB, or myoglobin between the allopurinol and control groups at any time. There was no diagnostic ECG evidence of perioperative infarction in any patient.**

***Conclusion*—Unlike previous reports this study did not show that allopurinol had a cardioprotective effect in patients with good left ventricular function undergoing elective coronary artery surgery.**

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Pretreatment with allopurinol in experimentally induced ischaemia may reduce infarct size and the incidence of arrhythmias and may improve myocardial function.[1-3] More recently allopurinol has been reported to reduce the mortality[4] and morbidity of cardiac surgery.[5,6]

Both experimentally and clinically the beneficial action of allopurinol has been attributed to its ability to interfere with the production or actions of oxygen derived free radicals. Free radicals, generated by the oxygenated reperfusion of ischaemic tissues, possess an unpaired electron and are highly reactive molecules capable of damaging biological structures. There is now a considerable body of experimental and clinical evidence to incriminate free radicals in myocardial dysfunction ("stunning") associated with reperfusion after an ischaemic interval.[7-12] Only recently, however, has conclusive evidence of their generation during cardiac surgery been presented.[11-13]

In experimentally induced ischaemia the most important effect of allopurinol (or its primary active metabolite oxypurinol) is the inhibition of xanthine oxidase. In mammalian hearts, however, there is little xanthine oxidase activity[14] and the main sources of free radicals are probably the mitochondria, activated neutrophils, and the arachidonic acid cascade.[13] It has been postulated that the protective mechanism of allopurinol or oxypurinol in the mammalian heart may be due directly to its free radical scavenging properties[15]; whatever the mechanism allopurinol has been reported to significantly improve the results of cardiac surgery.[4-6]

To investigate clinically the proposed cardioprotective efficacy of allopurinol we randomised 20 patients undergoing elective coronary artery surgery to receive allopurinol (1200 mg in two divided doses) or to act as controls. Evidence for any cardiac protective effect of allopurinol was assessed by clinical course, electrocardiographic changes, and serial measurement of cardiac troponin T (cTnT), the MB-isoenzyme of creatine kinase (CK-MB), and myoglobin.

Methods

The study was approved by the Hospital Ethics Committee and all patients gave written informed consent.

We studied 20 men undergoing elective coronary surgery. To keep the group as homogeneous as possible the following patients were excluded: those already taking allopurinol: those aged over 70 or those

Table Clinical characteristics of patients

	Control (n=10)	Allopurinol (n=10)
Age (yr)	60	60
Ejection fraction (%)	56	49
Grafts (n)	2·8	3·0
Use of internal mammary artery	10	9
Cardiopulmonary bypass time (min)	63	70
Ischaemic time (min)	33	34

There was no significant differences between groups.

requiring emergency surgery; those with ejection fractions estimated to be less than 30%; and those requiring endarterectomy or combined procedures: those with renal impairment (metabolism of allopurinol impaired).

RANDOMISATION

Patients were randomised to allopurinol or no treatment by a computer generated programme.

DRUG TREATMENT

Patients allocated to allopurinol (1200 mg) received the drug in two divided doses (600 mg the evening before and 600 mg at 0600 on the morning of operation).

SURGERY

Cardiopulmonary bypass was performed with non-pulsatile flow at 2·4 l/m^2 of body surface area/minute with the body temperature allowed to drift to 34°C. The coronary anastomoses were performed with alternating brief periods (about 10 minutes) of aortic cross clamp and fibrillation for the distal anastomosis and reperfusion during the proximal anastomosis.

BLOOD SAMPLES

Blood samples for measurement of CK-MB, myoglobin, and troponin T were obtained preoperatively and subsequently at one, six, 24, and 72 hours after the end of cardiopulmonary bypass. Samples were collected into tubes containing lithium heparin and centrifuged within 30 minutes. The plasma was separated from the cells, and stored at −20°C until analysed.

BIOCHEMICAL ANALYSES

cTnT was measured by an enzyme linked immunoadsorbent assay technique (ELISA Troponin T Kit, Boehringer Mannheim, Lewes, UK). The coefficient of variation between assays was 4·3% at troponin T concentrations of 4·8 μg/l and 12·9% at concentrations of 0·2 μg/l. CK-MB was measured by microparticle enzyme immunoassay with the Abbott IMX CK-MB kit and an Abbott IMX analyser (Abbott Diagnostics Division, Maidenhead, UK). Myoglobin was assayed by a double antibody radioimmunoassay (Myoglobin RIA Test Kit, Biogenesis, Bournemouth, UK).

ELECTROCARDIOGRAPHIC DIAGNOSIS OF MYOCARDIAL INFARCTION

Serial electrocardiograms were performed at one, six, 12, 24, and 72 hours after surgery. A new persistent Q wave (>0·04 ms) or loss of >25% of R waves in at least two leads were considered indicative of perioperative infarction. Minor ST-T wave changes and changes in conduction were not, by themselves, considered diagnostic of myocardial infarction.

STATISTICAL ANALYSES

Data from patients are presented as mean (SD). Biochemical data are presented as median (SEM) to allow comparison with previously published data. Serial changes within and between the allopurinol and control groups were compared with the Wilcoxon rank sum test.

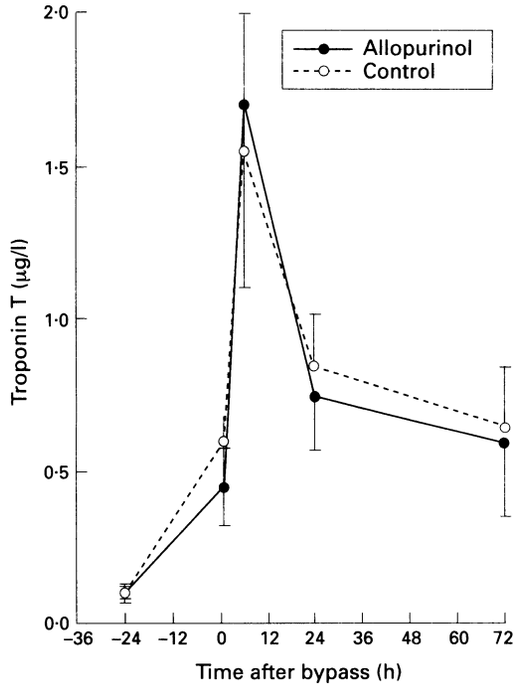

Figure 1 cTnT concentration (mean (SEM)) in allopurinol and control groups.

Results

The study comprised 20 men undergoing elective coronary artery surgery randomised to receive allopurinol or no drug treatment. There were no significant differences in age, ejection fraction, number of grafts, bypass times, or cross clamp times between the two groups (table).

There was a highly significant increase in cTnT concentration one hour after the end of cardiopulmonary bypass (fig 1). By contrast with CK-MB and myoglobin, cTnT peak concentrations were not reached until six hours after cardiopulmonary bypass and were 16 times higher than baseline concentrations. At 24 hours cTnT concentrations were six times the baseline concentrations in both groups with little further change by 72 hours. There was no signficant difference between the groups.

In both groups there was a highly significant ($p < 0·01$) rise in the CK-MB isoenzyme concentration throughout the postoperative period with peak concentrations between one and six hours after the end of cardiopulmonary bypass (fig 2). CK-MB remained raised at 24 hours but had returned towards baseline concentrations by 72 hours. There was no significant difference between the groups.

In both groups there was a highly significant rise ($p < 0·01$) in myoglobin with peaks between 1 and 6 hours after the end of cardiopulmonary bypass (fig 3). Myoglobin concentrations remained significantly raised at 24 hours and had returned towards, but

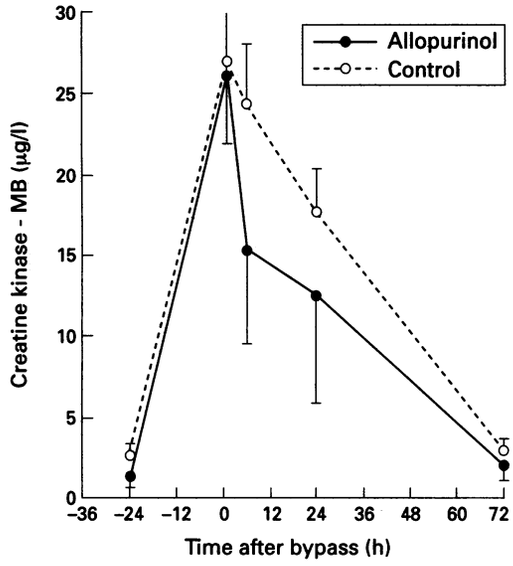

Figure 2 CK-MB concentration (mean (SEM)) in allopurinol and control groups.

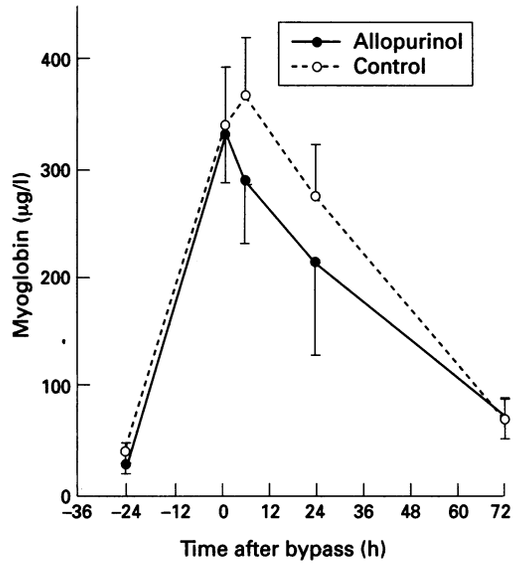

Figure 3 Concentration of myoglobin (mean (SEM)) in allopurinal and control groups.

were still about double, baseline concentrations by 72 hours. There was no significant difference between the groups.

Serial electrocardiograms in the postoperative period only showed occasional minor ST-T wave changes and no Q wave infarcts. All patients had an uneventful recovery and were discharged home on the seventh or eighth day after operation.

Discussion

Before discussing the results of this trial it is appropriate to comment on the methods for assessing postoperative myocardial damage.

Measurement of cardiac performance is the best method of measuring myocardial injury but it is difficult in clinical practice.[16] Consequently, conventional assessment of myocardial damage is based on serial changes in cardiac enzymes and the electrocardiogram. Although these techniques can detect or confirm major myocardial damage[17] they are of limited use in quantifying more subtle levels of myocardial injury. During cardiac surgery creatine kinase and lactate dehydrogenase are released from both cardiac and non-cardiac tissues,[18,19] and non-specific ST segment and T wave changes are common electrocardiographic findings. The MB isoenzyme of creatine kinase, although more cardiospecific than creatine kinase, is not entirely cardiospecific and can originate from skeletal muscle during cardiac operations.[18-20] Myoglobin rises first and is the earliest indicator of myocardial injury.[20] Although it improves the accuracy of quantifying myocardial damage after cardiac operations it is also released from skeletal muscle.

T cTnT is a cardiospecific protein derived from the tropomyosin binding protein of the troponin regulatory complex (subunits I, C, and T) on the thin filament of the myocardial contractile apparatus.[21] Because cTnT exists as a unique isoform distinct from the skeletal muscle isoform[22] it can specifically identify myocardial damage in various clinical settings.[23-28] Katus *et al* compared circulating cTnT and CK-MB isoenzyme in 56 patients undergoing cardiac surgery and 34 control patients undergoing non-cardiac surgery. cTnT was raised in all patients undergoing cardiac surgery and the most persistent rises were in the five patients with Q wave infarcts.[23] cTnT was not raised in any of the control patients whereas CK-MB was raised in 25%.

Our trial showed no significant difference in any of the biochemical indices of myocardial damage between the allopurinol and control groups. Mair *et al* reported that cTnT concentrations of <2·5 μg/l rule out clinically relevant myocardial injury.[25] The peak concentration of cTnT in both our groups was approximately 1·7 μg/l, similar to that previously reported in patients undergoing uneventful cardiac surgery and less than one fifth the value found in patients with perioperative infarction.[22] The peak concentration of the CK-MB isoenzyme in both our groups was < 30 μg/l, similar to that previously reported in patients undergoing uneventful cardiac surgery and less than one third the value found in patients with acute myocardial infarction.[20,23] The peak concentration of myoglobin in both groups was <400 μg/l, similar to the concentration previously reported in patients undergoing uneventful cardiac surgery and less than one eighth the value found in patients with acute myocardial infarction.[20]

These results, together with the lack of any electrocardiographic evidence of Q wave infarction imply that none of our patients sustained major myocardial injury. Nevertheless, as the half life of troponin T is two hours,[23] six hours for CK-MB,[29] and eight hours for myoglobin[30] the continuing release of cTnT, CK-MB, and myoglobin at 24 to 72 hours may imply ongoing minor myocardial injury and be consistent with the minor ST-T wave changes often found. Katus *et al* have shown that cTnT occurs in myocytes both within a small cytosolic pool and a larger structurally bound fraction.[31] It is possible that the six

hour peak in cTnT is due to leakage of troponin from the cytosolic pool, indicating reversible cellular damage whereas the continuing increase in cTnT concentrations beyond 24 hours probably reflects ongoing release from disintegration of contractile myofibrils.[23 26 31]

Our failure to detect any cardioprotective effect of allopurinol contrasts with previously published reports[4-6] although we used a similar dose regimen and studied comparable patients in terms of age and ejection fraction to those described in these studies. Allopurinol is absorbed rapidly from the upper gastrointestinal tract and 60% is converted to its primary active metabolite oxypurinol, which has a half life of 18–30 hours compared with 1·25 hours for allopurinol.[10] Consequently a once daily dose achieves a therapeutic effect.

In a randomised trial of 169 patients undergoing elective coronary artery surgery Johnson *et al* reported a reduction in mortality from 18% in the placebo group to 4% in the allopurinol group.[4] The mortality in the control group, however, (elective patients with a mean age of 61 years and a mean ejection fraction of 47%) seemed particularly high. In a randomised (but non-blinded) study of 90 patients undergoing coronary revascularisation Rashid *et al* reported no difference in mortality but a significant reduction in arrhythmias, infarction, and requirement for inotrope or an intra-aortic balloon pump in the allopurinol group.[5] Again, however, the need for inotropes or an intra-aortic balloon pump in 38% of the control group (mean age 63 years, most with an ejection fraction >50%) seemed excessively high. In a non-randomised study of 90 patients undergoing cardiac surgery Tabayashi *et al* reported a significant reduction in cardiac enzyme release with a high dose of allopurinol.[6] The differing nature of the cardiac operations in their allopurinol and control groups, however, confused interpretation of the results.

Das *et al* have reported that allopurinol and oxypurinol are direct scavengers of free radicals.[15] This explains their beneficial effects in mammalian cardiac ischaemia even in the absence of xanthine oxidase. Our failure to show any beneficial action of allopurinol could be due to an insufficient dose of allopurinol (although it was similar to that used in other clinical studies) or the possibility that free radicals are not important determinants of myocardial injury in cardiac surgery.

There is still no consensus on the optimal technique of myocardial protection during cardiac surgery. Cold crystalloid cardioplegia is the most widely used but many surgeons still use non-cardioplegic techniques for coronary revascularisation with excellent clinical results.[32-34] Our cTnT results suggest that the intermittent ischaemic arrest technique results in only minor myocardial damage, comparable with that in which cardioplegia was used for myocardial protection.[24 25]

In summary our study did not show any cardioprotective effect of allopurinol in patients with good left ventricular function undergoing elective coronary artery surgery. Whether allopurinol may be of benefit in older and sicker patients with unstable angina or poor left ventricular function is unknown.

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ABSTRACTS IN CARDIOLOGY

Does X equal endothelial dysfunction?

In people with angiographically normal coronary arteries, angina caused by myocardial ischaemia (syndrome X) is probably the result of microvascular dysfunction. The finger of suspicion has been pointed at the endothelium but without convincing evidence until now (abstract). Egashira and colleagues, however, have now shown that the response of coronary blood flow to acetylcholine (an endothelium-dependent vasodilator) in the coronary microcirculation of these patients is impaired. So is endothelial dysfunction the cause of the angina and the end of the story?

The physiological role of endothelium-dependent dilatation in the microcirculation is not well understood. Impairment of endothelium-dependent dilatation of the coronary microvasculature has been demonstrated in patients with hypercholesterolaemia, hypertension, and heart failure. It does not apparently cause chest pain in these patients. The implications of the current study by Egashira *et al* are either that coronary microvascular endothelial dysfunction is somehow more pronounced in microvascular angina or that some other factor must be abnormal for chest pain to develop.

The challenge to understand this syndrome remains. This new finding is important, but probably not alone equal to X.

CHRIS J H JONES

Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms

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Abstract

***Background*—**A group of patients has been described who have chest pain resembling angina and positive exercise tests, but normal coronary angiograms and no coronary-artery spasm. This constellation of features has sometimes been called syndrome X or microvascular angina. We attempted to determine whether endothelium-dependent vasodilatation of the coronary vasculature was impaired in patients with this syndrome.

***Methods*—**We infused the endothelium-dependent vasodilator acetylcholine and the endothelium-independent vasodilators papaverine and isosorbide dinitrate into the left coronary artery of nine patients and 10 control subjects. The diameter of the left anterior descending coronary artery was assessed by quantitative angiography, and changes in coronary blood flow were estimated with the use of an intracoronary Doppler catheter.

***Results*—**Acetylcholine, given in doses of 1, 3, 10, and 30 μg per minute, increased coronary blood flow in a dose-dependent manner in both groups. However, the mean (±SD) acetylcholine-induced increases in coronary blood flow were significantly less ($P < 0.001$) in the patients (8±14, 37±37, 59±67, and 103±77 percent, respectively) than in the controls (62±52, 186±93, 341±128, and 345±78 percent, respectively). The changes in coronary blood flow in response to 2 mg of isosorbide dinitrate (236±66 percent vs. 280±56 percent) and 10 mg of papaverine (366±168 percent vs. 411±92 percent) did not differ significantly between the patients and controls. The administration of papaverine resulted in myocardial lactate production in the patients but not in the controls. The three lower doses of acetylcholine caused a similar degree of dilatation of the left anterior descending coronary artery in the two groups, and the highest dose caused a similar degree of constriction in the two groups. Isosorbide dinitrate and papaverine caused a similar degree of dilatation in both groups.

***Conclusions*—**These findings suggest that endothelium-dependent dilatation of the resistance coronary arteries is defective in patients with anginal chest pain and normal coronary arteries, which may contribute to the altered regulation of myocardial perfusion in these patients. (*N Engl J Med* 1993;328:1659–64.)