Diazepam is a psychotropic with sedative and hypnotic effects, additionally, it also has anticonvulsive actions. Its action results in inhibitory effect of GABA-nergic transmission. Diazepam is currently approved for oral, intravenous, intramuscular, or rectal administration. Diazepam is not known to metabolise in the skin and has not been successfully delivered by patch or other topical preparation.

We have developed a transdermal drug delivery system (TDS®), Transdermal Technologies Inc, Florida, USA which is a liquid formulation that can be combined with drug entity to form a novel and more convenient, patient compliant pharmaceutical dosage form (spray form), to enhance drug delivery through the skin. Recent studies of the TDS system, e.g., TDS-Lidocaine can give acceptable anesthesia in five minutes post application[1], and TDS®-Testosterone was bioequivalent to AndroGel®[2].

We would like to acknowledge Transdermal Technologies Inc., Florida, USA for the test materials and The Langford Institute, Florida, USA for the grant, which supported this study.

**Methods**

**Study materials**

TDS®-diazepam was supplied as a liquid formulation, delivered at 0.2 mL per spray metered pump, with each spray containing 2 mg diazepam. Diastat® was supplied as a gel in a unit-dose containing 10mg diazepam.

**Study design and treatments**

A single-dose, two-period, cross-over phase I (pharmacokinetic) comparative study involving two treatments and two periods with a minimum of a 14 day washout period was conducted.

**Subjects**

Twelve healthy subjects successfully completed the protocol. The study was approved by St Thomas Hospital Research Ethics Committee, and received an acceptance from MHRA UK.

**Diazepam Analysis**

Diazepam and metabolites concentrations were measured in plasma using a HPLC/MS.

**Results**

**Table 1:** Bioequivalence parameters for diazepam and desmethyl-diazepam, TDS diazepam (Test formulation (A)), versus Rectal diazepam (Reference formulation (B)).

<table>
<thead>
<tr>
<th></th>
<th>Rectal</th>
<th>Rectal t(_{\text{max}})</th>
<th>TDS t(_{\text{max}})</th>
<th>TDS - Rectal Difference</th>
<th>Rectal C(_{\text{max}})</th>
<th>TDS C(_{\text{max}})</th>
<th>Rectal / TDS Ratio</th>
<th>(\text{AUC}_0-72) (B:A)</th>
<th>(\text{AUC}_0-72) (A:B)</th>
<th>C(_{\text{max}}) (B:A)</th>
<th>C(_{\text{max}}) (A:B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>59.2 (121.7)</td>
<td>1.0 (24.3)</td>
<td>24.0 (56.0)</td>
<td>10.1% (46.6)</td>
<td>3099.3 (25.9)</td>
<td>1104.5 (42.9)</td>
<td>27.2% (40.8)</td>
<td>715.8 (990.1)</td>
<td>715.8 (990.1)</td>
<td>56.0 (36.2)</td>
<td>46.6% (33.7)</td>
</tr>
<tr>
<td>Desmethyl-diazepam</td>
<td>27.2% (40.8)</td>
<td>-0.4 (12)</td>
<td>7.3 (32.13)</td>
<td>37.6 (45.0)</td>
<td>33.4 (22.24)</td>
<td>172.9 (227.5)</td>
<td>12.7% (14.0)</td>
<td>7.3 (10.1)</td>
<td>7.3 (10.1)</td>
<td>37.6 (45.0)</td>
<td>37.6 (45.0)</td>
</tr>
</tbody>
</table>

**Table 2:** Derived diazepam and desmethyl-diazepam Geometric mean (CV percentage) for rectal and TDS diazepam (10 mg).

**References**


**Figure 1:** Mean plasma diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

**Figure 2:** Mean plasma desmethyl-diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

**Figure 3:** Results continued