convulsant treatment was never started. The patient also had severe brittle asthma and died later at home in status asthmaticus. Postmortem examination was not carried out.

Comment

We believe that the temporal relation of the seizures to the administration of factor VIII on three occasions makes the factor VIII the most likely aetiological factor in precipitating the seizures. Unusual intravascular particulate material has been noted in the cerebral white matter of a haemophiliac treated with large quantities of factor VIII concentrates,[1] and deposition of such particles in a brain with an underlying tendency to seizures may perhaps have been sufficient stimulus to evoke these seizures. The prevalence of electroencephalographic abnormalities in adult haemophiliacs is normal[2]; the fact that seizures have not previously been noted after infusions of factor concentrates but were in this case may be because this patient, despite repeated warnings, occasionally injected the concentrate over a period of one to two minutes.

[1] Ghatak NR, Husain MM. Unusual intravascular material in the brain. *Am J Clin Pathol* 1976;**65**:508-12.
[2] Forbes CD, Renfrew S. Electroencephalography in haemophilia and Christmas disease. *Haemostasis* 1975;**4**:36-9.

(*Accepted 20 January 1983*)

University Department of Medicine and Department of Neurology, Royal Infirmary, Glasgow G4 0SF
M SMALL, MRCP, registrar in medicine
W F DURWARD, MRCP, consultant neurologist
C D FORBES, MD, FRCP, senior lecturer in medicine

Correspondence to: Dr M Small.

Effect of verapamil on enzyme release after early intravenous administration in acute myocardial infarction: double blind randomised trial

Verapamil has infarct reducing properties in experimental myocardial infarction and experimental myocardial ischaemia. In dogs comparisons of different agents with these properties showed a 20% reduction in infarct size after propranolol and a 40% reduction in size after verapamil.[1] Decreased elevation of the ST segment has been reported in several studies. Reduction of myocardial necrosis as quantified histologically and prevention of haemodynamic deterioration have also been described.[2] Nayler *et al* found that verapamil protected ischaemic rabbit hearts as shown by release of intracellular enzymes, depletion of adenosine triphosphate reserves, and diminishing ultrastructural cellular damage, the best results occurring after prophylactic use of the drug.[3]

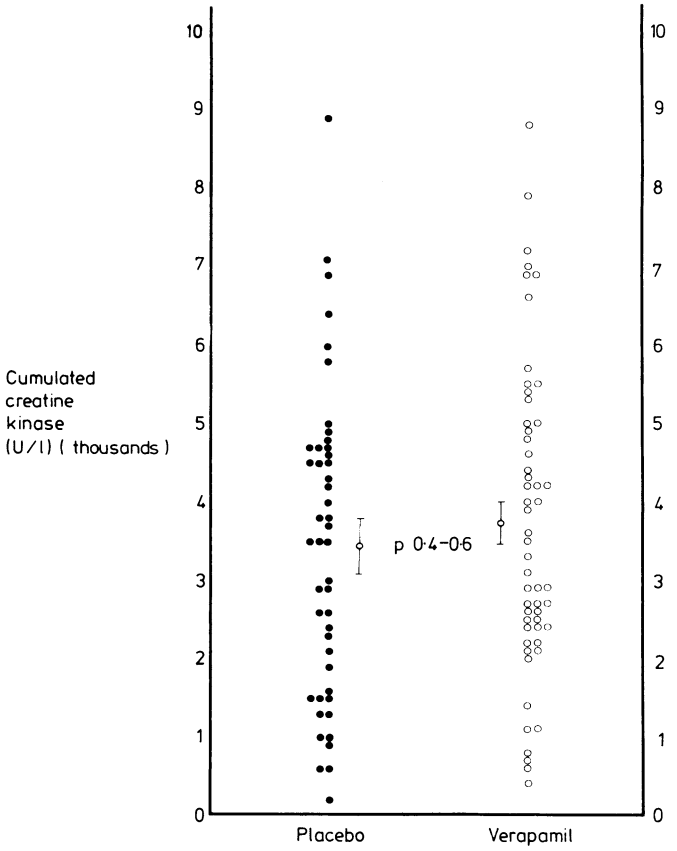
We have conducted a clinical trial to assess whether verapamil administered early in acute myocardial infarction reduced infarct size as estimated by the release of creatine kinase into the circulation. The study was performed during the Danish Multicentre Study on Verapamil in Acute Myocardial Infarction.[4]

Patients, methods, and results

All patients aged up to 75 who had been admitted to the coronary care unit from July 1979 to August 1981 were assessed for the trial. Acute myocardial infarction was defined according to the WHO criteria. Contraindications to the trial were: treatment with beta-blockers, nifedipine, or verapamil; blood pressure below 90 mm Hg; severe pulmonary congestion; cardiac arrest before or at arrival; first degree atrioventricular block (PQ > 0·3 s); second degree or third degree atrioventricular block; bradycardia < 45 beats/min; valvular heart disease; and severe chronic disease. Patients were allocated at random to receive verapamil or placebo. The initial dose of verapamil was 0·1 mg/kg given slowly intravenously followed by 120 mg by mouth thrice daily. Blood samples were taken on arrival and every four hours for 72 hours. Serum total creatine kinase activity was assayed as described by the Scandinavian Committee on Enzymes. The patients received no intramuscular injections during the sampling period. Cumulated creatine kinase value was calculated as described by Norris *et al*,[5] the fractional disappearance rate being calculated for each patient.

During the trial period 417 patients were admitted to the unit. Two hundred were excluded from the trial and the remaining 217 began treatment. Of the 119 of these patients who fulfilled the WHO criteria for acute myocardial infarction, 19 were later excluded because cumulated creatine kinase values could not be calculated. Reasons were: admission after maximal values had been attained (nine patients), insufficient blood samples (five), death during first 72 hours (two), defibrillation (one), refusal to participate (one), and administrative mistakes (one). Of the 19 patients, 13 were in the verapamil group and six in the placebo group. Cumulated creatine kinase values were therefore available for 100 patients.

The median time from onset of pain to admission was four hours (range 0·5-12·0 hours). Fifty four of the patients received verapamil, and their mean cumulated creatine kinase value was 3711 ± SEM 269 U/l. Forty six patients received placebo, and their mean cumulated creatine kinase value was 3436 ± SEM 288 U/l. The difference was not significant ($t = 0·70$, df = 98, $0·4 < p < 0·6$) (figure). There was no difference between the treatment groups in age, sex, fractional disappearance rate of creatine kinase, or site of the infarct.



Cumulated creatine kinase values in 100 patients with acute myocardial infarction treated with placebo (n = 46) and verapamil (n = 54).

Comment

Using the cumulated creatine kinase value as an indication of myocardial damage, this study failed to confirm experimental evidence of infarct reducing properties of verapamil. Dosages of the drug were equivalent to those used in the animal experiments, and the delay before treatment was of the same magnitude as that in the beta-blocker studies reporting a reduction of infarct size. In the experimental studies, however, verapamil was administered either before or shortly after the induced coronary event. Hence the four hour delay in our study might have been responsible for the negative result.

We thank the County of Ringkjøbing, Denmark, for financial support and Knoll, Ludwigshafen, West Germany, for the supply of drugs.

[1] Marocco PR. Experimental infarction studies. *Clin Invest Med* 1980;**3**: 139-42.
[2] Smith HJ, Singh N, Nisbeth HD, Norris RM. Effects of verapamil on infarct size following experimental coronary occlusion. *Cardiovasc Res* 1975;**9**:569-78.
[3] Nayler WG, Gray A, Slade A. A protective effect of verapamil on hypoxic heart muscle. *Cardiovasc Res* 1976;**10**:650-62.

[4] Danish Multicentre Study Group on Verapamil in Acute Myocardial Infarction. Verapamil in acute myocardial infarction. *Clin Exp Pharmacol Physiol* 1982;**6**,suppl:89-96.
[5] Norris RM, Whitlock RML, Barrat-Boyes C, Small CW. Clinical measurement of myocardial infarct size: modification of a method for the estimation of creatine phosphokinase release after acute myocardial infarction. *Circulation* 1975;**51**:614-20.

(*Accepted 12 January 1983*)

Departments of Medicine and Clinical Chemistry, General Hospital, Holstebro, Denmark
LEIF THUESEN, MD, registrar
JØRGEN R JØRGENSEN, MD, registrar
HANS J KVISTGAARD, MSC, pharmacist
JENS A SØRENSEN, MD, registrar
MICHAEL VÆTH, MSC, lecturer
EVA B JENSEN, MSC, lecturer
JENS J JENSEN, MD, registrar
LEIF HAGERUP, MD, consultant

Correspondence and requests for reprints to: Dr Leif Thuesen, University Department of Cardiology, Aarhus Kommunehospital, 8000 Aarhus C, Denmark.

Unilateral somatic symptoms due to hyperventilation

Recurrent unilateral sensory or motor symptoms (or both) are a poorly recognised presentation of the hyperventilation syndrome. We have seen 12 such cases during the past two years and here describe two cases in detail and 10 in tabular form.

Case reports

Case 1—A 19 year old school leaver unable to find work gave a six month history of recurrent episodes of numbness and weakness of her left hand and arm. Each episode lasted a few minutes and she simultaneously felt dizzy, light headed, had difficulty taking a deep breath, and felt tightness in the chest. Investigation elsewhere for suspected epilepsy proved negative. Physical examination showed no abnormality, though she was overtly anxious: voluntary hyperventilation reproduced all her symptoms. She was reassured and the mechanism explained. A physiotherapist taught her breathing exercises, which she continued for a few weeks. When reviewed two years later she was well without recurrence of symptoms.

Case 6—A 30 year old male banker had had intermittent paraesthesiae affecting the left face, arm, and leg for four months. Episodes lasted several minutes and could recur up to three times a week. He was referred with suspected cerebrovascular disease. Physical examination showed no abnormality but he was anxious about his job. Voluntary hyperventilation reproduced his attacks but no other symptoms such as dizziness. After explanation he was taught breathing exercises by a physiotherapist and remained free of symptoms when reviewed two years later.

The table summarises details of 12 cases (including the above). Individual episodes lasted from two to 20 minutes and had been present for between one month and two years. Left limbs were more commonly affected than the right. Only one patient complained of breathlessness even on direct questioning, and dizziness was not always present. Each patient had a background of anxiety. Physical examination showed no abnormality, but in each case voluntary hyperventilation evoked the presenting symptoms within a half to three minutes. It was often necessary to encourage the patient to maintain an adequate depth and frequency (20-30/minute) of respiration. In each case breathing exercises were demonstrated by us or by a physiotherapist.

All patients had improved at follow up (from four to 24 months after diagnosis) irrespective of any change in their underlying anxiety state, and no other neurological disturbance had developed.

Comment

Unilateral symptoms on hyperventilation were described in 1964 in healthy young subjects without concomitant asymmetry in the electroencephalogram and in patients without structural lesions in the nervous system.[1] This report gained little attention. Cases of intermittent unilateral motor or sensory symptoms are often diagnosed as epilepsy, transient ischaemic attacks, demyelination, or migraine. In view of the absence of other symptoms or physical signs, reproduction or symptoms by voluntary hyperventilation, improvement of symptoms after diagnosis and treatment, and the failure of other symptoms to develop during follow up, we think that we can exclude these diagnoses in our patients, though the follow up period in two cases was too short to exclude a structural lesion.

Are these transient unilateral symptoms due to a peripheral or central mechanism? Peripheral nerve excitability could increase with alterations in ionised calcium concentrations and peripheral vasoconstriction of the vasa-nervorum with respiratory alkalosis.[2] Experimentally cooling or rendering a limb ischaemic hastened the onset of local symptoms, while sympathectomy delayed or abolished the onset.[3] Nevertheless, only a central mechanism could explain the dizziness, confusion, or even coma that hyperventilation can induce, presumably by reducing cerebral blood flow due to hypocapnia. The excess of left-sided symptoms (eight of our 12 cases and 12 out of 14 healthy subjects[1]) raises further difficulty. Is lateralisation due to cerebral dominance or to anatomical differences in the peripheral nerves and their nutrient vessels?

When the simple procedure of hyperventilation reproduces the patient's symptoms no further investigation is necessary. We would, however, advise follow up for about a year after onset of symptoms and further investigation in those whose symptoms do not rapidly resolve with the treatment described.

We thank Sir Roger Bannister for permission to include a patient (case 4) he asked JNB to see.

Since preparation of this paper we have seen four further cases—all left-sided.

[1] Tavel ME. Hyperventilation syndrome with unilateral somatic symptoms. *JAMA* 1964;**187**:301-3.
[2] Kugelberg E. Activation of human nerves by hyperventilation and hypocalcaemia. *Archives of Neurology and Psychiatry* 1948;**60**:183-4.
[3] Ames F. The hyperventilation syndrome. *Journal of Mental Science* 1955;**101**:466-525.

(*Accepted 12 January 1983*)

National Hospital, Queen Square, London WC1N 3BG
J N BLAU, MD, FRCP, consultant neurologist
C M WILES, PHD, MRCP, senior registrar

Northwick Park Hospital, Harrow, Middlesex
F S SOLOMON, MB, MRCP, honorary clinical assistant in neurology

Correspondence to: Dr J N Blau.

Clinical details of 12 patients with unilateral somatic symptoms due to hyperventilation

Case No	Age	Sex	Unilateral somatic symptoms and side affected	Other symptoms	Previous diagnosis	Period of follow up
1	19	F	Numbness and weakness of arm. Left side	Dizziness. Chest felt tight	Epilepsy	>2 years
2	23	F	Numbness of hand, tongue, and lips. Left side	Tension headache	Migraine	9 months
3	24	F	Paraesthesiae of arm and face. Right side	Dizziness and nausea	Multiple sclerosis	20 months
4	26	M	Numbness of hand and arm. Right side	Tension headache	Migraine	20 months
5	30	F	Paraesthesiae and clumsiness of hand and facial paraesthesiae	Heavy sensation in chest	Arteriovenous malformation	22 months
6	30	M	Paraesthesiae of arm, leg, and face. Clumsy leg. Gait disturbance. Left side	None	Cerebrovascular disease	>2 years
7	30	M	Paraesthesiae and numbness of arm, leg, and face. Cold feeling down side of body. Right side	None	Brachial neuritis	18 months
8	32	F	Numbness of arm and leg. Left side	Dizziness and palpitations	Uncertain	4 months
9	35	F	Paraesthesiae of arm and foot. Left side	None	Multiple sclerosis	17 months
10	37	M	Paraesthesiae of hand and heaviness in chest. Left side	Panic attacks	Angina	>2 years
11	55	M	Numbness and heaviness of arm and leg. Tightness of chest. Left side	Dizziness and visual blurring	Malingering	>2 years
12	66	M	Weakness and numbness of hand and arm. Left side	Dizziness and fatigue	Cerebrovascular insufficiency	>2 years