Limb ischaemia after intra-arterial injection of Temazepam gel: Histology of nine cases

T J Dodd, R N Scott, K R Woodburn, J J Going

Abstract
Aims—To record the histopathological findings associated with intra-arterial injection of Temazepam gel by nine drug misusers.

Methods—Standard histological examination and immunocytochemistry for endothelial markers (factor VIII related antigen, Ulex europaeus lectin) were carried out.

Results—Intra-arterial injection of Temazepam gel may cause severe vascular injury and lead to amputation of fingers or limbs. Histological changes include myocyte necrosis, interstitial oedema, extensive arterial, venous, and capillary thrombosis, and sometimes vasculitis, endothelial swelling, and denudation.

Conclusions—Inadvertent injection of Temazepam gel into arteries may cause catastrophic ischaemic damage, possibly as a result of toxic effects on endothelial cells.

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Ischaemic necrosis of limbs, leading in some cases to major amputations following intra-arterial injection of “solid gel” Temazepam has been reported from several centres in the United Kingdom. In response to previous misuse of Temazepam by injection a new “solid gel” formulation replaced “liquid fill” capsules, but hopes that this formulation would curtail abuse have been dashed. Heating the capsule contents with water gives a viscous but injectable product. A similar vascular syndrome has succeeded intra-arterial “liquid fill” injection, but it seems to be more frequently associated with the gel formulation.

Cases and methods
Seventeen people were admitted to Glasgow Royal Infirmary after intra-arterial injection of “solid gel” Temazepam during 1991–1992. Of these, 15 had severe reactions. Eleven required multiple fasciotomies for the relief of acute compartment syndromes. Rhabdomyolysis was common, and four patients...
Clinical and histological details of patients studied

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age/sex</th>
<th>Clinical event</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33 M</td>
<td>Left above-knee amputation</td>
<td>Arterial and venous thrombosis; intravascular foreign material; necrosis, vasculitis</td>
</tr>
<tr>
<td>2</td>
<td>31 M</td>
<td>Above-elbow amputation of arm</td>
<td>Arterial and venous thrombosis; necrosis; vasculitis</td>
</tr>
<tr>
<td>3</td>
<td>23 M</td>
<td>Fasciotomy Amputation of toes</td>
<td>Arterial and venous thrombosis; vasculitis</td>
</tr>
<tr>
<td>4</td>
<td>25 M</td>
<td>Fasciotomy—calf</td>
<td>Arteriolitis; viable muscle</td>
</tr>
<tr>
<td>5</td>
<td>30 M</td>
<td>Fasciotomy, renal failure</td>
<td>Arterial and venous thrombosis; necrosis; vasculitis</td>
</tr>
<tr>
<td>6</td>
<td>20 F</td>
<td>Fasciotomy, no amputations</td>
<td>Arterial and venous thrombosis</td>
</tr>
<tr>
<td>7</td>
<td>22 M</td>
<td>Fasciotomy—calf</td>
<td>Fibrin thromb; necrosis</td>
</tr>
<tr>
<td>8</td>
<td>29 M</td>
<td>Fasciotomy—calf</td>
<td>Intravascular foreign material, no necrosis or vasculitis</td>
</tr>
<tr>
<td>9</td>
<td>28 M</td>
<td>Fasciotomy right forearm</td>
<td>No necrosis or vasculitis</td>
</tr>
</tbody>
</table>

Figure 3  Arterial thrombosis (case 1). Even at this low power there is a suggestion of endothelial swelling.

Figure 4  Venous thrombosis (case 1).

Discussion

The catastrophic vascular syndrome associated with intra-arterial injection of Temazepam gel is more severe than the powder embolism experienced by injecting drug misusers, and simple embolism seems unlikely to be responsible. Temazepam is toxic to vessels. Intravenous injection of a parenteral preparation (0.5–1 mg/kg) caused moderate or severe pain in 22 of 62 patients, and of 11 patients examined 14 days later, nine had antecubital vein thrombosis. Severe complications have been described following intra-arterial injection of the liquid preparation. Launchbury and colleagues have stated that it was impossible to formulate a parenteral preparation of Temazepam which did not cause unacceptable venous damage.

Endothelial damage is perhaps the most plausible explanation for the syndrome. Endothelial swelling identified in some cases is consistent with this. Abnormal permeability of injured vessels could account for the pronounced oedema often seen, and more severe loss of endothelial function for vascular
Thrombosis. Thus two potent ischaemic mechanisms (increased compartment pressure and vascular thrombosis) potentially contribute to a myocyte necrosis that is sometimes severe. It is not clear why the solid-gel Temazepam preparation should apparently cause more problems than the liquid-filled capsules. Launchbury has pointed out that the macrogol vehicle is water soluble but Temazepam itself is highly insoluble, and would be expected to form an insoluble precipitate when heated with water. Perhaps this change of state is responsible for the apparent potentiation of toxicity under these circumstances. The vasculitis may reflect non-specific damage.

The possibility of such a mechanism, and the severity of the toxicity following intra-arterial injection, leads us to wonder about the possible effects of Temazepam solid-gel capsule abuse on the pulmonary vasculature following intravenous injection. Precipitated Temazepam might be retained in, and damage, pulmonary vessels. Death has followed intravenous injection of crushed Temazepam tablets suspended in water; in that case the pulmonary vasculature contained embolised foreign material, but its nature was not established. If endothelial injury is indeed the major pathogenetic mechanism of this severe adverse reaction, then it may be appropriate for therapeutic interventions to be directed towards modifying endothelial cell function. This strategy was used by Nott and colleagues, and may have been beneficial.

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