those published by others.[12-14] The incidence and severity of side effects were low, which we attribute to the following factors: firstly, that the drug was given as a single daily dose; secondly, that on the fourth day the patients returned to the pretreatment steroid dosage, without any "tailing-off" period; and, thirdly, that background steroid treatment was stopped during the three treatment days. Certain additional advantages of oral prednisolone became apparent during the study. Many hospital visits were avoided, since the drug may be taken at home while each dose of intravenous methylprednisolone requires attendance at hospital. By the same token, interruption of school attendance and social activities was much reduced. The patients universally disliked intravenous methylprednisolone, which produces a variety of unpleasant sensations during injection and requires additional needles, a special problem with younger children. Finally, the cost of a course of treatment with oral prednisolone is less than £1, compared with about £45 for three doses of intravenous methylprednisolone.

We conclude that oral prednisolone, in three single daily doses of 3 mg/kg, is as effective as high-dose intravenous methylprednisolone in reversing acute rejection episodes in children with renal allografts and is attended by few serious side effects; we recommend its adoption as the treatment of choice in the routine management of paediatric transplant recipients.

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SHORT REPORTS

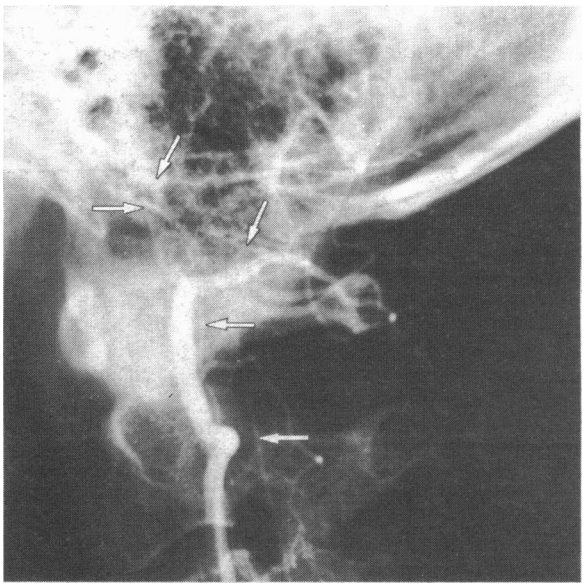
Arterial complications of migraine treatment with methysergide and parenteral ergotamine

Cluster headaches, which are associated with abnormal dilatation of the carotid artery and wall oedema,[1] may be managed with methysergide and ergotamine. These drugs promote arterial constriction. Large artery spasm may rarely complicate treatment with either drug and is more likely when ergotamine is administered parenterally. We report on two patients in whom arterial spasm and tissue infarction developed during concurrent treatment with methysergide and parenteral ergotamine. This combination appears to create a particularly high risk of arterial spasm.

Case reports

Case 1—A 34-year-old man who took small amounts of methysergide prophylactically for recurrent cluster headaches and smoked lightly was treated during a cluster with methysergide 2 mg thrice daily and subcutaneous ergotamine tartrate 0·5 mg at night. Seven days after starting this combination he developed right faciobrachial thermoanaesthesia, vertigo, dysphagia, and hoarseness. He continued ergotamine injections for five more days and methysergide for three weeks, when left Horner's syndrome, reduced left gag reflex, and impaired pain, temperature, and light touch sensation over the right face, shoulder, and arm were found. Arteriography disclosed left vertebral artery occlusion for 1·5 cm upwards from the foramen magnum, collateral circulation, and right vertebral artery spasm (figure). Signs gradually resolved after withdrawal of the drugs, except for persistent right faciobrachial thermoanaesthesia.

Case 2—A 27-year-old man was treated during a bout of cluster headaches with methysergide 2 mg thrice daily, pizotifen 0·5 mg thrice daily, and intramuscular ergotamine tartrate. Oral and rectal ergotamine preparations had been ineffective. The dose of parenteral ergotamine was increased from 0·5 mg at night to 1 mg twice daily over 16 days. Three days later popliteal and pedal pulses were impalpable and the right foot was ischaemic. Arteriography disclosed a 22 cm segment of spasm in the right superficial femoral



Case 1. Left vertebral arteriogram, lateral view. Oblique arrows indicate proximal and distal ends of occluded vessel; horizontal arrows indicate collateral vessels.

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.

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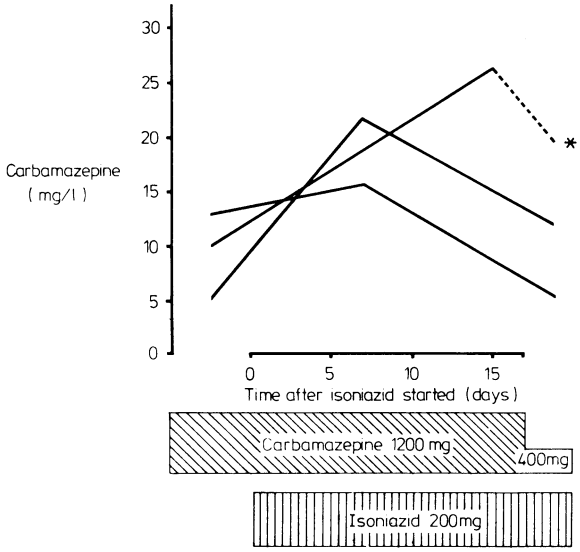
Carbamazepine intoxication caused by interaction with isoniazid

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