Plasma Concentrations of Posaconazole Administered via Nasogastric Tube in Patients in a Surgical Intensive Care Unit

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Abdominal surgery may affect intestinal absorption and the resulting levels of posaconazole in the blood. We measured plasma posaconazole levels in surgical intensive care unit (SICU) patients and tried to develop a predictive population pharmacokinetics model. A total of 270 samples from 15 patients receiving posaconazole via nasogastric tube were measured by high-performance liquid chromatography (HPLC). SICU patients showed lower plasma drug concentrations, a higher apparent clearance, and a higher volume of distribution than those in hematology patients, possibly due to poor absorption.

The use of posaconazole in patients with hematological malignancies has been published extensively (4, 6, 19, 20). Although recipients of solid organs and patients undergoing major abdominal surgery are also at risk for developing invasive fungal infections, and case reports show the suitability of posaconazole for this population (14, 15), no pharmacokinetic data on posaconazole are yet available for patients of a surgical intensive care unit (SICU). Application of posaconazole via nasogastric tube in healthy volunteers resulted in up to 20% decreased plasma drug concentrations (5), but this has not yet been studied in seriously ill patients with high APACHE II and SOAP II scores. It is not clear whether and to what extent posaconazole pharmacokinetics is affected in these patients.

The aims of the prospective POLICE trial (posaconazole via gastric tube) were to determine posaconazole concentrations in SICU patients in order to control if sufficient concentrations are achieved and to develop a population pharmacokinetics (PopPK) model.

Posaconazole concentrations were determined by reversed-phase high-performance liquid chromatography with UV detection as previously published (16). PopPK modeling was performed using nonlinear mixed-effects modeling (NONMEM version VI) with the first-order conditional estimation (FOCE) method and INTERACTION option (3). The influence of the following candidate covariates was examined consecutively: body weight, body height, body mass index, sex, age, albumin, γ-glutamyltransferase, glutamine-oxalacetic transaminase, glutamate-pyruvate transaminase, and bilirubin.

Two hundred seventy samples from 15 SICU patients who underwent extensive abdominal surgery were eligible for evaluation. They received posaconazole for prophylactic or therapeutic purposes, regardless of participation in the study. Demographic parameters are shown in Table 1.

All patients received 200 mg posaconazole every 6 h (q6h) as absorption was considered saturable. Daily posaconazole doses were administered via nasogastric tube; only twice was a jejunal or duodenal tube used. Other medication was not restricted during posaconazole treatment. Each patient received pantoprazole intravenously (40 mg/day) to prevent development of stress ulcers.

In transplant patients (n = 6), immunosuppressive therapy was mostly performed with tacrolimus or cyclosporine. Enteral nutrition was either normocaloric or high energy (3.0 to 5.8 g fat/100 ml) and supplied via nasogastric tube with a continuous flow rate of 10 to 80 ml/h. The median caloric intake was 36.1 (range, 0 to 105.7) kcal/h, and the median fat intake was 1.3 (range, 0 to 4.1) g/h. No patient was excluded from the trial due to toxicity or adverse events.

The mean posaconazole plasma concentration (PPC) was 175 μg/liter (± 77 μg/liter), with a mean maximum concentration of 295 μg/liter (± 152 μg/liter) and a mean minimum concentration of 86 μg/liter (± 38 μg/liter). No dose adjustments were made based on plasma drug concentration measurements.

### Table 1 Demographic parameters of the patients in the POLICE trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of male patients</td>
<td>6</td>
</tr>
<tr>
<td>No. of female patients</td>
<td>9</td>
</tr>
<tr>
<td>Age (yr, median)</td>
<td>58 (41–79)</td>
</tr>
<tr>
<td>Body mass index (kg/m², median)</td>
<td>27.8 (21.1–35.2)</td>
</tr>
<tr>
<td>Glutamine-oxalacetic transaminase (U/liter)</td>
<td>29 (6–4,937)</td>
</tr>
<tr>
<td>Glutamate-pyruvate transaminase (U/liter)</td>
<td>25 (4–2,512)</td>
</tr>
<tr>
<td>Glutamate-pyruvate transaminase (U/liter)</td>
<td>126 (26–1,272)</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.8 (0.2–21.6)</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>24.7 (15.7–42.2)</td>
</tr>
<tr>
<td>APACHE II score at admission (median)</td>
<td>29 (22–43)</td>
</tr>
<tr>
<td>SO2 II score at admission (median)</td>
<td>63 (36–73)</td>
</tr>
</tbody>
</table>

Received 18 November 2011 Returned for modification 8 February 2012 Accepted 27 April 2012 Published ahead of print 14 May 2012

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doi:10.1128/AAC.06167-11

4468 www.aac.asm.org Antimicrobial Agents and Chemotherapy p. 4468–4470 August 2012 Volume 56 Number 8
A one-compartment model was best for describing the pharmacokinetics of posaconazole in SICU patients. As concomitant food intake improves oral bioavailability (\(F\)) of posaconazole (9), the influence of food was implemented categorically into the model ("yes/no"). A direct dependence on the concomitantly applied amount of calories or fat was not significant. The statistical model consisted of interindividual variability (IIV) and intraindividual variability (IOV), each for clearance (CL) and volume of distribution (\(V\)), and a combined residual error model. No covariate showed a clear correlation for either \(V\) or CL. While individual prediction of the model was precise, the PopPK model was not able to predict peak posaconazole concentrations (Fig. 1). A substantial shrinkage in empirical Bayes estimates (ETA shrinkage) (18.1\%) was observed. Estimated parameters of the final model are presented in Table 2.

Our data correlate well with those presented by Ray et al. reporting mean steady-state plasma drug concentrations in critically ill patients of 115 \(\mu\)g/liter for 200 mg q6h (12). One possible explanation for the very low PPC in our population may be reduced absorption due to mandatory proton pump inhibitor (PPI) intake, gastrointestinal dysfunction, and malabsorption, as well as the application via nasogastric tube, resulting in a low bioavailability (2, 5, 7). In comparison to AbuTarif et al. (1) and Kohl et al. (8)—who investigated hematological patients—we calculated greater values for the apparent volume of distribution (3,280 versus 2,250 and 835 liters, respectively) and apparent clearance (195 versus 65 and 67 liters/h, respectively). A common characteristic of intensive care patients—capillary leakage and edema—may also increase volume of distribution. Most likely due to the small number of patients, the IIV in CL/\(F\) and \(V/\)\(F\) is greater than those reported by AbuTarif et al. and Kohl et al. (1, 8). In a population of lung transplant recipients, only 50% achieved a PPC of >500 \(\mu\)g/liter, which appeared to be associated with better outcomes. Only 10\% of patients with levels of <500 \(\mu\)g/liter experienced therapeutic success. Absence of PPI resulted in higher levels (13). Lebeaux et al. determined that low PPCs (<500 \(\mu\)g/liter) in a prophylactic...
lactic setting are potentially associated with subsequent invasive fungal infections (11). Meanwhile the Food and Drug Administration (FDA) suggests average PPCs of 350 g/liter and 700 μg/liter on days 2 and 7 during prophylaxis, respectively. Transferring these recommendations to our results shows that only one patient reached a single PPC of >350 μg/liter on day 2. During treatment with posaconazole, only six patients (40%) exceeded this value at all, but none of them did so consistently. On day 7, no patient displayed the target concentration of 700 μg/liter; the maximum PPC was at 531 μg/liter.

As in previous published PopPK models for posaconazole, the population model is not predictive for peak plasma posaconazole concentrations in SICU patients (Fig. 2). Previous PopPK studies identified covariates like diarrhea, PPI intake, liver enzyme elevations, and age. These parameters appeared to be statistically, but not clinically significant (1, 8). In our model, these covariates could not be confirmed because no patient suffered from diarrhea and all patients received PPI.

Our results indicate that application of posaconazole via nasogastric tube in SICU patients leads to inadequate plasma drug concentrations, most likely due to a lack of absorption, and seems to be less suitable for treatment or prophylaxis of fungal infections in surgical intensive care patients because of the need to quickly reach therapeutic drug concentrations in the bloodstream. Due to the availability as an oral suspension only, use of posaconazole is limited to stable patients with reliable enteral absorption.

ACKNOWLEDGMENTS

We thank Lenka Taylor for assistance with language and spelling. There has been no specific funding for this study; it was performed during the routine work of our organization.

D.S. and C.L. received travel grants from Essex. M.A.W. has served as a speaker for Essex. T.H.-T. has served as speaker for Essex and is a member of advisory board from Essex. All other authors have no potential conflicts to declare.

REFERENCES

10. Reference deleted.
17. Reference deleted.
18. Reference deleted.

Table 2. Population pharmacokinetics parameters of the final model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result for parameter (RSE [%])</th>
<th>% IIV (RSE [%])</th>
<th>% IOV (RSE [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F</td>
<td>195 liters/h (16.7)</td>
<td>51.8 (39.9)</td>
<td>48.4 (15.6)</td>
</tr>
<tr>
<td>V/F</td>
<td>5,280 liters (29.3)</td>
<td>52.0 (53.3)</td>
<td>21.1 (31.6)</td>
</tr>
<tr>
<td>k_{ao}</td>
<td>0.77 h^{-1} (35.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor on F</td>
<td>1.34 (9.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual error</td>
<td>11.6% (53.2)</td>
<td>2.8% (32.1)</td>
<td></td>
</tr>
</tbody>
</table>

* RSE, relative standard error; IIV, interindividual variability; IOV, intraindividual variability; CL, clearance; F, bioavailability; V, volume of distribution; k_{ao}, absorption rate constant.