and popliteal arteries and similar areas in the left superficial femoral and both profunda femoris arteries. Flow to the lower legs was reduced. Treatment, including right lumbar sympathetic blockade and catheter dilatation of the right superficial femoral and popliteal arteries, restored peripheral pulses and perfusion in three days. Clinical and electromyographic evidence of right common peroneal and tibial neuropathies (presumably ischaemic) persisted.

Comment

These two patients developed occlusion of major arteries while taking methysergide and parenteral ergotamine for cluster headache. Arteriograms showed arterial spasm and collateral vessels, which are features of ergotism.[2] These signs have been described in both ergotamine and methysergide toxicity in many areas of the arterial circulation. Thrombosis may also occur.[2]

Ergotamine is a direct vascular smooth-muscle stimulant.[3] Parenteral administration increases potency tenfold through faster and more complete absorption and raises the risk of arterial spasm.[3] Methysergide is a derivative of methylergonovine,[3] independently capable of producing arterial spasm.[4] Arterial spasm persisted after withdrawal of the drugs in both cases. This is typical of ergotism and presumably represents tissue binding of the drugs, since the half lives of methysergide and ergotamine are only 2·7[5] and 2·0[3] hours respectively. Accumulation in tissue also explains the delay between introduction of the drugs and the development of toxicity in these patients.

Neither patient was predisposed to ergotism through fever, sepsis, hepatic disease, thyrotoxicosis, or atherosclerosis.[3] Flow studies using xenon-133 indicate increased cerebral blood flow during headache.[1] Pizotifen, which was also taken by the second patient, is not known to produce arterial spasm. It appears, therefore, that methysergide and parenteral ergotamine together create a particularly high risk of arterial spasm. The combination should be avoided.

We thank Dr J Scopa for permission to report case 2.

Requests for reprints should be addressed to Dr S S Gubbay, Royal Perth Hospital, PO Box X2213, Perth, Western Australia 6001.

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Department of Neurology, Royal Perth Hospital, Perth, Western Australia 6001
D A JOYCE, MB, BS, neurology registrar (present appointment: rheumatology registrar, Royal Perth (Rehabilitation) Hospital)
S S GUBBAY, MD, FRACP, head of department

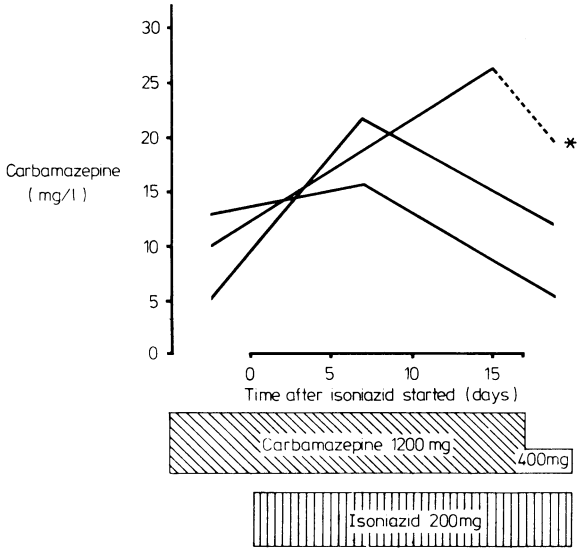
Carbamazepine intoxication caused by interaction with isoniazid

Several chemotherapeutic agents have been reported to inhibit drug-metabolising liver enzymes, with consequent interference with biotransformation.[1] An example is isoniazid, which has been implicated as an enzyme inhibitor in epileptics taking phenytoin, who became toxic while receiving the two drugs simultaneously.[2] We report a similar apparent interaction between isoniazid and carbamazepine.

Case reports

Changes were observed in 10 out of 13 epileptic patients, resident in a mental subnormality hospital, when they were given prophylactic isoniazid in addition to existing treatment with carbamazepine because they were contacts of an inpatient who had active tuberculosis. The signs noted in these previously stabilised patients were disorientation, listlessness, aggression, lethargy, and in one case extreme drowsiness. Serial serum carbamazepine concentrations were available for only three of the affected patients, as symptoms were initially thought to be due to infection.

In one patient initially receiving carbamazepine alone the serum concentration increased to 26·2 mg carbamazepine/l with an unchanged dose (1200 mg daily) after isoniazid (200 mg daily) was started. When the dose of carbamazepine was lowered to 400 mg, against a fixed dose of isoniazid, the serum concentration fell to the therapeutic range (5-12 mg/l). Two further patients who had previously tolerated 1200 mg carbamazepine daily, in addition to sodium valproate, became confused and ataxic after starting isoniazid. Their carbamazepine concentrations were found to be 15·2 and 13·4 mg/l respectively; their valproate concentrations remained constant. When the dose of carbamazepine was halved the concentrations fell to 10·6 and 5·8 mg/l and toxic signs disappeared. Doses of valproate were kept at previous levels. Serum carbamazepine concentrations in the remaining seven patients who became intoxicated were not recorded; when the dose of carbamazepine was lowered, however, their toxic signs were alleviated. Three patients who took isoniazid and carbamazepine together did not develop symptoms.



Serum carbamazepine concentrations before and after isoniazid was introduced.
*Toxic symptoms disappeared when carbamazepine dosage was reduced; serum concentration was not recorded.

Comment

Carbamazepine is metabolised principally to its epoxide by the hepatic "mixed-oxidase" system. It is a potent enzyme inducer, and after about two weeks' dosing autoinduction occurs, the mean half life falls from 30 to 18 hours, and the serum concentration may fall.[3] Isoniazid is a potent hepatic enzyme inhibitor. It is acetylated in the liver at a rate that varies between individuals and shows a bimodal distribution in the population, with slow and rapid acetylators. Slow acetylators have a much greater risk of experiencing the interaction between isoniazid and phenytoin.[4] Metabolism of carbamazepine is probably inhibited in the liver by isoniazid in the same way as that of phenytoin, though from our findings we cannot be certain whether a similar relation exists between acetylator status and the development of this interaction. The other possibility is that carbamazepine and isoniazid have a combined synergistic effect that increases the neurotoxic effects of each drug, though restlessness and insomnia occur more frequently in isoniazid toxicity than the lethargy and drowsiness that occurred in most of our patients. The raised plasma concentrations in the three patients monitored and the liver-enzyme-inhibiting effect of isoniazid tend to support the case for an intrahepatic interaction.

Because the nature of the problem was initially unknown, serum carbamazepine concentrations were measured in only three patients. One of these (whose concentration rose to 26·2 mg/l) was taking carbamazepine alone; the two others were taking additional sodium valproate. Valproate concentrations remained constant while isoniazid was being taken: the interaction was apparently not dependent on sodium valproate.

The signs of toxicity were consistent with those previously reported for carbamazepine,[5] and, though five of the patients who became toxic but in whom serum concentrations were not measured were

taking additional valproate, all recovered when the carbamazepine dose alone was reduced. The remaining two patients who became toxic were initially taking only carbamazepine. The main importance of the interaction arises from the tendency for tuberculosis to occur in long-term hospitals that may have a large epileptic population. Whenever the two drugs are prescribed simultaneously close monitoring of carbamazepine concentrations is indicated.

We thank Dr G W Hearn and Dr C Skinner for their help and permission to report on patients under their care.

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Chelmsley Hospital, Marston Green, Birmingham B37 7HL
V C VALSALAN, MB, DPM, consultant psychiatrist

Ciba-Geigy Pharmaceuticals Division, Horsham, West Sussex RH12 4AB
G L COOPER, MB, MRCGP, medical adviser

Insulin resistance and hypomagnesaemia: case report

Magnesium is essential for many enzyme systems, especially those utilising high-energy phosphate bonds.[1] Though its importance to normal cellular function is increasingly acknowledged, the potential loss occurring during severe diabetic ketoacidosis[2] is often ignored. We present a case illustrating the benefit of replacing this essential ion.

Case report

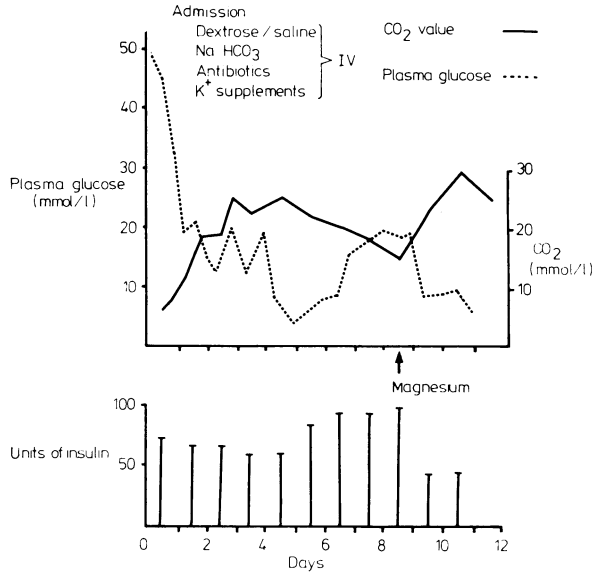
A 34-year-old type I diabetic woman who had been well controlled for 20 years with 42 units isophane insulin daily was admitted in severe ketoacidosis precipitated by a urinary tract infection. Treatment was instituted with intravenous fluids supplemented with potassium, intravenous antibiotics, and intramuscular insulin according to the Alberti regimen. Initial response was good, resulting in a rapid fall in the plasma glucose concentration with electrolyte values and acid-base balance returning to normal within 48 hours. This was achieved with a diet of 120 g carbohydrate and 64 and 60 units insulin being given during the first and second 24-hour periods.

Within three days the plasma glucose concentration had become increasingly difficult to control and there was a profound deterioration in the patient's clinical condition, with anorexia, nausea, and vomiting indicating the return of ketoacidosis. The urinary tract infection was responding well, but despite increasing the dose of Actrapid MC from 50 to 100 units in 24 hours she showed no improvement. The plasma magnesium concentration was estimated, and as this was 0·67 mmol/l (1·6 mg/100 ml) (normal range 0·80-1·04 mmol/l; 1·9-2·5 mg/100 ml) 60 mmol magnesium sulphate was given intravenously over six hours and oral treatment begun. The insulin requirement fell rapidly to 44 units daily and she showed a remarkable improvement, the acid-base balance again returning to normal (figure).

Comment

The neurological manifestation of hypomagnesaemia may vary from tetany or muscle weakness to depression or frank psychosis, while the cardiac manifestations are those of electrocardiographic and rhythm changes. A previously reported case[3] of asystole associated with hypomagnesaemia during diabetic ketoacidosis illustrated the benefit that magnesium replacement may bring. It has been pointed out[4] that the loss of magnesium during the treatment of diabetic ketosis follows the same pattern as potassium loss, and it has been suggested that magnesium should be added to intravenous fluids in a concentration of 5 mmol.

In our patient initial control of the diabetic ketosis was easily achieved, and it was only when stabilisation would normally have been expected that difficulties in control arose. Though an anti-insulin hormonal response precipitated by increasing ketosis or the urinary tract infection may have been responsible for the increasing insulin requirements, we think that magnesium deficiency was more likely, especially in view of the dramatic response to the magnesium infusion. While we



Effect of intravenous magnesium sulphate on insulin requirement and plasma glucose and carbon dioxide concentrations.
Conversion: SI to traditional units—Plasma glucose: 1 mmol/l ≈ 18 mg/100 ml. Carbon dioxide: 1 mmol/l ≈ 4·4 mg/100 ml.

accept that the administration of magnesium sulphate in 500 ml 5% dextrose might have caused some plasma expansion thereby decreasing the insulin requirements, we think that this decrease was so pronounced as to merit some other mechanism. This mechanism may have been the improvement of enzyme systems through which insulin must eventually function. The rapid response to magnesium replacement has been noted by others.[3 5]

We suggest that the possibility of magnesium depletion should be borne in mind more often, especially when diabetic ketoacidosis proves difficult to control. Replacement is easily achieved with 60-80 mmol magnesium sulphate given intravenously over four to six hours followed by 10 ml magnesium chloride (20% solution) twice daily. With children or those with a light body build the dose is 0·5 to 1·0 mmol/kg body weight.

We thank Dr A P Grant for permission to publish the details of this patient, who was under his care.

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Cardiac Unit, Belfast City Hospital, Belfast BT9 7AB
KENNETH W MOLES, MB, MRCP, senior registrar
J KENNETH McMULLEN, MB, MRCP, senior registrar