LETTERS TO THE EDITOR

- The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.
- All letters must be typed with double spacing and signed by all authors.
- No letter should be more than 600 words.
- In general, no letter should contain more than six references (also typed with double spacing).

Immunoglobulin response to intravenous streptokinase in acute myocardial infarction

Sir,—Lynch et al’s study (Br Heart J 1991;66:139-42) contributes to the growing body of information on the immune response after administration of intravenous streptokinase for acute myocardial infarction. The current focus has been on the length of the period during which important titers of antibodies to and neutralising capacity for streptokinase persist (these do not always correlate precisely). Studies by Lynch et al’ and Jalilal and Morris’ showed that this period extends at least to 12 months, and further work is awaited to determine the outer limit of this period. During this period streptokinase should not be re-administered because of fears of an anaphylactic reaction and also that the drug will be neutralised and hence ineffective.

The current recommendations of the 1990-91 Data Sheet Compendium are that a second dose of streptokinase should not be given within a period of five days to six months after the first. A recent Drug and Therapeutics Bulletin states that this will soon be amended to a 12 month interval. Recent authoritative papers’ have been broader in their recommendations, suggesting that streptokinase and anistreplase should not be re-administered within a year, and the latter paper concluded with the assertion that tissue plasminogen activator (alteplase) should be used if repeat thrombolysis is required (no time limit was stated so it presumably extended indefinitely from day 0). A policy of not repeating streptokinase for a year from day 0 has been widely adopted. These conclusions are important because alteplase costs ten times as much as streptokinase.

This policy loses sight of the early window that exists before the development of a significant immune response to streptokinase. This is a worthwhile opportunity given that 9% of patients will reinfarct in the first year after thrombolysis. In a substantial number of these patients reinfection requiring repeat thrombolysis occurs in the first few days after thrombolysis. In White et al’s 1990 study of repeat thrombolysis after myocardial infarction 31 patients were treated for recurrent myocardial infarction after thrombolysis between one and 716 days after initial thrombolysis. The median interval was only five days and 10 of the 31 patients were treated in the first three days. Lynch et al’s study shows that antibody titres to streptokinase (IgG) do not rise above baseline until day four, suggesting a significant immune response (either anaphylactic or neutralising) is unlikely before this. The work of Massel et al on neutralising antibody showed a neutralising capacity equivalent to 1 x 10⁵ units streptokinase between day one and nine in all of their patients’ (this small study (11 patients) may not have adequately defined the normal range). This again suggests that there is an early opportunity for non-streptokinase thrombolytic safety and effectively. Indeed though White et al recommended that streptokinase should not be re-administered within a year they did show that readministration within this period was effective (albeit with an increased incidence of minor side effects).

This evidence suggests that streptokinase can be readministered safely and effectively from 0 to 3 days after the initial event. A further large study of neutralising capacity would be helpful because the most recent study dealt only with antibody response and a previous study of neutralising capacity was small. If this policy is refined to be readministered on the day 0 to 1 year policy, which seems to be emerging, it is likely to have an impact on coronary care unit drug bills.

SCD GRANT
Department of Cardiology, Wythenshawe Hospital, Beechmore Road, Manchester M23 9LT

4 Drug Ther Bull 1991;29:16.

This letter was shown to the authors and an advisor, who reply as follows:

This letter’s author is Harold Grant, MD, FRCP, FRCPA, Clinical Director, Cardiology, Royal Brisbane Hospital, Brisbane, Australia.

Sir,—We are grateful to Dr Grant for his comments. We agree, as stated in our final paragraph, that it would be prudent to avoid repeating the dose between three days and at least one year after the initial treatment with streptokinase. After treatment with streptokinase, the antibody titre (IgG, subclass IgGl) virtually disappears, presumably because the antibodies react with the antigen, streptokinase. Subsequently, there is a gradual rise in antibody titre, which does not become significantly higher than baseline titre until day 4. During this time window of 3-12 days, when there are no higher than pretreatment titres, it is probably as safe and effective to re-administer streptokinase in the event of a repeat infarction as in the case of the initial infarct. We are continuing a multinational streptokinase administration study in five countries that includes 20 patients, who have now reached the 18 month time point. Though they are gradually declining, the mean (SD) IgG titres to streptokinase are still significantly raised at two years (86±42 vs 90±42 IU/ml, p<0.05). Repeat infarction after 72 hours and until at least 18 months after the initial infarct should probably be managed with a non-streptokinase thrombolytic agent until the significance of these antibodies is known.

MARY LYNCH BL PENTECOST BL WA LITTLE
WA STOCKLEY
Lung Immunobiochemical Research Group, Department of Cardiology, General Hospital, Steeplehouse Lane, Birmingham B4 6NH and Department of Cardiology, Queen Elizabeth Medical Centre, Birmingham

Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease

Sir,—McCance and Forfar (Br Heart J 1991;66:316-9) reported the effects of adrenaline on the development of ischaemia and arrhythmia in patients with ischaemic...
heart disease. One of their principal findings was that adren aline produced ischaemia at a lower rate-pressure product than exercise. This raises many important questions about the mechanisms through which catecholamines produce ischaemia and about how such ischaemia can be prevented.

McCance and Forfar postulate that redistribution of coronary flow is the mechanism underlying the greater ischaemic effect of exercise compared with recent biochemical data suggest an alternative explanation. Adrenaline (released from the adrenal medulla during stress) is a more potent stimulator of the β-2 subtype of adrenoreceptor than adrenaline (released from the sympathetic nerve endings during exercise). Stimulation of cardiac β-2 adrenoreceptors, like β-1 adrenoreceptors, may possess different inotropic and chronotropic effects. However, biochemical studies have shown important differences in the linkage of β adrenoreceptor subtypes to cardiac adenylyl cyclase, with a higher proportion being linked to β-2 adrenoreceptors than to β-1 adrenoreceptors. Not all adenylyl cyclase when activated leads to increased contractility; therefore, adrenaline activation of adenylyl cyclase not linked to contraction (possibly involving other metabolic pathways) may lead to a further increase in oxygen consumption. This differential coupling to adenylyl cyclase may explain why adrenaline infusions produce greater ischaemia than exercise for a given rate-pressure product.

Whatever the underlying mechanism, this study has important therapeutic implications. By failing to block β-2 adrenoreceptors selectively β-1 blockade will be inferior to non-selective β-blockade at antagonising the effects of adrenaline. Additional selective β-1 blockade may actually lead to an enhancement of the ischaemic and arrhythmogenic effects of adrenaline because β-1 blocker treatment leads to a selective enhancement of the sensitivity of the heart to β-2 adrenoreceptor stimulation. This may have enhanced the differences between exercise and adrenaline infusions seen in McCance and Forfar’s study since 13/14 patients were taking a β-1 selective blocker (atenolol, metoprolol, and bisoprolol) until a few days before the study. Therefore this study adds further weight to the argument that non-selective β blockade may have advantages over β-1 selective blockade during stress—for example, myocardial infarction.


This letter was shown to the authors who reply as follows:

Sir,—We thank Hall and Ferro for their interesting comments on our paper. The mechanism of our observation that adrenaline produced ischaemia at a lower rate-pressure product than exercise is still speculative, but we agree that the mechanism proposed by Hall and Ferro is also consistent with our data.

It is interesting to consider the ideal properties of β blocks in the setting of acute myocardial infarction. The β-1 selective agent atenolol was shown in ISIS-1 to reduce mortality when used early in acute myocardial infarction, a benefit largely due to a decrease in ventricular fibrillation. No other β blocker has been shown to decrease mortality when given acutely. But both propranolol1 and metoprolol2 have shown to reduce ventricular fibrillation in acute myocardial infarction. In animal studies timolol, pindolol, propranolol, metoprolol, and labetalol all increased the ventricular fibrillation threshold to a similar extent. The mechanisms of this are likely to be of direct relevance in causing late mortality after acute myocardial infarction but the question of which β blocker to use orally after acute myocardial infarction is as important as the question of which β blocker to use acutely. Propranolol, timolol, and metoprolol are all reported to reduce mortality and particularly sudden death after acute infarction.3 The mechanisms of beta receptors are now many and are probably different from those when β blockers are used acutely.4 It may be that here lip solubility is more important than β-1 selectivity. An overview of the long-term β blocker trials has not suggested any difference between the β-1 selective and non-selective β blockers,5 though it seems that β blockers that do not have partial agonist activity may be more effective than those that do. There are insufficient data to say whether lip solubility is important in this respect but all the drugs known to be efficacious are lipid soluble. Given the uncertainty about the importance of the ancillary properties of β blockers it seems reasonable to suggest that only β blockers with proven effects should be used for postinfarction prophylaxis6 and, despite the theoretical advantages of non-selective β blockade as proposed by Hall and Ferro, the same is probably true of the use of intravenous β blockers in acute infarction. Thus we believe that, in the absence of proof of the relative benefits of non-selective and selective β blockers, the safest option is to select a β blocker that will be available for the present the first line intravenous β blockers in acute myocardial infarction.

ALASTAIR M McCANCE
Groby Road Hospital
Groby Road
Leicester LE2 1QZ
J COLIN FORFAR
John Radcliffe Hospital
Oxford OX3 9DU


Cyclopion treatment and nitric oxide release in human coronary arteries

Sir,—We read with interest the report by Dr O'Neil and colleagues (British Heart Journal 1991;66:212-6) of the lack of effect of cyclosporin on nitric oxide release by human coronary arteries. The data they presented are most valuable because they were obtained from human studies. However, we feel that the conclusion of the paper should be re-examined in the light of their results.

To assess the effect of cyclosporin in vitro, O'Neil et al applied the protocol that we have previously described. After three hours of incubation with cyclosporin, the maximal relaxation (mean (SEM)) to substance P was reduced from 76-6 (7-4)% in control coronary artery rings to 63-0 (11-5)% and 62-2 (11-1)% in rings pretreated with cyclosporin 1000 and 2000 ng/ml, respectively. This difference was not statistically significant. However, at lower concentrations (10-10 and 10-9 mol/l) of substance P, the relaxant responses were significantly reduced in coronary rings incubated with cyclosporin compared with control rings (shown by O'Neil et al in fig 1). Substance P is known as an endothelium-dependent vasodilator7 and has already been used by O'Neil et al to test the ability of the coronary circulation to release nitric oxide in vitro in humans.4 As with other human vascular diseases,8 the mechanisms for relaxation of the underlying vascular smooth muscle in response to nitrovasodilators are not affected by cyclosporin (shown by O'Neil et al in fig 2). We therefore cannot see any other interpretation than the one suggesting that nitric oxide release is indeed impaired in rings incubated with cyclosporin even with low concentrations (10-10 and 10-9 mol/l) of substance P. Usually when they find no statistical difference between the maximal responses of the rings washed with cyclosporin or with the authors who reply as follows:

5 Hall JA, Kaumann AJ, Brown MJ. Selective β-1
Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease.

J A Hall and A Ferro

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