Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage

G NEIL-DWYER, P WALTER, J M CRUICKSHANK, B DOSHI, P O'GORMAN

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Summary and conclusions

A study was set up to assess the effect on the clinical course of subarachnoid haemorrhage (SAH) of giving propranolol 80 mg eight-hourly plus phentolamine 20 mg three-hourly by mouth for three weeks. Out of the 90 patients studied, 14 died. Two of the deaths occurred in an open pilot study of 10 patients, the remaining 12 deaths occurring in patients in a randomised double-blind placebo-controlled study. Postmortem examination was carried out on 12 of the patients, six of whom had been receiving placebo and six propranolol plus phentolamine. Necrotic myocardial lesions were present in the hearts of all six patients (age range 30-59 years) who died while taking placebo (all had had abnormal electrocardiograms (ECGs)). In contrast, no necrotic lesions were found in the hearts of the six patients (age range 28-59) who died while receiving the drugs (all had previously had normal ECGs).

We conclude that the necrotic myocardial lesions were induced by catecholamines and that propranolol had a cardioprotective effect. While death from a further haemorrhage in cases of SAH is not affected by propranolol and phentolamine, propranolol may have a beneficial effect in other potentially lethal stresses.

Introduction

The bizarre electrocardiographic abnormalities that are often associated with subarachnoid haemorrhage (SAH) probably result from increased sympathetic outflow.^{1,2} Propranolol abolishes many of these changes.³ Simulated SAH in an animal model is accompanied by similar electrocardiographic changes and subendocardial necrotic lesions; both abnormalities may be prevented by surgical (C2 cordotomy) or medical (propranolol) intervention.⁴ The necrotic myocardial lesions are identical with those induced by administration of catecholamines⁵ and those found in the hearts of patients who have died from SAH.⁶ These cardiac lesions may well influence the morbidity and mortality of such conditions as SAH and head injury.⁷

The present study was set up to investigate the effect of propranolol on the clinical course of SAH and in particular on the incidence of myocardial necrotic lesions. Phentolamine, an alpha-blocker, was also given so that the effect of both drugs on the lethal course of cerebral arterial spasm after a SAH might be studied.

Patients and methods

We studied 90 consecutive patients with SAH proved by lumbar puncture who were admitted to the South-east Thames regional neurosurgical unit at the Brook General Hospital between November 1976 and April 1978. Only patients who were admitted into the unit within 48 hours after their haemorrhage were placed in the trial. Those aged over 60 or with a history of hypertension, ischaemic heart disease, congestive cardiac failure, or obstructive airways disease were omitted.

The first 10 patients entered a pilot study set up to guard against an unexpected interaction between patient and treatment. All 10 were given 20 mg of phentolamine three-hourly plus 80 mg of propranolol eight-hourly for three weeks. When necessary the tablets were crushed and given by nasogastric tube. The next 80 patients entered the randomised, double-blind between-patient study; 40 received the above treatment for three weeks and 40 received matching placebo tablets. The patients were randomised in pairs by computer.

Clinical assessments of level of consciousness, neurological state, mean pulse rate, and blood pressure were recorded daily. On days 1, 3, 7, 10, 14, and 21 a standard 12-lead electrocardiogram (ECG) was obtained (reported blind by JMC) and a 24-hour urine collection started to measure the excretion rates of urinary catecholamines—namely, adrenaline, noradrenaline, 3-methoxy-4-hydroxymandelic acid, and metadrenaline. The methods used to measure these excretion rates have been described elsewhere.⁸⁻¹⁰ Cerebral angiography was performed when considered to be clinically necessary. The anaesthetists broke the code for individual patients at operation, but this information was not available to the rest of the staff. Drug treatment continued during the preoperative and postoperative periods.

Postmortem examination was carried out on all patients who died for whom permission was obtained, particular attention being paid to the histology of the hypothalamus and heart. Three blocks were taken from each hypothalamus at the levels of the optic chiasm, the tuber cinereum, and the mammillary bodies for paraffin section. The sections were stained with haematoxylin and eosin, haematoxylin and van Gieson, and Luxol fast blue and cresyl violet. The coronary arteries were examined in all cases, and one block was taken from each of the five following areas of the left ventricle for paraffin section: posterior wall, lateral wall, anterior wall, interventricular septum, and apex. The sections were stained with haematoxylin and eosin and haematoxylin and van Gieson. The pathologist routinely examines the hypothalamus and heart of every patient who dies after a SAH and so was unaware of which patients were in the trial.

Results

Fourteen patients died, of whom two were in the open pilot study and 12 in the blind control study. Of the latter 12 deaths, six occurred in patients taking placebo and six in patients taking propranolol and phentolamine. Postmortem examination was not carried out in two cases, and so this analysis is confined to the 12 patients remaining (six of whom received placebo and six the drugs).

Of the 12 patients who died, the two groups were reasonably well matched (table I) except for the preponderance of men among the patients receiving the drugs and of women among those receiving placebo. Modes of death differed between the two groups. In the treated group all six deaths were due to further haemorrhage, while in the untreated group two patients died from haemorrhage and the remaining four died after a gradual deterioration due to cerebral arterial spasm, though one of these patients may have had a pulmonary embolus. Two of these four died after surgery. The incidence of radiographic evidence of cerebral arterial spasm was similar in both groups.

Table II shows the haemodynamic, metabolic, and pathological changes in the two groups. The slower mean pulse rate in the treated group (65.0 compared with 80.9 beats/min, $P < 0.05$) is evidence of

Brook General Hospital, Woolwich, London SE18 4LW

G NEIL-DWYER, MS, FRCS, consultant neurosurgeon

P WALTER, BSC, FRCS, neurosurgical registrar

B DOSHI, MRCPATH, consultant neuropathologist

P O'GORMAN, MRCPATH, consultant, chemical pathology department

Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfield, Cheshire SK10 4TG

J M CRUICKSHANK, DM, MRCP, medical adviser

TABLE I—Data on 12 patients on whom necropsy was carried out

	Propranolol 80 mg eight-hourly by mouth + phentolamine 20 mg three-hourly by mouth	Placebo
No of patients	6	6
Age range in years	28-59	30-58
Sex	5 M, 1 F	6 F
Level of consciousness	1 patient in coma throughout; 3 patients drowsy throughout; 2 patients initially alert but becoming drowsy	1 patient drowsy throughout; 1 patient alert throughout; 4 patients alert, becoming drowsy and lapsing into coma
Operations	None	2 direct attacks on aneurysms
Cerebral angiography	Shown spasm in 4 patients (2 local, 2 severe)	Shown spasm in 3 patients (1 local, 2 severe)
Disease of intracranial arteries	2 PCA 1 ICA 2 MCA 1 ACA	2 PCA 3 ICA 1 MCA
Times of death after last SAH (days)	3 5 6 21 16 4 } mean 9.2 days	8 5 5 14 15 11 } mean 9.3 days
Reason for death	Recurrent haemorrhage in all cases	Recurrent haemorrhage in 2 cases; probable cerebral arterial spasm in 3; and ? spasm ? pulmonary embolus in 1

PCA = Posterior communicating artery aneurysm. ICA = Internal carotid artery aneurysm. MCA = Middle cerebral artery aneurysm. ACA = Anterior communicating artery aneurysm.

TABLE II—Clinical details and findings at necropsy in 12 patients who died

	Propranolol 80 mg eight-hourly by mouth + phentolamine 20 mg three-hourly by mouth	Placebo
Mean pulse rate (beats min)	65.0 ± 2.2	80.9 ± 6.7
Mean blood pressure (mm Hg)	143 ± 3.0 84 ± 2.6	140 ± 7.1 83 ± 3.7
Appearance of ECG	Entirely normal in 3 patients; in remaining 3, ECGs taken on day 1 were abnormal and all subsequent ECGs normal. Abnormalities were peaked P, S-T, peaked T, and large U waves	All ECGs of 5 patients were abnormal. In remaining patient 1 of 4 ECGs was abnormal. Abnormalities included short P-R interval, peaked P wave, depressed S-Ts, flat or inverted T waves, and large U waves
Mean 24-hour urinary catecholamine excretion rates (and ranges)*	Adrenaline 281.0 ± 122.6 (23-564) nmol/24 h Noradrenaline 959 ± 409.4 (143-2156) nmol/24 h Metadrenaline 3.1 ± 0.26 (1.3-5.9) μmol/24 h HMMA 38.5 ± 8.1 (17-116) μmol/24 h	503.0 ± 85.2 (246-752) nmol/24 h 912.4 ± 687.6 (49-6345) nmol/24 h 2.2 ± 1.2 (0.1-8.0) μmol/24 h 28.7 ± 4.0 (11-39) μmol/24 h
Disease of coronary artery	2 patients had no atheroma or occlusion; 4 had mild atheroma and no occlusion	2 patients had no atheroma or occlusion; 4 had mild atheroma and no occlusion
Appearance of left ventricular myocardium	No lesions	2 patients had focal necrotic lesions of muscle fibres; 4 had focal necrotic lesions with inflammatory cell infiltration
Appearance of hypothalamus	All had hypothalamic lesions—perivascular haemorrhage and endothelial oedema with cuffing by polymorphonuclear leucocytes	5 had lesions similar to those in treated group; 1 had a complete hypothalamic infarct

HMMA = 3-Methoxy-4-hydroxymandelic acid.
*Normal ranges: adrenaline 0-275 nmol/24 h; noradrenaline 110-1100 nmol/24 h; metadrenaline 0-4.0 μmol/24 h; HMMA 10-35 μmol/24 h.
Conversion: SI to traditional units—Adrenaline: 1 nmol/24 h ≈ 0.18 μg/24 h. Noradrenaline: 1 nmol/24 h ≈ 0.17 μg/24 h. Metadrenaline: 1 μmol/24 h ≈ 0.18 mg/24 h. HMMA: 1 μmol/24 h ≈ 0.2 mg/24 h.

FIG 1—Appearance of ECG (lead V5) in patient taking placebo, showing S-T depression and T-wave inversion.

beta-blockade. There was also a pronounced difference in electrocardiographic pattern between the two groups, the basic normality of the ECGs of the treated group contrasting with the abnormality of all those in the placebo group. Figure 1 shows the ECG of one of the patients in the placebo group. The "stressed" condition of the patients was evidenced by the fairly high mean concentrations of urinary catecholamines in both groups. Although there was no statistical difference between the two groups the mean urinary adrenaline concentration was high in the untreated group and virtually normal in the treated group. Several patients at times had urinary catecholamine concentrations equivalent to those found in patients with pheochromocytomas. No severe coronary arterial disease was seen in any patient.

None of the six patients in the group receiving the drugs had necrotic myocardial lesions. In contrast, all six patients who died while taking placebo had focal necrotic lesions of the left ventricular muscle fibres with or without inflammatory cell infiltration. Figure 2 shows an example of such a lesion (which arose in the patient whose ECG is shown in fig 1). All patients in both groups had hypothalamic lesions comprising perivascular haemorrhages with oedema of the

vessel wall affecting the endothelial cells and perivascular cuffing of polymorphonuclear leucocytes. One patient in the untreated group had a complete infarct of the hypothalamus.

FIG 2—Necrotic muscle fibre in heart with interstitial inflammatory cell infiltration. (Haematoxylin and eosin, × 160)

Discussion

Simulated SAH,⁴ hypothalamic stimulation,¹¹ and parenteral administration of catecholamines⁵ in animals produce necrotic myocardial lesions, which may be prevented by severing the cord at C2 level or by administering reserpine or propranolol.⁴ A possible effect of the hypothalamic lesions after a SAH¹² is to produce an abnormal reaction of the autonomic nervous system resulting in persistently high excretion rates of urinary catecholamines.² The close association between the hypothalamus and the autonomic nervous system, coupled with the high correlation between hypothalamic and myocardial lesions after SAH,¹³ points to a catecholamine-linked origin of the myocardial necrosis.

The pathological results of this study should be interpreted in the light of results (unpublished) of a recent survey, which showed that out of 54 patients who died of SAH at the South-east Thames regional neurosurgical unit, 49 had hypothalamic lesions similar to those found in this study and 42 of these patients (78% of the whole) had necrotic myocardial lesions. Thus the fact that in our study all six patients who died in the drug-treated group had "clean hearts" (with normal ECGs) while all six in the placebo-treated group had focal necrotic myocardial lesions (and abnormal ECGs) becomes important. Due to the probable absence of alpha-receptors in the myocardium¹⁴ we presume that propranolol rather than phentolamine was the agent responsible.

What are the clinical implications of these results? Excessive amounts of catecholamines may induce heart failure, as in the cardiomyopathy associated with pheochromocytomas.¹⁵ Some other types of congestive cardiomyopathy may well result from an abnormal interaction between catecholamines and the myocardium and benefit from beta-blockade.¹⁶ A recent report¹⁷ described such a cardiomyopathy, which was cured by stopping treatment with ephedrine. Some authors consider that catecholamines play a crucial part in the onset of myocardial infarction,¹⁸ thus suggesting an explanation for the protective effect of beta-blockade on the ischaemic myocardium. Despite its "cardioprotective effect," propranolol did not influence mortality in cases of SAH and accompanying myocardial damage. This is because lethal secondary events such as a

second SAH are not critically influenced by propranolol or phentolamine, though the results of this preliminary study suggest a possible protective action of these two drugs with regard to cerebrovascular spasm. In other "stress areas" with associated myocardial necrotic lesions and unstable cardiac rhythms, such as head injuries,⁷ beta-blockade may have an important role. The source of hearts for cardiac transplantation is another important, though perhaps more remote, factor to be considered. If, as is often the case, the donor has died after a cerebrovascular accident or head injury then early administration of a beta-blocker to the potential donor might be wise.

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Requests for reprints should be addressed to G Neil-Dwyer.

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National Childhood Encephalopathy Study: an interim report

DAVID L MILLER, EUAN M ROSS

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Summary and conclusions

Data from the first year of the National Childhood Encephalopathy Study were reviewed to see whether any relation was apparent between pertussis vaccination and brain disease. Three hundred and eighty-seven cases of encephalitis and other specified neurological

conditions in which the children were admitted to hospital were reported, of which 267 satisfied the study criteria. Control children were matched for age with the index cases, and medical and immunisation histories were reviewed. Few of the index cases had been vaccinated within 28 days before admission to hospital, so that no close association between vaccination and brain disease existed in most cases.

The number of children who had recently been immunised was too small for any statistically useful conclusion to be reached about the risk associated with pertussis vaccine. The study is continuing.

Department of Community Medicine, Middlesex Hospital Medical School, London NW10 7NS

DAVID L MILLER, MD, FRCP, professor of community medicine
EUAN M ROSS, MD, MRCP, senior lecturer in child health and community medicine

Introduction

Allegations that immunisation against pertussis carries a risk of causing permanent brain damage in an appreciable