towards treating end stage renal failure in more elderly people and those with underlying diseases such as diabetes, and the less skilled they will be in diagnosing chronic renal failure. These findings suggest that intraregional variation should be examined more closely, as the findings may have implications for the organisation of treatment for end stage renal failure in the National Health Service.

We thank the strategic planning group, renal interest group, and clinical and scientific services directorate of North West Thames Regional Health Authority. We are also particularly grateful to Julie Kelly for her excellent secretarial help.

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Loperamide toxicity in a child after a single dose

Loperamide has been used in Britain for diarrhoea since 1975. Respiratory depression and coma may occur after overdosage¹ and long term therapeutic use² and have been shown to be reversible by injection of naloxone.¹ So far as we know the following is the first report of opioid toxicity after a single therapeutic dose.

Case report

A 15 month old girl weighing 8 kg was admitted to hospital after accidental scalding, superficial burns covering 35% of the body area. She was rehydrated with intravenous fluids, treated with flucloxacillin and penicillin, and on day 5 transferred to a plastic surgery unit for assessment. At the time she was taking fluids and had copious green watery diarrhoea. Clinical examination showed no other abnormality and she was well hydrated. Results of investigations were: haemoglobin concentration 94 g/l, urea and electrolyte values normal, stools negative for reducing sugars and culture, urine culture negative. The diagnosis was diarrhoea as a stress response to burns.

On day 9 she was still having the diarrhoea, and at 1330 she was prescribed an initial 1 mg oral dose of loperamide. Fifty minutes later she was collapsed, pale, and unresponsive to pain; pulse was 120/min and respiratory rate 14/min. She had not vomited or convulsed. She was resuscitated with oxygen by Ambu bag and given 0.3 mg naloxone intravenously. By two minutes conscious level was improved and respiratory rate 30/min. Next day she was still drowsy. Blood values were: haemoglobin 87 g/l, urea and electrolytes normal, alanine aminotransferase activity 327 U/l, total protein 36 g/l, albumin 11 g/l. She was transfused 200 ml whole blood and 100 ml plasma protein fraction. Conscious level was normal on day 11. Serum alanine aminotransferase activity was 76 U/l, total protein concentration 48 g/l, and albumin concentration 18 g/l. The diagnosis was changed to cows' milk protein intolerance, as the diarrhoea resolved on withdrawal of milk.

Apart from antibiotics she received papaveretum 1.5 mg intravenously on eight occasions on days 1-3 and five doses of morphine elixir 2.5 mg on days 3-5 without ill effects. No opioids had been given within four days of the reaction to loperamide. At that time she was receiving up to 360 mg paracetamol syrup daily and had had a single dose of 200 mg chloral hydrate the previous evening.

Comment

The 1 mg dose used for this child (0.125 mg/kg) may have been greater than necessary, as the manufacturer's data sheet recommends the dose for children aged 4-8 as 1 mg every six hours until diarrhoea settles, and *Martindale* states that loperamide should not be used in the very young.³ Doses in clinical trials have ranged from 0.045 to 4.0 mg/kg/day with few

side effects, though convulsions occurred in a 4 month old infant treated for 11 weeks, the dose being 4 mg/kg/day over the previous week,⁴ and possible ileus after a single dose of 0.045 mg/kg in a 1 year old.⁵

The reason for toxicity in this case is unclear. The low serum protein concentration may have been contributory (loperamide is 97% protein bound) and absorption may have been increased by damage to the gut wall. The raised serum alanine aminotransferase activity suggests that a temporary hepatic disturbance might have impaired handling of the drug.

As loperamide is available over the counter, doctors should be alert to the possible hazards of accidental ingestion of this drug by small children and the specific treatment that may be required. Naloxone appears to be an effective antidote. Reports to the National Poisons Unit suggest that though this drug causes symptoms in most cases of accidental overdosage, serious toxicity is rare.

We thank Dr N R C Robertson and Mr R C Campbell, of Addenbrooke's Hospital, Cambridge, for permission to report this case.

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Insulinoma unmasked by the Cambridge diet

Hypoglycaemia is not usually a feature of adherence to very low energy diets. We describe a patient who, for the first time, developed symptoms attributable to hypoglycaemia within three days of starting the Cambridge diet and was subsequently found to have an insulinoma.

Case report

A previously fit 46 year old man (height 179 cm, weight 82 kg, body mass index 25.6) was referred to the neurology department by his general practitioner because of a history of intermittent unsteady gait, slurred speech, and intellectual impairment which began three days after he started a self prescribed very low energy diet (the Cambridge diet; 1.38 MJ/day). His wife described how, while out walking, he began to stagger and his speech became slurred. The patient described feelings of unsteadiness, weakness, and intoxication. The symptoms completely resolved within 30 minutes of eating a light meal. Symptoms recurred two days later while he was still taking the Cambridge diet and again resolved after a light meal. Two days later he awoke confused and disorientated, wide eyed, and smiling inanely. On attempting to rise he staggered about the room. His symptoms resolved on eating breakfast. Physical examination showed no abnormality and investigations for spontaneous hypoglycaemia were initiated.

A random plasma glucose estimation while the patient was symptom free was 7.1 mmol/l. Next morning, after a 15 hour fast, the plasma glucose concentration was 2.6 mmol/l but unaccompanied by symptoms. The fast was continued with exercise. After 22 hours without food his responses to intellectual testing were slow and an electroencephalogram showed slight slowing of the α rhythm to 9 Hz during overbreathing. Intravenous injection of saline given as a control produced no change but 25 g glucose given similarly restored his mental state and returned the α rhythm to 10 Hz. The preinjection plasma glucose concentration was 1.6 mmol/l, β -hydroxybutyrate concentration less than 0.02 mmol/l, immunoreactive insulin concentration 55 mU/l, and C peptide concentration 3.6 μ g/l. The finding of inappropriately high plasma insulin and C peptide values and suppressed β -hydroxybutyrate concentration in the presence of hypoglycaemia was highly suggestive of insulinoma. Computed tomography showed nothing abnormal.

At laparotomy a well encapsulated tumour 1 cm in diameter was removed from the posterior aspect of the head of the pancreas. Immunohistologically the tumour contained many insulin and a few somatostatin containing cells. Recovery was uneventful. Five days postoperatively the overnight fasting plasma glucose value was 7.1 mmol/l. Immunoreactive insulin (6.7 mU/l), C peptide (3.3 μ g/l), and β -hydroxybutyrate (0.12 mmol/l) concentrations were all appropriate for the

plasma glucose value. By using an antiserum which does not cross react with insulin (Guildhay Antiserum, Guildford), much of the circulating immunoreactive insulin was subsequently shown to be proinsulin.

Comment

Very low energy diets have been used clinically as an aid to weight loss in gross obesity.¹ The recent more general availability of such diets has enabled them to be used without medical supervision by people with moderate to minimal obesity. The present case illustrates an interesting though rare manifestation of very low energy intake; indeed, low energy, low carbohydrate diets were advocated as a provocative test for insulinoma in lieu of total fasting.² Signs and symptoms of hypoglycaemia are not a feature of low energy diets in the absence of organic disease and their occurrence, as in this case, should lead to further investigation.

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Verapamil in atrial fibrillation in hyperthyroidism

Hyperthyroidism is a well known cause of atrial fibrillation, and until hyperthyroidism is properly controlled atrial fibrillation is often difficult to treat.¹ Verapamil is effective in the treatment of atrial fibrillation in euthyroid patients,² and we therefore tried it in the treatment of hyperthyroid patients with atrial fibrillation.

Patients, methods, and results

Nine patients were included in the study, seven women and two men, aged 52-87. On admission hyperthyroidism was confirmed in all patients by finding raised hormone concentrations, and subsequently by the absence of any thyrotrophin response to thyrotrophin releasing hormone. At the time of verapamil treatment one patient had received antithyroid treatment for one week: none of the remaining patients had received such treatment.

On admission all patients had atrial fibrillation with a heart rate of 120 beats/min or more. Six patients had cardiac failure. Details of antiarrhythmic treatment and its effects are shown in the table. Seven patients received digoxin without adequate control of heart rate, but after the addition of verapamil this was achieved in all patients. In case 4, a patient who was unresponsive to a combination of digoxin and a β blocker, the heart rhythm was immediately converted to sinus rhythm after intravenous verapamil. Two patients were

treated with verapamil only, and both converted to sinus rhythm. One of these patients had an overt thyrotoxic crisis. In spite of this sinus rhythm was maintained with oral verapamil.

Verapamil caused no further deterioration of left ventricular function in any of the patients; advanced atrioventricular block was not observed.

Comment

Electrophysiological investigations of the heart in hyperthyroidism have shown a shortening of the action potential owing to an increased rate of diastolic depolarisation in atrial cells.³ This shortening predisposes to atrial fibrillation,² which occurs in 15-30% of patients with hyperthyroidism and is often the presenting feature. Digoxin is usually the first drug of choice, but altered pharmacodynamics and decreased sensitivity to digoxin may make treatment difficult. Supplementary treatment with a β blocker without an intrinsic sympathomimetic effect is often tried. Nevertheless, on admission a substantial number of patients with hyperthyroidism and atrial fibrillation have cardiac failure and β blockers may further decrease the left ventricular function.^{4,5} Hence β blockers are relatively contraindicated in these patients, and verapamil may be an alternative. Neither verapamil nor β blockers affect the duration of the action potential of atrial muscle cells, but both have a pronounced effect on the conduction time of the atrioventricular node.^{2,3}

Our results indicate that verapamil is effective in controlling the heart rate in hyperthyroid patients, even when digoxin or β blockers, or both, have proved ineffective. Hence it is probably a suitable alternative to these, but randomised studies comparing all three agents in treating hyperthyroid patients with atrial fibrillation are needed.

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Persistent mesenteric ischaemia in a young woman

Mesenteric ischaemia is an uncommon cause of abdominal pain, usually being considered only in older patients with vascular or haematological disease. We describe a young woman with typical symptoms in whom the condition remained undiagnosed until emergency laparotomy despite investigation by five consultants in four hospitals over 18 months. Surprisingly, she later developed recurrent pain from ischaemia despite almost total resection of the small bowel.

Effects of antiarrhythmic treatment on nine patients with hyperthyroidism with atrial fibrillation on admission

Case No	Treatment on admission (daily dose)	Heart rate on admission (beats/min)	Initial treatment	Effect of initial treatment (rhythm (beats/min))	Verapamil dosage	Effect of verapamil treatment (rhythm (beats/min))
1	Digoxin 125 μ g $\times$ 2	120	Verapamil 80 mg $\times$ 3	Atrial fibrillation (70)	80 mg $\times$ 3	Atrial fibrillation (70)
2		160	Digoxin 1000 μ g	Atrial fibrillation (160)	5 mg intravenously and 80 mg $\times$ 4	Intermittent sinus rhythm
3	Digoxin 65.5 μ g $\times$ 2 Digoxin 125 μ g $\times$ 2 propranolol 40 mg $\times$ 4	160	Verapamil intravenously	Intermittent sinus rhythm	80 mg $\times$ 3	Intermittent sinus rhythm
4		160-180	Practolol (drip)	Atrial fibrillation (160-180)	5 mg intravenously and by drip and 80 mg $\times$ 4	Sinus rhythm
5		160	Verapamil 5 mg intravenously	Sinus rhythm	80 mg $\times$ 3	Sinus rhythm
6		170-180	Digoxin 1000 μ g	Atrial fibrillation (170)	10 mg intravenously and by drip and 80 mg $\times$ 3	Atrial fibrillation (100)
7	Digoxin 62.5 μ g $\times$ 3	160	Verapamil 10 mg intravenously and by drip	Sinus rhythm	80 mg $\times$ 4	Sinus rhythm
8		120	Verapamil 80 mg $\times$ 4	Atrial fibrillation (100)	80 mg $\times$ 4	Atrial fibrillation (90)
9		150-160	Digoxin 1000 μ g	Atrial fibrillation (140)	5 mg intravenously and 80 mg $\times$ 3	Intermittent atrial fibrillation (70)