Pharmacokinetics and tolerability of sublingual fentanyl in healthy Japanese and Caucasian volunteers: Phase I, open-label, single-dose study

Ulrike Lorch1, Fiona Farrell2, John Kilborn3, Masami Tamaoka1, Rob Derrick3, Julian Howell4

1 Richmond Pharmacology Ltd, St George’s University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK
2 Kyowa Hakkei UK Ltd, Bath Road, Slaugth, Berkshire, SL1 4DX, UK
3 Kyowa Hakkei Kaya Co Ltd, 1-6-1 Ohigaheda, Chiyoda-ku, Tokyo 100-8185, Japan
4 ProStrakan Group plc, Colshill Business Park, Colshill, WD1 1QH, UK

Background

• Breakthrough pain (BTP) is a transitory exacerbation of severe pain occurring on a background of otherwise controlled persistent pain.
• Oral transmucosal fentanyl, an opioid with rapid onset of action, is recommended as a supplement to the fixed-opioid schedule in the treatment for BTP4.
• Sublingual fentanyl (SLF) is a new rapidly disintegrating transmucosal delivery formulation of fast-acting fentanyl citrate developed for the management of BTP in opioid-tolerant cancer patients.

Objectives

• The objectives of this study were to:
  • determine the PK and tolerability profiles of single-dose SLF in healthy male Japanese and Caucasian subjects
  • assess whether differences in the rate and extent of fentanyl absorption and elimination exist between different ethnic groups.

Methods

• This was a Phase I, UK-based, single-centre, open-label study consisting of four ascending single-dose treatment periods (Figure 1).

Study population

• Twenty-one healthy male Japanese and Caucasian volunteers aged 20–45 years were recruited. Subjects had to have a body weight of 55–85 kg, a body mass index of 18–25 kg/m², and be non-smokers or light smokers.
• Subjects with any relevant clinically significant, abnormal clinical history, any major illness within 3 months of study start or a history of opioid intolerance or severe allergic disease were excluded. Subjects using any medications within 5 days of study start or any concomitant medications, excluding anti-emetics and naloxone, were also excluded.

Assessments

• The primary PK parameters included:
  • maximum plasma concentration of fentanyl (Cmax)
  • time to Cmax (tmax)
  • area under the plasma concentration versus time curve from time 0 to the last quantifiable sampling point (AUC0–tmax)
  • area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC0–∞)
  • terminal half-life of the drug (t1/2).

Statistical analysis

• The study was designed to include 10 evaluable Japanese subjects and 10 evaluable Caucasian subjects.
• Individual PK parameters were determined using non-compartmental methods.

Results

Baseline demographics

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Number of subjects</th>
<th>Age, Mean, years (range)</th>
<th>Weight, Mean, kg (range)</th>
<th>Height, Mean, m (range)</th>
<th>BMI, Mean, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>11</td>
<td>25.7 ± 6.1 (20–38)</td>
<td>69.1 ± 7.4 (56–89)</td>
<td>1.77 ± 0.06 (1.69–1.87)</td>
<td>22.09 ± 2.03</td>
</tr>
<tr>
<td>Japanese</td>
<td>10</td>
<td>26.7 ± 3.0 (23–36)</td>
<td>65.7 ± 7.0 (55–81)</td>
<td>1.72 ± 0.07 (1.59–1.83)</td>
<td>22.13 ± 2.18</td>
</tr>
<tr>
<td>Japanese &amp; Caucasian</td>
<td>21</td>
<td>26.2 ± 4.8 (20–38)</td>
<td>67.4 ± 7.7 (55–81)</td>
<td>1.75 ± 0.07 (1.59–1.87)</td>
<td>22.13 ± 2.18</td>
</tr>
</tbody>
</table>

Table 1. Baseline demographics (in total 21 recruited subjects, ranges are shown in brackets). BMI body mass index.

Conclusions

• Fentanyl plasma concentrations increased as a function of ascending dose.
• Plasma concentration data indicate that fentanyl was rapidly absorbed (Cmax and tmax), irrespective of ethnicity or dose.
• SLF had a good tolerability profile within these volunteers, with no differences attributable to ethnicity.
• The lack of ethnic differences in kinetics is encouraging and suggests that no specific modifications in dosing between Caucasian and Japanese subjects are needed.

References

3 Zapparella G and Rabino HDB. Cochrane Database of Systematic Reviews 2006, Issue 1.