Subject instructions and exercise restrictions.

Methods

A regular sleep-wake cycle (23:00-07:00) was scheduled for 17 days in order to study the overall effects of both morning and evening dosing on sleep-wake cycles. For the first period and morning dosing, subjects were asked to void at 08:00 and the urine discarded. Subjects were then asked to void at the end of each 2h (or 4h) collection period with all urine collected within each period.

Subjects were randomized to one of two different dosing sequences, either to Evening (8 pm) active dose in the morning or morning (8 am) active dose in the evening, over a period of 5 days. On Day 5, subjects were asked to void at 08:00 and to complete a Physical Activity Questionnaire (PAQ) at 09:00. In addition, CTX-I measurements in urine were adjusted for urine creatinine.

Serum CTX-I analysis was performed using an immunoradiometric assay (IRMA), while urine CTX-I/Cr was determined by relevant commercial assay. The data were analyzed using Wilcoxon signed rank test at a two-sided significance level of 5%.

Overall a similar number of subjects reported TEAEs after morning dosing (12/12 subjects [100%]) and evening dosing (12/13 subjects [92.3%]). Procedural site reaction was more frequently reported after evening dosing (7/13 subjects [53.8%] compared to 4/12 subjects [33.3%] after morning dosing). Nausea was the most frequently reported treatment-related TEAE (reported by 3/12 subjects [25.0%] following morning dosing and 1/13 subjects [7.7%] following evening dosing).

Figure 2. Mean Plasma concentration of ONO-5334 on Day 5 (N=11)

Table 3. PK parameters of ONO-5334 on Day 5 (N=11)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/L)</td>
<td>25.0 (14.0)</td>
<td>27.5 (15.9)</td>
</tr>
<tr>
<td>AUC0-24h (µg*hr/L)</td>
<td>10.7 ± 2.9</td>
<td>20.0 ± 5.0</td>
</tr>
<tr>
<td>M/E: Morning dosing / Evening dosing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Acknowledgements

The study was sponsored by Ono Pharmaceutical Co. Ltd, Osaka, Japan.

References


