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Surgical bleeding: unexpected effect of a calcium antagonist

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Calcium antagonists are among the most commonly used cardiovascular drugs. They have received regulatory approval for their antianginal and anti-hypertensive actions. While these agents provide appreciable improvement in symptoms in patients with angina pectoris, they have not yet been shown to prevent fatal and non-fatal cardiovascular events. Indeed, evidence suggests an adverse effect in survivors of myocardial infarction and in patients with angina.¹

Speculation about a neuroprotective effect of calcium antagonists is based on the observation of an excessive influx of calcium at the time of neuronal death. This postulated mechanism, together with vasodilation, formed the theoretical basis for a clinical trial in patients undergoing replacement of a cardiac valve. It has been documented that patients placed on cardiopulmonary bypass are subject to arterial microemboli.² The recognised clinical consequences of this phenomenon are neurological, neuro-ophthalmological, and neuropsychological deficits ranging from transient psychomotor deficits to stroke.

Methods and results

We performed a randomised, placebo controlled, double blind clinical trial of patients undergoing replacement of a cardiac valve to test whether nimodipine, a dihydropyridine, in a dose of 30 mg started 12 hours before surgery and given for five days four times a day would reduce the combined incidence of neurological, neuroophthalmological, and neuropsychological deficits over six months compared with placebo. Anticipating that at least half of the patients would experience one or more of these deficits, we estimated the sample size of this single centre trial at 400, with 90% power for detecting a 17% difference ($\alpha=0.05$) in deficit rates. Randomisation was balanced within surgeon.

From an interim analysis of 149 enrolled patients, an independent monitoring committee recommended suspension of recruitment due to an excess mortality in the patients receiving nimodipine compared with those receiving placebo (8/75 (11%) v 1/74 (1%) (small sample odds ratio: 8.6; 95% confidence interval 1.1 to 392)). Comparison of over 50 preoperative variables (demographics, functional state, medical history, and

haemodynamics) showed only minor imbalances between the two groups. Major bleeding seemed to occur often so we undertook a detailed review. Bleeding was defined as major if the patient (a) needed more than 10 units of blood products during the operation or (b) had a postoperative chest tube drainage exceeding 2400 ml in the first 24 hours.³ Twelve patients met this criterion (two (3%) in the group receiving placebo, 10 (13%) in the group receiving nimodipine (Fisher's exact test, $P=0.03$)). Six of the nine deaths (five in patients receiving nimodipine and one in a patient receiving placebo) occurred among the patients with major bleeding. Four of the six deaths were a direct result of blood loss despite transfusion: one patient receiving placebo died from surgical trauma during repeat sternotomy, and two of the remaining three patients who died (who were all receiving nimodipine) had pre-existing blood disorders (chronic lymphocytic leukaemia, thrombocytopenia). The remaining two deaths among the six patients with major bleeding occurred in patients receiving nimodipine at 31 and 162 days due to multiple organ failure associated with appreciable blood loss. In two of the remaining three deaths (all due to multiple organ failure) that did not meet the criterion for major bleeding, bleeding was a possible contributing cause of death.

Comment

This observation of major surgical bleeding associated with a calcium antagonist has not been reported previously. Calcium antagonists have been linked, however, with increased frequency of intracerebral haemorrhage among survivors of myocardial infarction given thrombolysis ($P=0.009$)⁴ and with increased blood loss from ear incisions in a rabbit model ($P=0.003$).⁵ The bleeding may be the result of vasodilation promoted by the calcium antagonists or by the drugs' known antiplatelet action.⁶ This unexpected finding, observed in a post hoc analysis, requires further exploration. Until definitive data are available it seems prudent to evaluate carefully the use of dihydropyridines in the perioperative period.

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Prescription of regular aspirin in patients with chest pain referred to a cardiology outpatient clinic

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Recent trials have established the prophylactic value of aspirin in patients with stable angina.^{1,2} In the United Kingdom an estimated 22 000 new cases of angina pectoris present yearly, most of which are managed by general practitioners.³ Though the use of aspirin by general practitioners has been reported in suspected myocardial infarction and after established infarction, there has been no systematic study of aspirin use in patients with suspected stable angina. We report such a study.

Patients, methods, and results

The study population consisted of patients referred by general practitioners to the cardiac clinic between March and June 1994. Basic demographic data, aspirin status, contraindications to aspirin, and conventional antianginal treatments used were obtained from the clinic doctor by questionnaire. Treatment prescribed for other indications (hypertension, for example) was disregarded. Referrals were categorised into the following diagnostic groups: (1) non-specific chest pain; (2) suspected angina pectoris; (3) established coronary artery disease (for example, previous myocardial infarction); and (4) previous coronary artery bypass grafting or percutaneous coronary angioplasty.

It was usually clear from the referral letter whether the general practitioner suspected angina or non-specific chest pain. When there was doubt the referral was classified as "non-specific chest pain." Finally, the clinic doctor's diagnosis—suspected angina or non-specific chest pain—was established.

Between March and June 1994, 227 patients were referred with chest pain. Thirty one (14%) were referred for suspected non-cardiac chest pain and 17 (7%) had a recognised contraindication to regular aspirin. The remaining 179 (79%) were analysed. The table gives the results. In patients with suspected angina who were taking regular aspirin the mean (SD) drug score was 1.63 (0.9); the corresponding score in patients not taking aspirin was 1.15 (1.0). The clinic

doctor agreed with the diagnosis of suspected angina in 37 (86%) patients taking regular aspirin and 55 (69%) patients not.

Comment

Most patients with established ischaemic heart disease were taking aspirin regularly—particularly those after coronary artery bypass surgery or percutaneous coronary angioplasty, among whom uptake was 95% (18 of 19 patients). Only 43 of 123 patients (35%) referred for suspected angina were taking aspirin regularly.

Among patients not taking aspirin daily, arguably their general practitioners had considered the probability of angina to be below the "therapeutic threshold" for aspirin. For example, the average number of antianginal agents taken daily by patients not taking aspirin was less than among patients taking aspirin. In addition, the clinic doctor agreed with the provisional diagnosis of angina more often in patients taking aspirin. However, prescription of regular antianginal treatment is reportedly a reliable indicator that the general practitioner considers the diagnosis to be angina.³ Of 80 patients with suspected angina who were not taking aspirin, 54 were receiving one or more antianginal agents daily and 30 two or more.

The limited use of regular aspirin in patients with suspected angina contrasts with the widespread use of conventional antianginal treatment, which when compared with aspirin is expensive and may have appreciable adverse effects. General practitioners and other health care personnel should be aware of the benefits of regular aspirin—not only in patients with suspected ischaemic heart disease also in patients with clinical evidence of arterial disease.⁴

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Demography, use of aspirin, and use of antianginal agents by diagnostic group

Diagnostic group†	No of subjects	Mean age in years (SD)	No (%) male	No(%) taking aspirin	No (%) taking antianginal agents daily			
					Nil	1 Agent	2 Agents	3 Agents
2	123	60.5 (11)	74 (60)	43 (35)	31 (25)	37 (30)	41 (33)	14 (11)
3	37	63.4 (10)	29 (78)	28 (76)	4 (11)	12 (32)	7 (19)	14 (38)
4	19	60.7 (10)	18 (95)	18 (95)	4 (21)	5 (26)	9 (47)	1 (5)

†Group 2 suspected ischaemic heart disease; group 3 established ischaemic heart disease; group 4 previous coronary artery bypass grafting or percutaneous transluminal angioplasty.

Correction

Parental refusal to have children immunised: extent and reasons

A typesetting error occurred in this article by Dr Neil Simpson and colleagues (28 January, p 227). In the third paragraph of the subjects, methods, and results section the third sentence should have read: "The commonest reasons for refusal were homeopathy (22 children; 21%) and religious beliefs (17; 16%)."