Bioavailability of gabapentin
assessed by cumulative urine sampling compared
with a model for the saturated absorption of gabapentin.

K.C. Carlsson*, M. Bergjord*, E.R. Moberg* and N.O. Hoem*

*Dept. of Pharmacology, School of Pharmacy, and "Inst. Of Pharmacology, Faculty of Medicine, University of Oslo, Norway.

Introduction

Gabapentin is well established in the treatment of seizures and also has a demonstrated analgesic effect in patients with chronic neuropathic pain. The absorption of gabapentin is saturable in a dose dependent manner involving an active transport process mechanism by an L-amino acid transporter. This is believed to explain the lack of effect experienced in many patients as well as a relative low incidence of toxic reactions.

Gabapentin does not bind to plasma proteins, is not metabolized and is excreted unchanged in the kidneys.

Individualized dosing of gabapentin is critically dependent on a robust and reliable method of estimating its individual bioavailability. Closer monitoring of gabapentin could improve analgesic effect in patients with sub-optimal dose regimens, reduce adverse effects and reveal patients lacking effect despite optimal dosing.

The aim of this study was to investigate if, in our patient population, a mathematical model could be used to estimate F. This was achieved by comparing such estimates with estimates of F based on urine collection. The model estimates for F is to be used in a population PK (PPK) model developed for clinical monitoring purposes.

Subjects

Patients with chronic, neuropathic pain receiving gabapentin as their main pain treatment were included in the study. The patients were recruited from the Pain Clinic, Aker University Hospital. Two female and 5 male patients were recruited. Average (SD) age was 43 ± 10 years, weight was 73 ± 17 kg and creatinine clearance was 95 ± 9 ml/min.

The subjects were monitored during one dose interval (6 / 8 h) when in steady state. The bladder was emptied before the gabapentin dose was taken. Total urine volumes were measured and gabapentin concentrations in urine measured by LC/MS-MS. Serum samples were collected during the same interval and analyzed by LC/MS-MS.

Methods

Estimates of F were found by using a model for gabapentin absorption developed by Gidal et al. These authors report a Michaelis-Menten type relationship between bioavailable fraction (F) and total daily dose (DD) where the bioavailability estimated by the model (FM) was found to be:

\[ FM = \frac{D_{\text{max}}}{(D_{50} + DD)} \]

The maximal absorption rate (D_{max}) was found to be 2720 mg/day while DD is daily dose of gabapentin and A_U is amount of drug excreted in the urine. The two different estimates for bioavailability (F_U and F_M) where compared (table 1). A_U was calculated based on the length of urine collection, urine volume and concentration of drug in the urine.

Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>A_U (mg/24h)</th>
<th>DD (mg)</th>
<th>F_U</th>
<th>F_M</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1240</td>
<td>3200</td>
<td>0.3764</td>
<td>0.3736</td>
<td>-3.7</td>
</tr>
<tr>
<td>2</td>
<td>1105</td>
<td>2400</td>
<td>0.4198</td>
<td>0.4198</td>
<td>-9.7</td>
</tr>
<tr>
<td>3</td>
<td>614</td>
<td>1200</td>
<td>0.3567</td>
<td>0.3567</td>
<td>-9.7</td>
</tr>
<tr>
<td>4</td>
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<td>2400</td>
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<td>43.5</td>
</tr>
<tr>
<td>5</td>
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<td>3600</td>
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<td>0.3567</td>
<td>-29.0</td>
</tr>
<tr>
<td>6</td>
<td>795</td>
<td>1800</td>
<td>0.4626</td>
<td>0.4626</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>546</td>
<td>1200</td>
<td>0.4549</td>
<td>0.4549</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Average 935 ± 2257 0.4250 ± 0.4372 1.9 ±22.3

Conclusions

A good consistency was found between the two estimates of F. F_M was close to F_U in 5 out of 7 patients. Average bioavailability for the seven patients was almost the same for model and urine collection, 42.5% and 43.7% respectively. This demonstrates that the absorption model can be included in pharmacokinetic models to be used in the monitoring of gabapentin.

A limit to this comparison is the uncertainty in the estimate of A_U. However, the good correlation between this estimate and an estimate of A_U from serum samples supports its use.

References