Self-poisoning with sustained-release aminophylline: secondary rise in serum theophylline concentration after charcoal haemoperfusion

Theophylline poisoning can result in nausea, vomiting, hypotension, cardiac dysrhythmias, and seizures. Mortality may be as high as 50%, and life-threatening events may occur without premonitory symptoms.¹ Because of this, treatment is indicated when serum theophylline concentrations are very high. Charcoal haemoperfusion is effective in lowering serum concentrations of theophylline.² We report a case of self-poisoning with sustained-release aminophylline, in which secondary rises in serum theophylline concentrations occurred after treatment with charcoal haemoperfusion.

Case report

A 26-year-old woman was admitted having taken an unspecified quantity of sustained-release aminophylline tablets (Phyllocontin, Napp Laboratories) three hours earlier. On admission she was fully conscious and complaining of nausea and vomiting. She had a sinus tachycardia of 150/min and her blood pressure was 100/60 mm Hg. Gastric lavage produced little return and activated charcoal (50 g) was given orally.

Her serum theophylline concentration (EMIT, Syva Ltd) four hours after ingestion was 60 mg/l (therapeutic range approximately 10-20 mg/l). Extracorporeal haemoperfusion through a charcoal column (Haemocol 100, Smith and Nephew Pharmaceuticals Ltd) was performed initially for three hours. The charcoal column was placed in series with a Gambro 17 micron dialyser (surface membrane area, 1 m²). An arteriovenous shunt gave a blood flow rate of 200 ml/min.

With this treatment the serum theophylline concentration fell rapidly to 33 mg/l (figure). Her tachycardia settled to 100/min and blood pressure rose

Serum theophylline concentrations during treatment with charcoal haemoperfusion.

to 120/80 mm Hg. Ten hours later, however, the serum theophylline concentration had risen to 51 mg/l together with an increased pulse rate and further nausea and vomiting. Charcoal haemoperfusion was repeated for a further three hours, resulting in a fall in serum theophylline to 15 mg/l with appreciable clinical improvement. Nevertheless, 14 hours later (44 hours after ingestion) the serum theophylline concentration had risen to within the toxic range (34 mg/l). Charcoal haemoperfusion was not repeated and the subsequent clinical course was uneventful; 80 hours after admission serum theophylline was undetectable. Apart from a transient fall in platelet count (from $216 \times 10^9/l$ to $76 \times 10^9/l$) associated with macroscopic haematuria, treatment with charcoal haemoperfusion was well tolerated.

Comment

During charcoal haemoperfusion the serum theophylline concentration fell rapidly; during the first period of treatment drug clearance was 75 ml/min. This rate is lower than previously reported for clearance during charcoal haemoperfusion, presumably because the drug continued to be absorbed. During the second period of treatment

drug clearance was 233 ml/min, which is similar to other reported results.³ The rate of endogenous theophylline clearance, derived from serum concentrations 60 hours after ingestion, was 62 ml/min.

After both periods of charcoal haemoperfusion the serum theophylline concentration rose (figure). After the second period (44 hours after drug ingestion) it rose from within the therapeutic range to a toxic level. Sustained-release aminophylline is normally absorbed within eight hours⁴; this rise in serum theophylline concentration was probably due to compartmental distribution of the drug. After an oral dose, theophylline distribution is consistent with a two-compartment open kinetic model with central and peripheral compartments.⁵ When the drug is rapidly cleared from the central compartment (for example, during charcoal haemoperfusion), a gradient between the peripheral and central compartments develops. When rapid clearance stops, transfer of the drug from peripheral to central compartments allows serum theophylline concentrations to rise.³ It is important to realise that this may occur when the concentration of serum theophylline has been lowered to within the therapeutic range and that subsequent concentrations can rise to a value at which major adverse effects may occur.¹ Although charcoal haemoperfusion is effective in treating theophylline poisoning, serum theophylline concentrations need to be monitored after treatment has been discontinued, as serious rebound drug toxicity may occur during this period.

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¹ Zwillich CW, Sutton FD, Neff TA, *et al.* Theophylline induced seizures in adults. *Ann Int Med* 1975;**82**:784-7.

² Jefferys DB, Raper SM, Helliwell M, Berry DM, Crome P. Haemoperfusion for theophylline overdose. *Br Med J* 1980;**280**:1167.

³ Russo ME. Management of theophylline intoxication with charcoal column haemoperfusion. *N Engl J Med* 1979;**300**:24-6.

⁴ Boroda C, Miller RB, Leslie ST, Nicol EG, Thomson I. Comparison of bioavailability of aminophylline in a conventional base and in continuous release. *J Clin Pharmacol* 1979;**13**:383-8.

⁵ Ogilvie RI. Clinical pharmacokinetics of theophylline. *Clin Pharmacokinet* 1978;**3**:267-93.

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Comfortable splinting for intravenous infusion

The arm of a patient receiving an intravenous infusion is traditionally splinted by bandaging to a rigid flat board covered in plastic. This arrangement is uncomfortable and against orthopaedic principles. It is usually necessary to cover most of the arm with the bandage to achieve adequate immobilisation, so inspection of the drip site and of the skin overlying the infused vein is difficult. More effective and comfortable immobilisation may be achieved with splints made of Plastazote.

Construction and use of splints

Splints were made by moulding warmed 12 mm thick Plastazote (obtained from Hinders-Leslies Limited, Higham Hill Road, London E17) on to the arm of a model. The raw materials cost about £1.50 for an elbow splint and £1.30 for a wrist splint (cost dependent on the terms negotiated by each hospital for bulk purchase). Plastazote needs to be warmed in a special oven, which, presumably, any occupational therapy department using Plastazote would possess. It took about half an hour to make one splint, but in practice several splints could be made at the same time, and we in fact made a batch of four. Three or four Velcro straps were riveted to the splint. For male patients a strip of plastic was glued to the back of the splint. Right- and left-hand versions were needed for the wrist splint, but the elbow splint was suitable for both sides (figure).

A: Elbow splint. B: Left wrist splint with reinforcing plastic strip arrowed.

The cannula puncture site was covered with a small dressing and the drip tubing held in place with the usual Elastoplast strips.

The splints were used by 100 consecutive patients recruited for a trial to investigate infusion thrombophlebitis.¹ They were enthusiastically accepted by the patients and nurses. The absence of an all-embracing bandage permitted easy inspection of the drip site.

Four splints were made for the investigation. No complications attributable to the splint were encountered, and none of the splints wore out. They were cleaned with a cloth moistened with cetrimide.

Comment

Moulded Plastazote splints are a comfortable and cheap alternative to the traditional board in intravenous infusions.

¹ Woodhouse CRJ. Movelat in the prophylaxis of infusion thrombophlebitis. *Br Med J* 1979;i:454-5.

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Domperidone in the prevention of complete classical migraine

Clinically, migraine is usually associated with a disturbance of various autonomic functions. Objective measurements have suggested that gastric emptying is delayed during migraine attacks.^{1,2} Although studies of the autonomic nervous system during the prodromal period have not been performed an autonomic malfunction could possibly precipitate the migraine. Furthermore, since manifold interactions occur within the autonomic nervous system, correcting one defective function could possibly restore the autonomic balance and thus perhaps prevent an attack. In patients with complete migraine physical or psychic changes or both are experienced some 24 hours before an attack.³ In an open pilot study I found that the attack was prevented when patients were given a high dose (30 mg) of domperidone immediately the warning signals occurred. Domperidone is a peripheral dopamine-receptor antagonist with antiemetic and gastro-

kinetic properties.⁴ The present double-blind study was undertaken to confirm this observation.

Patients, methods, and results

I studied 19 patients with classical migraine, all of whom experienced warning phenomena (primarily sensory or psychic intolerance) which occurred from seven to 48 (median, 24) hours before a severe to incapacitating headache. Each patient was studied during four consecutive (imminent) attacks, two of which were treated prophylactically with domperidone and two with a placebo under double-blind randomised conditions. The patients were given either three 10 mg domperidone tablets or three matching placebo tablets as soon as they became aware of the warning symptoms.

No aura or headache was experienced in 25 out of the 38 (66%) attacks when domperidone was taken and in only two out of the 38 (5%) after the placebo (table). Ten patients, in whom the placebo failed twice to prevent an attack, had no attack on two occasions when treated with domperidone. In all but one patient the attacks were as severe as usual when treated prophylactically with the placebo. The effects of domperidone were not related to either the type of warning symptoms or to the time lag before the actual attack. There were no side effects.

Number of patients with complete classical migraine experiencing attacks after prophylactic treatment with domperidone 30 mg and placebo (n=19)

Placebo	No of attacks after administration of: Domperidone		
	0	1	2
0	1	0	0
1	0	0	0
2	10	3	5

Statistically significant difference between drug and placebo, $p < 0.001$ (Wilcoxon's matched-pairs signed ranks test).

Comment

I know of no investigators who have tried to prevent migraine attacks in patients with early warning phenomena. The present findings show, however, that this can be achieved in most cases with a relatively high dose of domperidone. How domperidone acts in this condition is nevertheless not known. Since it does not cross the blood-brain barrier⁴ its effects are unlikely to be mediated by the central nervous system, unless patients with migraine have a defective barrier.⁵ As it is a potent dopamine-antagonist domperidone would, however, provoke extrapyramidal symptoms if the blood-brain barrier was defective; no such problems have been reported in patients with migraine. Thus, domperidone probably does not act on the central nervous system, which is often thought to play a part in the pathogenesis of migraine. Whatever the mechanism domperidone, paradoxically, prevents migraine attacks when it is taken up to 48 hours before the attack even though its duration of action is about six hours. Thus, thorough investigation of patients with complete migraine during the day before an attack should give more information on the pathogenesis of the disease.

¹ Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol* 1975;2:57-63.

² Wilkinson M. The treatment of acute migraine attacks. *Headache* 1976; 15:291-2.

³ Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J* 1980;281:658-60.

⁴ Van Nueten JM, Schuurkes JAJ. Animal pharmacology of domperidone, anti-emetic and gastrokinetic properties. In: Towse G, ed. *Progress with domperidone, a gastrokinetic and anti-emetic agent*. London: Royal Society of Medicine, 1981:21-7.

⁵ Harper AM, McCulloch J, MacKenzie ET, Pickard JD. Migraine and the blood-brain barrier. *Lancet* 1977;i:1034-6.

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