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

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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.

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...
Limb ischaemia after intra-arterial injection of Temazepam gel

Clinical and histological details of patients studied

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age/sex</th>
<th>Clinical events</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 no amputations</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 thrombosis; necrosis</td>
</tr>
<tr>
<td>8</td>
<td>29 M</td>
<td>Fasciotomy—calf Intravascular foreign material, no necrosis or vasculitis</td>
<td></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).
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.10

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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