Intra-arterial temazepam

EDITOR,—We write to draw attention to complications resulting from the new "abuse resistant" 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 viscous 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 treatment⁸ 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 iliofemoral 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" 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

the patients were lost to follow up. This would be unacceptable in any trial in acute myocardial infarction or heart failure, in which I have considerable experience; I cannot understand why a study in hypertension would be different. This loss of patients indicates that the investigators have had serious problems monitoring their patients. Furthermore, it is known that patients lost to follow up differ from patients who remain in trials.

Secondly, the number of patient years during which patients received treatment as a proportion of the total number of patient years in the subgroups was 69% in the diuretic group, 55% in the β blocker group, and 69% in the placebo group. Obviously, if close to 50% of the assigned treatment is not administered it will not be possible to observe any effect.

Thirdly, the number of withdrawals from β blocker treatment in this single blind study is in contrast to the experience in the Swedish trial in old patients with hypertension (STOP trial): 177 patients treated with β blockers in the Medical Research Council's trial were withdrawn because of bradycardia compared with none in the STOP trial (B Dahlöf, personal communication).

Fourthly, the power of the trial was calculated to study active treatment versus placebo. There is clearly insufficient power to permit conclusions regarding lack of effects between the treatment subgroups and placebo group—even more so considering my second point above. Wisely, the STOP trial did not present its subgroup results.

None of these important flaws is discussed by the authors. I suggest that the trial should be discussed more in the context of pitfalls and flaws than in the context of treatment of hypertension.

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- 1 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304:405-12. (15 February.)
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EDITOR,—All physicians are asked to advise on the management of blood pressure and often feel lonely when competing with drug company promotion. This feeling is intensified when a report carrying the imprimatur of the Medical Research Council draws a misleading conclusion.¹ In this single blind study the only unexpected finding was the death rate—an end point not subject to the same influences as the others. Of the 4396 patients in the study, 823 died—409 in the treatment group and 414 in the placebo group, a difference of five deaths. Expressed in another way, there were five additional deaths in 25355 patient years of observation. About half of the patients were lost from the study, so the beneficial effect needs to be halved—one additional death in 10000 patient years.

Regardless of statistical games, can such marginal benefit warrant the time and trouble for these elderly patients and their enthusiastic doctors, whose additional time is at least financially rewarded? Similar sentiments expressed by others in reaction to the report relieve my feeling of isolation.² Drugs and matching placebo were kindly donated by drug companies. These “free” drugs are even more effective than free lunches in promoting sales.

Another paper on the management of elderly patients with sustained hypertension analyses the MRC's report and five others.³ None of the six studies were designed to detect a change in overall mortality, and five of the six failed to do so. Despite this failure of treatment to improve survival, treatment is advised because of the reported

improvement in cardiovascular morbidity and mortality.

But what treatment? For young independent people I have no hesitation in recommending weight reduction, exercise, and stopping smoking. In geriatric patients strictures on food and tobacco may be enforced by the carer but encouraging exercise is more difficult. I advise the avoidance of excess salt and alcohol, which is quite different from advising a moderate reduction; is there any convincing evidence that this helps in managing blood pressure?

And so to drugs. If “there is little to choose between individual thiazides” then the cheapest should surely be mentioned at its optimum low dose (bendrofluazide 2.5 mg daily).⁴ The safety of these inexpensive agents is emphasised in subsequent correspondence.⁵ The older the patient the more the reduction in renal function and the more the dangers of hyperkalaemia with triamterene or amiloride. β Adrenoceptor blocking drugs, both hydrophilic and lipophilic, have been used in trials that claimed benefit,⁶ but they are not much favoured because of unwanted effects.

“None of the newer agents have been subject to definitive controlled trials . . . nevertheless such drugs may be favoured on a number of theoretical and practical grounds.” The support of Bristol Myers Squibb is acknowledged. Which of the newer agents will be given to these elderly people, now patients, before proof of efficacy?

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EDITOR,—The results of the Medical Research Council's trial of treatment of hypertension in older adults raise at least two important questions that are not discussed.¹

Firstly, the trial reported that about a quarter of the patients were lost to follow up. About half of the patients stopped taking their randomised treatment and many patients received diuretic or β blocker treatment in addition to their original randomised treatment. The findings from this trial cannot be generalised to the elderly hypertensive population at large.

Secondly, total mortality and high mortality from coronary heart disease in hypertensive patients can be substantially reduced only if the risk of sudden coronary death can be reduced. β Blockers have prevented coronary death in secondary prevention trials, mainly by reducing the risk of sudden death.^{2,3} Possibly the therapeutic effects in this respect differ between β blockers. Benefits of β blockade on sudden death in patients after myocardial infarction have been shown only for the lipophilic β blockers. Data from several primary prevention studies indicate a lower risk for hypertensive men taking lipophilic β blockers than for those taking diuretics.⁴ In the metoprolol atherosclerosis prevention in hypertensives trial the risk of coronary events was 24% lower in hypertensive men receiving β blockade than in men receiving diuretics.⁴ Also, total mortality was reduced with the β blocker regimen due to a reduction in sudden cardiovascular deaths.⁵

Clinical and experimental data indicate that not

only ischaemia and increased sympathetic tone but also a low vagal tone (influenced by brain mechanism) play an important part in the development of atherosclerosis and in reduced cardiac electric stability.^{2,3,6-10} Experimental data with propranolol and metoprolol suggest that β blockade within the brain can decrease the risk of ventricular fibrillation and sudden death by increasing cardiac vagal tone.^{9,10} In one study spontaneous ventricular fibrillation was reduced with metoprolol but not with the hydrophilic β blocker atenolol.¹⁰ Possibly, relatively lipophilic β blockers, which easily pass the blood-brain barrier, more readily increase vagal tone and reduce the risk of ventricular fibrillation than hydrophilic β blockers, which pass the blood-brain barrier to only a small degree. Thus data obtained with one particular antihypertensive drug may not be generalised to other similar drugs as the effects (other than their blood pressure lowering effect) may differ even within one class of drugs. The results from this study should not be used to judge the relative importance of different antihypertensive drugs in preventing coronary heart disease.

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AUTHORS' REPLY,—We think that Karl Swedberg has not fully appreciated the practical demands and clinical implications of long term trials as distinct from the shorter term examples he cites.

As was pointed out in our paper, we used the NHS central register for notification of deaths; such notifications were provided whether or not we were still in touch with participants. Ascertainment of fatal events was therefore virtually complete. The duration of follow up averaged 5.8 years and, for some patients, was eight years. Clearly, some loss to follow up over these extended periods is inevitable: the proportion was 25% in each of the diuretic, β blocker, and placebo groups (considerably less than A B S Mitchell suggests), so biased ascertainment of non-fatal events is unlikely to have occurred.

Our trial was based on 226 general practices throughout the United Kingdom, and, to deal with Jaakko Tuomilehto's first point, its results indicate the extent to which supplementation of treatment and changes in treatment are likely to be needed in day to day clinical practice. Our “on treatment” analyses, in which departures from randomised treatment were allowed for, gave results similar to those of the intention to treat analyses. We have not seen the data on bradycardia in the Swedish trial in old patients with hypertension (STOP trial)