valproate was reduced to 200 mg twice daily even after treatment for three months.

We suggest that sodium valproate should be considered among the drugs of first choice in the management of hemiballismus caused by a vascular lesion in view of its apparent efficacy in this patient and the low incidence of side effects associated with its use, especially the absence of unwanted sedation.

¹ Brain Lord. *Brain's diseases of the nervous system*. London: Oxford University Press, 1977:623.

² Bachman DS, Butler IJ, McKhann GM. Long term treatment of juvenile Huntington's chorea with dipropylacetic acid. *Neurology* 1977;27:193-7.

³ Simon D, Penry JK. Dipropylacetic acid and the treatment of epilepsy. *Epilepsia* 1975;16 (4):549-73.

⁴ Hyland HH, Forman DM. Prognosis in hemiballismus. *Ann Neurol* 1957; 7:381-91.

(Accepted 24 March 1981)

University Department of Geriatric Medicine, City Hospital, Edinburgh EH10 5SB

R J LENTON, MB, MRCP, lecturer

M COPTI, MD, FRCP(C), neurologist

R G SMITH, MB, FRCPED, senior lecturer

Nocturnal wheezing in children: management with controlled-release aminophylline

Wheezing at night is an appreciable problem for asthmatic children and their parents. The short duration of action of most bronchodilator drugs and the physiological early-morning dip in pulmonary function exacerbate nocturnal symptoms. Although oral theophylline is an effective bronchodilator,¹ its half life is short and variable,² so that therapeutic values cannot be maintained while a child sleeps. Use of controlled-release aminophylline in children results in satisfactory serum³ and salivary⁴ theophylline concentrations eight hours after ingestion, coupled with improvement in respiratory function.⁵ Controlled-release aminophylline should be of benefit in the management of nocturnal symptoms; a double-blind trial was conducted to determine its efficacy in asthmatic children.

Patients and methods

We studied 25 asthmatic children aged between 5.2 and 15.3 years (mean age 9.3 years). They were chosen because nocturnal symptoms were a major clinical problem. Twenty-two children completed the study satisfactorily, the records of the three others being inadequate. The dosage of aminophylline (mean 11.3 mg/kg) was determined individually for each child with the aid of salivary theophylline assays.⁴

The study lasted two months: patients were randomly allocated to placebo or controlled-release aminophylline and switched to the alternative preparation after a month. Tablets were taken only at bedtime. Peak flow was recorded on waking (mini Wright peak flow meter). Regular and extra medication was recorded and the early-morning peak flow disregarded if other bronchodilator treatment had been used within six hours. Night symptoms were graded (0-5) and recorded by children or parents, or both, according to a diary card routinely used in our clinic.

Results and comment

The table summarises the results. Data for peak flow and night score were analysed separately by Mann-Whitney tests and showed a significant improvement in morning peak flow in most patients. The small range of possible responses in the night score resulted

Change in peak flow and night score during treatment with controlled-release aminophylline compared with placebo. (Figures are numbers of patients)

	Worse		No change	Improved			
	p<0.01	p<0.05		p<0.1	p<0.05	p<0.01	p<0.001
Peak flow	2	2	4	2	4	1	7
Night score		1	12		5	2	2

in most responses being "no change." When the morning peak flow results were combined with the parents or the child's assessment of the night then 16 children improved and six showed no change with controlled-release aminophylline compared with placebo ($p<0.05$). A non-parametric two-way analysis of variance showed that there was a highly significant increase in the number of good nights when controlled-release aminophylline was being used.

We conclude that controlled-release aminophylline is a useful preparation in asthmatic children with nocturnal symptoms; no side effects attributable to it were noted in this study.

We thank the children and their parents for their co-operation; Sister Gardner, Mr Smith, and Mr Pugsley for help and advice; Gill Smith for typing the manuscript; and Napp Laboratories for supplying controlled-release aminophylline (Phyllocontin Continus tablets) and placebo.

¹ Hambleton G, Weinberg M, Taylor J, *et al.* Comparison of cromoglycate (Cromolyn) and theophylline in controlling symptoms of chronic asthma. *Lancet* 1977;i:381-5.

² Ellis EF, Koysooko R, Levy G. Pharmacokinetics of theophylline in children with asthma. *Pediatrics* 1976;58:542-7.

³ McKenzie S, Baillie E. Serum theophylline levels in asthmatic children after an oral administration of two slow release theophylline preparations. *Arch Dis Child* 1978;53:943-6.

⁴ Evans N, Evans PWG, Boobis SW. Preliminary experience with controlled release aminophylline in asthmatic children; salivary levels and peak flow following a single dose. *J Int Med Res* 1979;7, suppl 1:93-7.

⁵ MacDonald TH, McWilliam R. Monitoring response to bronchodilator therapy in asthma in childhood. *J Int Med Res* 1979;7, suppl 1:87-92.

(Accepted 24 March 1981)

Royal Alexandra Hospital for Sick Children, Brighton, Sussex BN1 3JN, and University of Sussex, Falmer, Sussex

P W G EVANS, MB, MRCP, registrar

A CRAVEN, MSC, PHD, reader in mathematics

N EVANS, MB, MRCP, consultant

Fatal poisoning with methyl isothiocyanate

Methyl isothiocyanate is substituted for phenyl isothiocyanate in the Edman degradation test to determine the amino-acid sequences of peptides and proteins.¹ The compound donates a cyanide moiety and would therefore be potentially lethal if ingested. In animals the LD₅₀ is reportedly 97 mg/kg,² which produces corneal, liver, and kidney damage, but little is known about its toxicity in man. We describe a suicide with the compound.

Case report

A 23-year-old chemistry student was brought to the emergency department of Nehru Hospital within 20 minutes after intentionally drinking water containing 50 g methyl isothiocyanate (Mann Laboratories Inc, NY). Immediately after ingestion she had noticed severe retrosternal burning and epigastric pain and begun to vomit repeatedly. A few minutes later she began generalised tonic and clonic seizures and became unconscious.

She was admitted deeply comatose and with pulse 98/min and blood pressure 90/60 mm Hg. Chest, heart, and abdomen were normal. The pupils were slightly dilated but equal in size and reacted sluggishly to light. There was complete loss of all reflex and motor activity including oculocephalic reflex. Gastric lavage was performed with sodium thiosulphate, and sodium nitrite and sodium thiosulphate were given intravenously in doses for cyanide intoxication. Seizures were controlled with intravenous diazepam, and she was put on respirator. Peritoneal dialysis was instituted about one hour after admission. She continued to deteriorate with a further fall in blood pressure, however, and died about eight hours after admission. Necropsy a few hours later showed extensive mucosal necrosis of oesophagus, stomach, and proximal part of the duodenum (fig). Other organs showed only evidence of shock.

Comment

The toxic component of methyl isothiocyanate is probably thiocyanate, as our patient's symptoms were closely similar to those seen in acute poisoning with sodium, potassium, and ammonium thiocyanate.³ Thiocyanates are reduced partly to cyanide in tissues and

histotoxic symptoms may be due to these, but the exact mechanism of action of thiocyanates is not known.⁴ Thiocyanate intoxication with blood concentrations above 200 mg/l may be rapidly corrected by haemodialysis, which reportedly removes several grams of the drug.⁵ We tried peritoneal dialysis but in the absence of clearance studies, which we could not do, we cannot comment on the procedure for intoxication with this compound.

Distal part of oesophagus and stomach showing necrotic mucosa.

Requests for reprints should be sent to Professor Sharma.

- ¹ Waterfield M, Haber E. Amino acid sequence analysis with methyl-isothiocyanate. Resolution of the methyl hydantoins by gas liquid partition chromatography. *Biochemistry* 1970;9:832-9.
- ² Dreisbach RH. *Handbook of poisoning*. 10th ed. Los Altos, California: Lange Medical Publications, 1980:139.
- ³ Garvin FC. The fatal toxic manifestations of the thiocyanates. *JAMA* 1939;112:1125-7.
- ⁴ Thienes HC, ed. *Thiocyanates*. In: *Clinical toxicology*. Philadelphia: Lea and Febiger, 1972:212-3.
- ⁵ Winchester FJ, Gelfand MC, Kneppshield HJ, Schreiner GE. Dialysis and haemoperfusion of poisons and drugs: update. *Trans Am Soc Artif Intern Organs* 1977;23:808.

(Accepted 18 March 1981)

Postgraduate Institute of Medical Education and Research,
Chandigarh-160012, India

B K SHARMA, MD, MAMS, professor of internal medicine
SURJIT SINGH, MD, lecturer in internal medicine
R MEHTA, MD, senior resident in nephrology

Hyperglycaemic effect of nifedipine

Nifedipine is widely used for the treatment of angina pectoris,¹ and no adverse metabolic side effects have been reported. We recently observed that a patient with maturity-onset diabetes had appreciably decreased mean glucose concentrations after nifedipine was stopped. This led us to investigate whether nifedipine possesses diabetogenic properties.

Patients, methods, and results

The effects of nifedipine on an oral glucose tolerance test (100 g of glucose) were studied in five women and one man. None had evidence of endocrinopathy or were receiving drugs. Mean age was 46 (range 26-55) years. Body weights were within 10% of the ideal weight. After an initial oral glucose tolerance test 20 mg of nifedipine was administered by mouth eight hourly for three days. A second test was performed two hours after the last dose of nifedipine. The subjects received a diet of 6.7 MJ (1600 kcal) (women) or 8.4 MJ (2000 kcal) (men) (45% carbohydrate), beginning three days before the first oral glucose tolerance test. Results are expressed as means $\pm$ 1 SEM. Differences in the responses before and after nifedipine were assessed by paired Student's *t* test.

Nifedipine induced distinct glucose intolerance (figure). Fasting plasma glucose concentrations showed a significant increase of 10%; basal insulin concentrations were significantly reduced (26%). During the oral glucose tolerance test plasma glucose concentrations were appreciably raised after administration of the drug, and at 60, 90, and 120 minutes values of 9.56, 9.89, and 7.67 mmol/l respectively were observed (172, 178, and 138 mg/100 ml). This contrasted with the normal glucose tolerance in all subjects before administration of nifedipine. In five subjects insulin concentrations were reduced at 30 and 60 minutes; in this subgroup the effect was significant. At 30 minutes the mean insulin concentrations were 0.62 ± 0.12 v 0.85 ± 0.14 nmol/l (90 ± 18 v 123 ± 20 μ U/ml) ($p < 0.01$); and at 60 minutes 0.76 ± 0.17 v 1.13 ± 0.21 nmol/l (110 ± 24 v 164 ± 30 μ U/ml) ($p < 0.05$). In the sixth subject plasma insulin concentration was increased twofold and fourfold at 30 and 60 minutes respectively. This subject was the only one whose plasma glucose concentrations remained normal during the second oral glucose tolerance test. Fasting plasma glucagon concentration was measured by radioimmunoassay (Unger's 30 K antiserum) in three subjects and five additional normal subjects. Glucagon concentrations were significantly increased by nifedipine (0.045 ± 0.008 v 0.034 ± 0.006 nmol/l ($p < 0.05$) (153 ± 27 v 115 ± 22 pg/ml).

Results of oral glucose tolerance test in six normal subjects before (●—●) and after (○---○) nifedipine administration.

* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/dl. Insulin: 1 nmol/l $\approx$ 145 μ U/ml.

Comment

The present study shows that in subjects with normal glucose tolerance short-term administration of nifedipine increases fasting plasma glucose concentrations and induces appreciable glucose intolerance associated with a delay of the insulin response. Factors other than impaired insulin release may play a part in the nifedipine-induced glucose intolerance. Particularly relevant are the raised plasma glucagon concentrations that we observed, and the possibility of transient rises in plasma norepinephrine concentrations.²

While we were preparing this paper a study was reported in which the effects of nifedipine (30 mg/day by mouth for 10 days) on carbohydrate metabolism were measured.³ In subjects with normal glucose tolerance raised fasting plasma glucose concentrations were observed; in contrast to our findings, however, an improvement in glucose tolerance, paradoxically associated with a reduced insulin response during the oral glucose tolerance test, was described. In patients with glucose intolerance nifedipine was reported to induce further