Comparative pharmacokinetics and bioavailability of tapentadol following oral administration of immediate- and prolonged-release formulations

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Abstract. Objective: To evaluate the bioavailability and pharmacokinetics of orally administered tapentadol immediate release (IR) compared with tapentadol prolonged release (PR). Methods: Three randomized, open-label, crossover studies were conducted in subjects under fasted conditions. Studies 1 and 2 determined the absolute bioavailability and pharmacokinetics of oral tapentadol IR 86 mg and tapentadol PR 86 mg, respectively, relative to a 34-mg intravenous (i.v.) dose of tapentadol. Study 3 determined the relative bioavailability of tapentadol PR 86 mg vs. tapentadol IR 86 mg. Pharmacokinetic parameters were calculated using non-compartmental analysis and relative bioavailability using dose-adjusted, log-transformed analysis of variance models for maximum concentration (Cmax) and areas under the serum concentration-time curve (AUC0–t and AUC).

Adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), and laboratory parameters were assessed. Results: Absolute bioavailability was estimated to be 32% (95% confidence interval (CI), 29.4 – 34.8%; n = 24) for tapentadol IR 86 mg and 32% (95% CI, 28.0 – 35.9%; n = 18) for tapentadol PR 86 mg. Based on AUC, the relative bioavailability of tapentadol PR vs. tapentadol IR was 96% (90% CI, 87.8 – 104.4%; n = 16). Following IV administration, tapentadol had an elimination half-life of ~ 4 hours; in Studies 1 and 2, respectively, mean tapentadol volumes of distribution were 540 and 471 l, and mean clearance was 1,531 and 1,603 ml/min. Compared to tapentadol IR 86 mg, the prolonged-release characteristics of tapentadol PR 86 mg were evident with a lower Cmax (22.5 ng/ml vs. 64.2 ng/ml), a longer time to Cmax (5.0 h vs. 1.5 h), a higher half-value duration (HVD: 12.5 h vs. 3.6 h), and a longer mean residence time (MRT: 10.6 h vs. 6.0 h). The most common AEs reported were dizziness, headache, fatigue, nausea, somnolence, and dry mouth; most AEs were mild. No clinically relevant changes in vital signs, ECG parameters, or laboratory values were observed. Conclusions: Absolute bioavailability for both tapentadol IR and tapentadol PR was ~ 32% under fasted conditions. Extent of exposure (AUC) for tapentadol PR was very similar to tapentadol IR, whereas Cmax was lower and HVD/MRT longer for the prolonged-release formulation. Overall, the pharmacokinetic characteristics of tapentadol PR enable a twice-daily dosing regimen to be used; such a regimen is expected to improve patient compliance during chronic use.

Introduction

Tapentadol is a centrally acting analgesic with two mechanisms of action, µ-opioid receptor agonism and noradrenaline reuptake inhibition [1]. Tapentadol is available in two oral formulations for the relief of pain that can only be adequately managed with opioid analgesics [2, 3]. An immediate-release formulation is approved for the relief of moderate to severe, post-surgical pain [5, 6] and pain associated with end-stage joint disease [7]. Tapentadol prolonged release (PR; extended release in the United States) [4] 100 – 250 mg twice a day is effective for the management of moderate to severe, chronic pain and has been
studied in patients with osteoarthritis pain [8, 9], low back pain [10], and pain associated with diabetic peripheral neuropathy [11]. Both formulations have gastrointestinal tolerability profiles that are more favorable than that of oxycodone [5, 6, 7, 8, 10, 12, 13], which suggests that tapentadol may be a beneficial alternative to currently available pure μ-opioid analgesics.

Previous studies have characterized the single-dose pharmacokinetics of orally administered tapentadol IR in healthy subjects [14, 15] and population pharmacokinetics in healthy subjects and in patients with acute pain [16]. Tapentadol IR is rapidly and almost completely absorbed following oral administration, as indicated by the recovery of ~ 99% of a radiolabeled dose in the urine of subjects participating in a mass balance trial [23]. In the same radiolabeled dose study, extensive metabolism of tapentadol was indicated with only ~ 3% of administered drug excreted as the parent compound in urine [23]. Tapentadol is excreted almost exclusively by the kidneys, primarily as conjugated metabolites (the major metabolite is tapentadol-β-glucuronide) [14]. Terminal phase half-life of tapentadol from the immediate release form is ~ 4.3 hours. Tapentadol is a pure enantiomer, and none of its metabolites provide any clinically relevant contributions to its analgesic activity [17].

Tapentadol PR was developed to have a more constant rate of exposure than tapentadol IR. The goal was to create a prolonged-release formulation to minimize fluctuations in exposure over time but also enabling a simplified twice-daily dosing regimen. This was considered to be a convenient regimen for patients suffering from chronic pain, and was therefore expected to improve compliance of medication intake. Three Phase I studies were conducted under fasted conditions to evaluate the pharmacokinetics and bioavailability of oral tapentadol PR and tapentadol IR in healthy subjects. The elements of these three studies relating to absolute and relative bioavailability of tapentadol IR and tapentadol PR and providing basic pharmacokinetic data for tapentadol are presented. The objectives of these studies were to investigate the following: (a) the absolute bioavailability and basic pharmacokinetic properties of orally administered tapentadol IR 86 mg compared with an intravenous (i.v.) infusion of tapentadol 34 mg, (b) the absolute bioavailability and basic pharmacokinetic properties of orally administered tapentadol PR 86 mg compared with an i.v. infusion of tapentadol 34 mg and (c) the rate and extent of absorption and oral bioavailability of tapentadol PR 86 mg relative to tapentadol IR 86 mg.

Materials and methods

Subjects

Three randomized, open-label, single-dose, crossover, Phase I studies were conducted in healthy subjects to determine the pharmacokinetics and bioavailability of immediate-release and prolonged-release formulations of tapentadol. All three studies enrolled mentally and physically healthy male Caucasian subjects between 18 and 45 years of age who had a normal clinical examination and no clinically relevant deviations from reference ranges of laboratory values or electrocardiogram (ECG) parameters. Only male subjects were included in order to reduce potential sources of variability, and also because no substantial differences in pharmacokinetic characteristics of tapentadol between male and female subjects had been observed in two earlier trials following both oral and i.v. administrations. Subjects were excluded if they had signs of any significant acute or chronic abnormalities that might affect subject safety or drug absorption, distribution, metabolism, or excretion or if they had a history of alcohol or drug abuse. The use of over-the-counter and prescription medication was restricted prior to study initiation.

The studies were approved by independent Ethics Committees, were performed in compliance with legal regulations and the International Conference on Harmonisation Good Clinical Practice guidelines, and conformed to the requirements of the Declaration of Helsinki. The nature, purpose, possible risks and benefits, and duration of each study were explained to all subjects by a physician prior to screening, and all subjects provided written informed consent.
Materials

All tapentadol formulations used in the three studies described herein were manufactured and supplied by Grüenthal GmbH in accordance with Good Manufacturing Practices and German Drug Law (AMG). The immediate-release capsule formulation showed complete in-vitro dissolution after 15 minutes (Figure 1a), whereas the in-vitro dissolution profile of the tapentadol PR formulation showed a slow dissolution over 12 hours (Figure 1b).

The immediate-release capsule formulations and the prolonged-release hydrogel-membrane-based tablet used in these studies have been shown to be bioequivalent to the currently marketed tablet formulations of tapentadol IR and tapentadol PR, respectively (data on file).

Study designs

Subjects were hospitalized at the clinical unit from at least 11 hours prior to drug administration until at least 24 hours post-administration. Oral administration was conducted in each study with 200 ml of still water, and standardized meals were served at ~ 4, 7 and 11 hours post-dosing in each case. The intake of alcohol, coffee, tea, cocoa, cola, or grapefruit juice was forbidden throughout the study periods. Based on the terminal half-life of tapentadol, a wash-out period of 3 days between treatments was sufficient to ensure no carryover. Longer wash-out periods were chosen (see below) on pragmatic grounds to facilitate scheduling at the clinical units.

Study 1: Absolute bioavailability of tapentadol IR

In this randomized crossover study, the two treatment regimens relevant for this publication were tapentadol 34 mg as a 25-ml i.v. infusion given over 15 minutes following an overnight fast and tapentadol IR 86 mg as oral capsules (4 × 21.5 mg) given after an overnight fast. Fluid intake was allowed ad libitum throughout the study period. Treatments were separated by washout periods of at least 6 days but not more than 3 weeks.

Study 2: Absolute bioavailability of tapentadol PR

In this randomized crossover study, the two treatment regimens relevant for this publication were tapentadol 34 mg as a 50-ml i.v. infusion given over 15 min following an overnight fast and a tapentadol PR 86-mg film-coated tablet given after an overnight fast. No fluid was permitted from 30 minutes prior to 2 hours following dose administration and fluid intake was restricted to 3 l per day. Subjects were required to remain in a supine position until at least 5 hours after administration. Treatments were separated by washout periods of 7 – 21 days.

Study 3: Relative bioavailability of tapentadol PR vs. tapentadol IR

In this randomized crossover study, the two treatment regimens relevant to this
Comparative pharmacokinetics and bioavailability of tapentadol IR vs. tapentadol PR

Publication were a single tapentadol PR 86-mg tablet and a single tapentadol IR 86-mg capsule; treatments were administered after an overnight fast. No fluid was permitted from 30 minutes prior to 2 hours following dose administration and fluid intake was restricted to 3 l per day. Subjects were required to remain in a supine position until at least 5 hours after administration. Treatments were separated by washout periods of 7 – 21 days.

Assessments

Prior to the start of each study, subject medical histories, adverse events (AEs), and vital signs were recorded, and a urine sample was provided for drug testing. Vital signs and 12-lead ECGs were recorded before dosing (Time 0) and at frequent prespecified time points after tapentadol administration for 24 or 32 hours. After study completion, a final physical examination was performed, including standard hematology, biochemistry, and urinalysis laboratory assessments; vital sign measurements; and a 12-lead ECG.

Blood sample preparation and bioanalysis

Blood samples (6 or 7 ml) for pharmacokinetic analyses were collected at frequent predefined intervals for each treatment period. In Studies 1 and 2, for the 34-mg i.v. infusion of tapentadol, blood samples were taken prior to administration and from 5 minutes to 24 hours after the start of the infusion. In the oral tapentadol IR 86-mg treatment periods, blood samples were taken at Time 0 (prior to administration) and 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 20, 24, 28, and 32 hours after administration in Study 1, and 0, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 28, and 32 hours after administration in Study 3. In the oral tapentadol PR 86-mg treatment periods, blood samples were taken at 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 11, 16, 18, 24, 28, and 32 hours after administration in Study 2, and at 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 28, and 32 hours after administration in Study 3.

Following solvent extraction, serum tapentadol concentrations were determined using a validated ion-pair, reversed-phase high performance liquid chromatography method with fluorescence detection. Calibration was performed using peak area ratios of the analyte and an internal standard. In Study 1, the linear calibration range for tapentadol concentration was 0.96 – 192.6 ng/ml. Inter-assay accuracy of the control samples assayed parallel to the study samples was between 98.6% and 99.3%, and the corresponding precision was between 1.2% and 6.1%. This method was subsequently improved, and the lower limit of quantification was reduced from 0.96 ng/ml to 0.25 ng/ml (Studies 2 and 3) for an overall calibration range of 0.25 – 100 ng/ml. Accuracies of the quality control samples were in the ranges 98.1 – 99.4% and 95.2 – 99.5% for Studies 2 and 3, respectively; the corresponding ranges for precision were 1.28 – 6.98% and 0.94 – 4.35%.

Pharmacokinetic analyses

Pharmacokinetic parameters, including maximum serum concentration (C_{max}), time to reach maximum concentration (t_{max}), area under the serum concentration vs. time curve up to the last time with a quantifiable concentration (AUC_{0-t}), area under the serum concentration vs. time curve up to infinite time (AUC), half-life associated with the terminal phase (t_{1/2,z}), total tapentadol serum clearance (CL), apparent volume of distribution during the terminal phase of disposition (V_z), absolute bioavailability, and relative bioavailability were estimated using standard non-compartmental methods [18]. Mean residence time (MRT) was calculated as the area under the first moment curve/AUC. The half-value duration (HVD) was defined as the time interval during which the tapentadol serum concentrations were above 50% of C_{max}. The times at which the tapentadol serum concentrations were equal to 50% of C_{max} were determined by linear interpolation. All pharmacokinetic parameters were calculated for the tapentadol free base.

Statistical analyses

Descriptive statistics were calculated for all pharmacokinetic parameters for
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Each treatment. All calculations of pharmacokinetic variables were carried out using validated software modules based on SAS language and procedures (SAS 8.2; SAS Institute Inc., Cary, NC, USA), and all statistical calculations were performed using SAS software. Analyses of variance (ANOVA) using the method of least squares to fit general linear models [19] were performed on log-transformed data for all parameters except $t_{\text{max}}$ in Studies 2 and 3; these analyses were performed primarily to estimate the residual error used in the construction of confidence intervals (CIs) and to evaluate the presence of sequence or period effects. The effects considered in the ANOVA model were treatment, sequence, study period, first order carry over, and subject within sequence. The absolute bioavailability of tapentadol IR and tapentadol PR was determined by calculating the point estimate and 95% CI for AUC values for the oral treatments relative to i.v. treatment by dose-adjusted, log-transformed ANOVA. The relative bioavailability of orally administered tapentadol PR compared with tapentadol IR was given as ratios of $\text{AUC}_{0-t}$, AUC, or $C_{\text{max}}$ together with 90% CIs using log-transformed ANOVA.

### Results

#### Study 1: Pharmacokinetics and absolute bioavailability of tapentadol IR

24 healthy male Caucasian subjects were screened and enrolled in the study; all 24 subjects completed the study. Subjects had a mean age of 33.2 years (range, 19 – 44 years).
Comparative pharmacokinetics and bioavailability of tapentadol IR vs. tapentadol PR

Table 2. Tapentadol pharmacokinetic parameters after intravenously administered tapentadol (34 mg) and orally administered tapentadol PR (86 mg) (n = 18; Study 2).

<table>
<thead>
<tr>
<th></th>
<th>AUC (h×ng/ml)</th>
<th>AUC_{0→t} (h×ng/ml)</th>
<th>C\text{max} (ng/ml)</th>
<th>t\text{max} (h)</th>
<th>MRT (h)</th>
<th>HVD (h)</th>
<th>t_{1/2,z} (h)</th>
<th>CL or CL/f (ml/min)</th>
<th>V_{z} or V_{z}/f (L)</th>
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</thead>
<tbody>
<tr>
<td>Tapentadol 34 mg IV infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arith. mean</td>
<td>364</td>
<td>361</td>
<td>172</td>
<td>0.26</td>
<td>4.13</td>
<td>1.18</td>
<td>3.43</td>
<td>1,603</td>
<td>471</td>
</tr>
<tr>
<td>SD</td>
<td>52.2</td>
<td>51.9</td>
<td>78.5</td>
<td>0.10</td>
<td>0.52</td>
<td>1.33</td>
<td>0.46</td>
<td>226</td>
<td>62</td>
</tr>
<tr>
<td>Minimum</td>
<td>283</td>
<td>279</td>
<td>60.7</td>
<td>0.13</td>
<td>2.70</td>
<td>0.14</td>
<td>2.66</td>
<td>1,193</td>
<td>329</td>
</tr>
<tr>
<td>Median</td>
<td>356</td>
<td>354</td>
<td>180</td>
<td>0.22</td>
<td>4.12</td>
<td>0.46</td>
<td>3.43</td>
<td>1,606</td>
<td>479</td>
</tr>
<tr>
<td>Maximum</td>
<td>479</td>
<td>477</td>
<td>299</td>
<td>0.42</td>
<td>4.95</td>
<td>4.25</td>
<td>4.67</td>
<td>2,022</td>
<td>584</td>
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<tr>
<td>Geom. mean</td>
<td>360</td>
<td>358</td>
<td>153</td>
<td>0.25</td>
<td>4.10</td>
<td>0.63</td>
<td>3.40</td>
<td>1,588</td>
<td>467</td>
</tr>
<tr>
<td>Tapentadol PR 86 mg orally (fasted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arith. mean</td>
<td>298</td>
<td>290</td>
<td>22.0</td>
<td>4.81</td>
<td>11.3</td>
<td>11.7</td>
<td>4.20</td>
<td>5,087</td>
<td>1,804</td>
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<tr>
<td>SD</td>
<td>74.4</td>
<td>71.3</td>
<td>63.0</td>
<td>1.69</td>
<td>1.38</td>
<td>3.27</td>
<td>1.55</td>
<td>1,218</td>
<td>609</td>
</tr>
<tr>
<td>Minimum</td>
<td>188</td>
<td>185</td>
<td>13.3</td>
<td>1.00</td>
<td>9.24</td>
<td>7.14</td>
<td>2.69</td>
<td>3,328</td>
<td>1,007</td>
</tr>
<tr>
<td>Median</td>
<td>282</td>
<td>275</td>
<td>22.0</td>
<td>5.00</td>
<td>11.1</td>
<td>11.2</td>
<td>3.82</td>
<td>5,078</td>
<td>1,739</td>
</tr>
<tr>
<td>Maximum</td>
<td>430</td>
<td>425</td>
<td>37.7</td>
<td>7.00</td>
<td>14.8</td>
<td>19.9</td>
<td>9.12</td>
<td>7,830</td>
<td>3,110</td>
</tr>
<tr>
<td>Geom. mean</td>
<td>289</td>
<td>282</td>
<td>21.2</td>
<td>4.21</td>
<td>11.3</td>
<td>11.3</td>
<td>4.00</td>
<td>4,945</td>
<td>1,711</td>
</tr>
</tbody>
</table>

PR = prolonged release; AUC = area under the serum concentration vs. time curve to infinite time; AUC_{0→t} = area under the serum concentration vs. time curve at time points with measured concentrations above the limit of quantification; C\text{max} = maximum observed concentration; t\text{max} = time at which C\text{max} occurred; MRT = mean residence time; HVD = half-value duration; t_{1/2,z} = half-life associated with the terminal phase; CL = total body clearance; CL/f = total body clearance after oral administration; f = bioavailability; V_{z} = apparent volume of distribution during the terminal phase; V_{z}/f = apparent volume of distribution during the terminal phase after oral administration; IV = intravenous; SD = standard deviation.

Figure 3. Mean tapentadol serum concentrations over time following intravenous infusion of tapentadol 34 mg or oral administration of tapentadol PR 86 mg in the fasted state (Study 2). PR = prolonged release; IV = intravenous.

was similar to liver blood flow, with a value of 1,531 ± 177 ml/min. After IV administration, the mean estimated V_{z} was 540 l and the mean t_{1/2,z} of tapentadol was 4.09 ± 0.70 h; the observed mean t_{1/2,z} after oral administration in the fasted state was slightly longer (4.86 ± 0.72 h). The absolute bioavailability of tapentadol IR 86 mg (administered orally as 4 × 21.5 mg capsules in the fasted state) vs. tapentadol 34 mg i.v. was estimated to be ~32% (Table 4). No sequence effects were observed during the evaluation of this study, and only 1 period effect was found for C\text{max} (p = 0.03).

Study 2: Pharmacokinetics and absolute bioavailability of tapentadol PR

Twenty-four subjects were enrolled in the study. Subjects who were enrolled had a mean age of 33.1 years (range 18 – 44 years) and a mean (SD) body weight of 78.6 (8.3) kg. Six subjects discontinued the study prematurely: 4 subjects because of inadequate IV application (the treatment was erroneously applied manually rather than by perfusor), 1 subject because of a positive alcohol test during the study, and 1 subject because of...
vomiting during a treatment period. 18 subjects completed the study and constituted the data set for pharmacokinetic analyses.

Pharmacokinetic parameters for tapentadol administered as a 34-mg i.v. infusion and for a single dose of oral tapentadol PR 86 mg in the fasted state are summarized in Table 2. The corresponding mean tapentadol serum concentration profiles over time are presented in Figure 3. Tapentadol i.v. CL was similar to that observed in Study 1 (1,531 ± 177 ml/min in Study 1 vs. 1,603 ± 226 ml/min in Study 2). The Vz observed in this study was also comparable to that observed in Study 1 for the tapentadol IV infusion (540 ± 98 l in Study 1 vs. 471 ± 62 l in Study 2). The mean t1/2,z observed in this study was slightly shorter than that observed in Study 1 (4.1 hours in Study 1 vs. 3.4 hours in Study 2). The absolute bioavailability of oral tapentadol PR 86 mg vs. tapentadol 34 mg i.v. was estimated to be ~32% (Table 4).

No sequence effects were found during the evaluation of this study, and only one period effect for the parameter MRT was observed.

Study 3: Relative bioavailability of tapentadol PR vs. tapentadol IR

16 subjects were enrolled in the study, and all 16 subjects completed the study. Subjects had a mean age of 34.4 years (range 25 – 44 years) and a mean (SD) body weight of 76.0 (10.3) kg.

Pharmacokinetic parameters for orally administered tapentadol PR 86 mg compared with tapentadol IR 86 mg are summarized in Table 3. The corresponding mean serum concentration profiles over time for tapentadol PR compared with tapentadol IR are presented in Figure 4. The data indicate that the rate of absorption is substantially slower for tapentadol PR compared with tapentadol IR. Overlay plots of individual serum concentration time profiles for tapentadol are shown in Figure 5a (tapentadol IR) and Figure 5b (tapentadol PR). The scale of the concentration axis is different in the two graphs owing to the ~3-fold higher maximum concentra-

Table 3. Tapentadol pharmacokinetic parameters after single-dose oral administration of tapentadol PR (86 mg) and tapentadol IR (86 mg) (n = 16; Study 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tapentadol PR 86 mg orally (fasted)</th>
<th>Tapentadol IR 86 mg orally (fasted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h×ng/ml)</td>
<td>AUC0–t (h×ng/ml)</td>
<td>Cmax (ng/ml)</td>
</tr>
<tr>
<td>Arith. mean</td>
<td>299</td>
<td>235</td>
</tr>
<tr>
<td>SD</td>
<td>50.7</td>
<td>50.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>177</td>
<td>176</td>
</tr>
<tr>
<td>Median</td>
<td>304</td>
<td>299</td>
</tr>
<tr>
<td>Maximum</td>
<td>370</td>
<td>367</td>
</tr>
<tr>
<td>Geom. mean</td>
<td>295</td>
<td>290</td>
</tr>
</tbody>
</table>

PR = prolonged release; IR = immediate release; AUC = area under the serum concentration vs. time curve to infinite time; AUC0–t = area under the serum concentration vs. time curve at points with measured concentrations above the limit of quantification; Cmax = maximum observed concentration; tmax = time at which Cmax occurred; MRT = mean residence time; HVD = half-value duration; t1/2,z = half-life associated with the terminal phase; CL/f = total body clearance after oral administration; Vz/f = apparent volume of distribution during the terminal phase after oral administration; SD = standard deviation.

Table 4. Ratios and 95% confidence intervals for calculation of absolute and relative bioavailabilities for the tapentadol PR and IR formulations.

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Parameter</th>
<th>Ratio (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fabs (tapentadol IR)</td>
<td>32.0</td>
<td>29.4 – 34.8</td>
</tr>
<tr>
<td>2</td>
<td>Fabs (tapentadol PR)</td>
<td>31.7</td>
<td>28.0 – 35.9</td>
</tr>
<tr>
<td>3</td>
<td>Frel (PR/IR) for AUC</td>
<td>95.8</td>
<td>87.8 – 104.4</td>
</tr>
<tr>
<td>3</td>
<td>Frel (PR/IR) for Cmax</td>
<td>36.4</td>
<td>32.4 – 40.9</td>
</tr>
</tbody>
</table>

PR = prolonged release; IR = immediate release; CI = confidence interval; Fabs = absolute bioavailability; Frel = relative bioavailability.
Comparative pharmacokinetics and bioavailability of tapentadol IR vs. tapentadol PR

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Cmax was reached later following administration of a prolonged-release formulation compared with an immediate-release tablet. For tapentadol PR 86 mg, the mean of the individual Cmax values (22.5 ng/ml) was observed at a median time of 5.0 hours after administration. In contrast, for tapentadol IR 86 mg, the mean of the individual Cmax values (64.2 ng/ml) was observed considerably earlier, at a median time of 1.5 hours after administration. Comparison of other parameters in Table 3 also clearly shows the pharmacokinetic differences between tapentadol PR and tapentadol IR. The MRT and HVD times were longer for tapentadol PR compared with tapentadol IR. The overall extent of exposure (expressed as AUC0–t or AUC) was similar for tapentadol PR 86 mg and tapentadol IR 86 mg with the AUC ratio (tapentadol PR/tapentadol IR) being 96% (Table 4). The extrapolated area from the last quantifiable data point up to infinite time was <2% for all subjects after the IR formulation and <3% after the PR formulation; this indicates the high percentage of calculated area under the curve covered by observations, and supports the use of either parameter for describing the extent of exposure to tapentadol. Both CL/f and Vz/f were also very similar after oral administration of the tapentadol PR and IR formulations. The Cmax ratio was 36% (Table 4), indicating that the rate of absorption of the prolonged-release formulation is considerably lower than that of the immediate-release formulation.

No period or sequence effects were observed during the evaluation of this study.

**Safety and tolerability**

In all three studies, no deaths, serious AEs, or other significant AEs were reported. In Study 1, Study 2, and Study 3, 88% (21/24), 83% (20/24), and 56% (9/16) of subjects, respectively, experienced 1 or more
AEs. AEs were more commonly associated with IV treatment than with oral treatment, and there were fewer AEs reported after treatment with tapentadol PR than with tapentadol IR. Most AEs were mild, few were moderate, and in Study 2, 1 AE was severe (headache associated with nausea and vomiting after treatment with tapentadol PR 86 mg). The majority of AEs were determined to be drug-related. The most commonly reported AEs were dizziness, fatigue, headache, nausea, somnolence, and dry mouth; these AEs are all typical of centrally acting analgesics with µ-opioid activity [20]. There were no clinically relevant changes in vital signs, ECG parameters, or laboratory values in any of the studies.

Discussion

The three tapentadol studies presented here provide basic pharmacokinetic parameters for tapentadol following single oral and i.v. administration in healthy subjects and a comparison of the immediate- and prolonged-release formulation characteristics.

The absolute bioavailability of tapentadol under fasted conditions was estimated to be 32% for both the immediate-release capsule formulations and the prolonged-release hypromellose-based tablet; this value is attributed to substantial first-pass metabolism. Tapentadol is metabolized in the liver, primarily via conjugation with glucuronic acid to form its major metabolite, tapentadol-\(O\)-glucuronide [14]. The similarity observed for the absolute bioavailability of both the immediate-release and prolonged-release formulations indicates a stable first-pass metabolism. Tapentadol is metabolized in the liver, primarily via conjugation with glucuronic acid to form its major metabolite, tapentadol-\(O\)-glucuronide [14]. The similarity observed for the absolute bioavailability of both the immediate-release and prolonged-release formulations indicates a stable first-pass metabolism, independent of the absorption rate of the active compound, which is much slower for the prolonged-release formulation (median \(t_{\text{max}}\) = 5.0 hours) than for the immediate-release formulation (median \(t_{\text{max}}\) = 1.2 – 1.5 hours). Further evidence for the stability of tapentadol first-pass metabolism and its independence from the administered formulation comes from a previously reported study that used an oral solution of tapentadol, which again showed an absolute bioavailability of 32% [21].

The absolute oral bioavailability of tapentadol is comparable to or slightly higher than that of morphine, which also undergoes extensive first-pass metabolism to form glucuronide conjugates [22]. Published estimates of morphine bioavailability are between 19% and 47% [23], with most estimates in the range of 20 – 27% [22, 24, 25].

The total clearance of tapentadol is high, with consistent values (1,531 ± 177 ml/min and 1,603 ± 227 ml/min) observed in the two studies with i.v. administration. High values were also observed after i.v. administration for the volume of distribution of tapentadol associated with the terminal phase, again with consistent values between the two studies (540 ± 98 l and 471 ± 61.8 l). This large volume of distribution is typical for small basic and slightly lipophilic drugs, suggesting that intracellular distribution into tissues occurs to an appreciable extent. High volumes of distribution were also observed in rats and dogs during preclinical development, with extensive tissue distribution in the rat [26]. By way of comparison, the volume of distribution of morphine, although lower than tapentadol, is still quite high, with a value of 276 ± 72 l reported in one group of healthy volunteers [27].

Although tapentadol is widely distributed, the high total clearance ensures that the compound is nonetheless rapidly eliminated from the body. This combination of high clearance and high distribution volume results in a fairly short elimination half-life of ~ 4 hours, which means there is no concern about a potential “deep compartment” from which tapentadol slowly redistributes. This contention is further supported by the predictability of tapentadol pharmacokinetics after repeated dosing based on single-dose pharmacokinetics (data on file). If a slow redistribution of tapentadol from a “deep compartment” was occurring, then a higher than expected accumulation would be observed after repeated dosing, and this is not the case. Accumulation of tapentadol at steady state is largely accounted for by the terminal phase half-life and the time interval between dosing with steady-state concentrations being attained within 1 day (i.e., ~ 5 times the half-life) of treatment initiation in most subjects.

The overall exposure to tapentadol (in terms of \(\text{AUC}_{0-\infty}\) and \(\text{AUC}\)) was shown to be very similar for equal doses of the prolonged-
release and immediate-release formulations. Although the prolonged-release formulation described here represents an earlier version of the currently marketed tapentadol PR tablet, bioequivalence between these two formulations has subsequently been demonstrated (data on file). Comparison of the tapentadol concentration-time profiles for the immediate-release and prolonged-release formulations clearly demonstrated the prolonged-release characteristics of tapentadol PR; C_{max} was considerably lower for the immediate-release and prolonged-release formulations. The pharmacokinetic characteristics of MRT and HVD confirmed the prolonged-release characteristics; mean values of 10.6 hours and 12.5 hours, respectively, were observed for the prolonged-release formulation compared with 5.96 hours and 3.60 hours, respectively, for the immediate-release product.

Conclusion

Overall, the pharmacokinetic data derived in these studies support the suitability of the immediate- and prolonged-release formulations of tapentadol for the treatment of acute and chronic pain. Tapentadol is rapidly absorbed after administration of the immediate-release formulation, providing quick relief of acute pain conditions, and the characteristics of the prolonged-release formulation enable a convenient twice-daily dosing regimen to be followed for the treatment of chronic pain conditions over an extended period of time.

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