LETTERS

Intra-arterial temazepam

EDITOR,—We write to draw attention to complications resulting from the new "abuse resistant"[1] formulation of temazepam capsules. In the past six months we have seen 15 injecting drug misusers (13 men, two women, aged 19-35) with severe complications of intra-arterial injection (10 femoral, five brachial) of "solid" gel temazepam. Patients prepared the capsules by removing the soft gelatin shell, boiling the "solid" gel centre with water in a spoon, and injecting the warm suspension. All described instant pain in the region supplied by the injected artery.

Soon after injection examination may reveal no major abnormality. Typically a purplish mottled rash develops later, in the distribution of the injected artery. Swelling of the limb can be delayed but may be rapid, accompanied by compartment syndromes and severe rhabdomyolysis.

All patients had palpable distal pulses at presentation but six had severe pain and fixed mottling of digits. Eleven required fasciotomies; one required a high above knee amputation for extensive muscle necrosis; one required an above elbow amputation; another had the fingers of his dominant hand amputated; and in several cases digits were allowed to autoamputate. Histological examination showed early patchy vasculitis and oedema, followed by secondary thrombosis and ischaemia. Four patients needed temporary haemodialysis. Two developed deep venous thrombosis and one suffered pulmonary thromboembolism.

The Home Office requested withdrawal of liquid filled capsules containing temazepam because of injecting misuse.[2-5] Manufacturers responded by substituting "solid" gel formulations of temazepam in solution with macrogols (high molecular weight crystalline waxes). These preparations were considered "abuse resistant" because the viscid gel is insoluble in water and cannot readily be drawn into a syringe.[1] However, the Advisory Council on the Misuse of Drugs is aware that "solid" gel temazepam is being injected by misusers.[6] Blair and colleagues showed that the late results of intra-arterial injection of the new "solid" gel temazepam can be catastrophic.[7]

Injecting drug misusers who present with a painful limb soon after intra-arterial injection of "solid" gel preparations of temazepam should be admitted for observation, even if clinical examination gives normal results. Early, radical fasciotomies are needed to decompress tender swollen muscle compartments and reduce rhabdomyolysis. Combined with forced alkaline diuresis this may avert acute renal failure. For limb salvage the potential value of aggressive endoarterial treatment[8] may need to be considered.

We hope that the Advisory Council on the Misuse of Drugs will wish to consider the need for further action.

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EDITOR,—We describe a case of rhabdomyolysis after intra-arterial injection of temazepam.

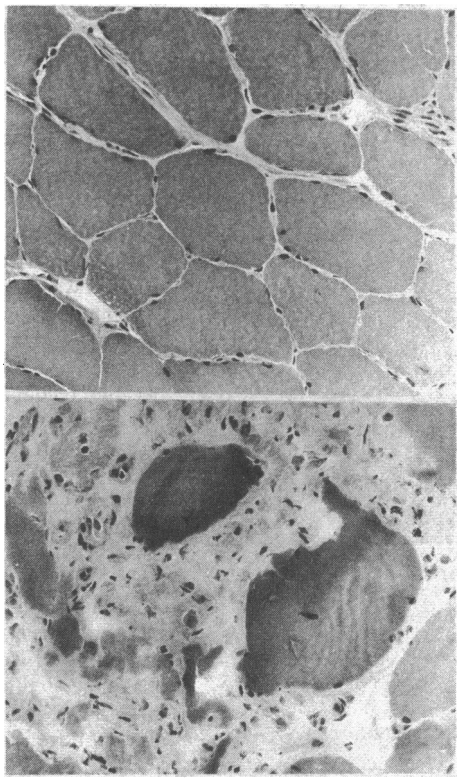
A 41 year old male intravenous drug misuser was admitted with an excruciatingly painful right leg immediately after he had injected temazepam gel into the femoral artery in his right groin; he had intended to use the femoral vein. Examination of the right leg showed massive, blotchy discoloration of the skin on all surfaces from groin to foot. The femoral, popliteal, dorsalis pedis, posterior tibial, and peroneal pulses were all palpable. There was no swelling and no pitting oedema of the ankle.

Epidural anaesthesia with bupivacaine, was given for three days, which completely relieved the pain. The patient was monitored for signs of rhabdomyolysis, oliguria, and a rise in compartment pressures. Twenty eight hours after admission the compartment pressures began to rise and a three compartment fasciotomy was performed. An alkaline diuresis was started together with intravenous mannitol and continued for three days. On the 10th day he developed a right ileofemoral vein thrombosis, confirmed with venography, which resolved with intravenous heparin.

Plasma creatine kinase rose to very high concentrations 18 hours after admission (about 24 hours after the injection) and reached 66 000 IU/l on the second day (normal <200 IU/l). Concentrations then declined to just over 1500 IU/l five days later and eventually to normal 18 days after admission. Plasma myoglobin concentration (normal <0·1 mg/l) showed a similar large rise, though it rose faster, being maximal 24 hours after the injection (>35 mg/l), and declined more rapidly than the creatine kinase concentration. Despite the evidence of massive rhabdomyolysis renal function was well preserved, urine flow was maintained, and the plasma creatinine concentration remained normal (50-125 μmol/l) throughout the admission. Of the two muscle samples taken from adjacent areas of the anterior tibialis on the third day of admission one showed normal structure and histochemical staining, and the other extensive degeneration and mononuclear cell infiltration (figure).

The intact pulses implied that the circulation to the limb muscles had been spared, but the blotchy discoloration suggested that the intra-arterial injection of fine particulate matter had produced a situation much like "trash limb"[1] with small vessels being blocked by microemboli and areas of muscle rendered ischaemic. The occurrence of rhabdomyolysis with the appearance of myoglobin and creatine kinase in the circulation was similar to that seen after vascular reconstruction and reperfusion of limbs in cases of acute ischaemia.[2] Fasciotomy did not prevent rhabdomyolysis, but, when compartment pressures rise this procedure will limit subsequent ischaemic damage.[3] The main clinical concern is to maintain renal function, which we managed to do with a large alkaline diuresis and mannitol.

The patchy distribution of muscle breakdown



Muscle biopsy specimens showing (top) little damage and (bottom) extensive degeneration and cellular infiltration (haematoxylin and eosin)

suggests that the muscle changes did not result from arterial spasm or from any pharmacological action of temazepam, both of which would be expected to affect the muscle uniformly. Also temazepam is not known to be myotoxic.[4] The semi-solid nature of the injected mixture probably indirectly damaged the muscle, first creating areas of critical ischaemia within the muscle, which, when the blockage had cleared, were susceptible to reperfusion injury.

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MRC trial of treating hypertension in older adults

EDITOR,—The Medical Research Council's trial of treatment of hypertension in older adults has been a major achievement.[1] A total of 4961 subjects were recruited over five years, randomised, and followed up for 25 355 patient years.

Unfortunately, several serious flaws jeopardise any conclusion from the trial. Firstly, a quarter of