Aggressive Management of Intra-arterial Temazepam Injection

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SUMMARY: Intravenous injection of the oral formulation of Temazepam is a common form of drug abuse. At the request of the Home Office, manufacturers have developed solid dose forms to replace the liquid filled capsules (1), but a number of cases of accidental intra-arterial injection of the new formulation have been reported, with varying management strategies advocated. A case is presented where prompt aggressive management using surgical and pharmacological measures resulted in complete limb salvage. Previous reported cases and management options are discussed.

Case Report
A 26 year old intravenous drug abuser presented to the A & E department 15 minutes after accidental injection of 60 mg of Temazepam gel into his left brachial artery. He immediately developed a painful blue hand with decreased range of movement. After a further 45 minutes, the area of cyanotic discoloration was limited to only the fingers, with associated neurological loss. One hour later the whole forearm became mottled and cyanotic, with severe intractable pain. Throughout this period both ulnar and radial pulses remained palpable and normal in volume and character.

Immediate treatment was commenced with an infusion of Prostacyclin (5ng/kg/min) and oral Nifedipine 10 mg tds. For the next 12 hours, the mottled cyanosis and pain increased. Conventional analgesia was ineffective because of tolerance produced by previous opiate abuse, and a brachial plexus block using a continuous infusion of 0.25% Bupivicaine was inserted to excellent effect.

Thirty six hours after injection, he developed an acute compartment syndrome, and the serum creatinine kinase had risen to 16,500 iu/ml. Full length fasciotomies were performed, releasing bulging muscle which otherwise appeared healthy. At the same procedure the brachial artery was explored and found to be in marked spasm, which promptly responded to 40 mg topical Papaverine. A further 40 mg of Papaverine was infused into the artery over two minutes, with an immediate improvement to the distal circulation.

Postoperatively there was a continued improvement in the distal circulation and active hand and forearm movements. The fasciotomy wounds were closed after two days and the Prostacyclin and Nifedipine were continued for ten days.

Full movements of the hand and forearm returned with intensive physiotherapy. At review after three weeks all wounds had healed well and the affected skin of the finger pulps had sloughed to reveal healthy tissue. Unfortunately further review was prevented by the patient's failure to attend.

Discussion
Increasing intravenous misuse of liquid filled Temazepam capsules led to the development of an abuse resistant gel formulation. However the new formulation oral Temazepam capsules continued to be abused, often, as in our case, by dissolving the gel in hot water for subsequent injection. Consequently a number of cases of accidental intra-arterial injection have been reported (2,3,4).

In all cases a similar clinical picture was seen, with mottled cyanosis, excruciating pain and normal peripheral pulses. The aetiology underlying this picture has been the subject of some discussion, and is likely to be a combination of microembolism and vasospasm.
Contrary to common belief, the macrogols used to produce the gel formulation are highly soluble in water. It is the Temazepam which is insoluble in water (maximum solubility less than 0.01%) and is precipitated out forming fine particles (5).

This phenomenon was easily reproduced by the authors when the contents of a 20 mg Gel capsule was readily dissolved in 4 ml of cold water. This may well cause a microembolic effect, supported by the observation of blotchy, nonuniform cyanosis and histology of muscle biopsies (3).

The role of vasospasm is supported by the fact that the Temazepam molecule itself is extremely irritant, which was the reason for the abandonment of the development of an intravenous formulation of the drug (5). Accidental injection of the liquid form has also been reported as causing severe rhabdomyolysis (6).

Management of previously described cases has included early fasciotomy, forced alkaline diuresis and intravenous heparinisation, with many patients requiring subsequent amputations. For optimum results, treatment must be started early with the aim of reversing vasospasm, maintaining the microcirculation and opening collaterals.

Prostacyclin infusion has been reported as successful in a similar case when used alone (7), but was inadequate in this case. Brachial plexus block has also been successfully used as a treatment modality (8), but in this case its most beneficial effect was that of analgesia.

Early fasciotomy has also been widely reported, and in this case was combined with exploration of the injection site. This confirmed large vessel vasospasm which responded well to topical Papaverine. The use of intra-arterial Papaverine has been employed successfully in cases of accidental intra-arterial drug injection (9), and Silverman et al demonstrated angiographic evidence of improvement with intra-arterial administration of Tolazoline, a potent vasodilator (10). In this case a benefit was clearly demonstrated, with an immediate improvement of the peripheral cyanosis.

We feel that for limb salvage, early aggressive surgical and pharmacological treatment is appropriate in the management of intra-arterial injection of Temazepam.

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