Relevance of Timing for Determination of Posaconazole Plasma Concentrations

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Received 15 January 2011/Returned for modification 13 March 2011/Accepted 9 April 2011

For posaconazole, drug monitoring is suggested, but the relevance of timing for the determination of posaconazole concentration (PC) remains unclear. We investigated the variation of PC before and 4 and 8 h after the administration of 400 mg of posaconazole. Mean concentrations were 645, 678, and 616 ng/ml. The differences between trough and maximum concentrations were below 20% in 17 and below 30% in 20 of 25 patients. Hence, untimed posaconazole plasma concentrations give reliable information for most patients.

Posaconazole was shown to be effective in preventing invasive fungal infections (4, 21). Additionally, the compound is recommended for salvage therapy of invasive fungal infections (1, 15). Low posaconazole plasma concentrations have been associated with a reduced success rate of salvage therapy (22) and an increased risk of clinical failure in the prophylactic indication (8).

Remarkable interindividual variation and low or undetectable plasma concentrations in a significant number of patients have been published (6, 11, 17). Posaconazole has a terminal elimination half-life of 15 to 35 h (6) and is only available for oral administration. Pharmacokinetics may be altered by numerous factors (2, 7, 13), e.g., absorption is impaired by reduced gastric acidity or diarrhea and can be improved by administration together with a fat-containing meal (6, 12, 18).

Several assays for the determination of posaconazole concentration (PC) have been published (5, 9, 19), but for adequate therapeutic drug monitoring, additional issues have to be clarified. Particularly, the time point for sampling after the administration of the drug remains an open question. In clinical practice, the trough level is most often determined in the morning. In the case of suspected toxicity or a breakthrough infection, PC might be of immediate interest, and delaying sampling can become difficult. The purpose of this study is to evaluate first the impact of timing and then the intradaily variability of posaconazole plasma concentration.

This study was conducted as an open, single-center trial, in accordance with the local ethical regulations. Patients with hematological malignancies, receiving posaconazole for any indication with a dosage of 400 mg twice a day (BID), were enrolled. Other doses and intervals, particularly 200 mg three times a day (TID), have been excluded, as higher doses and longer intervals are expected to cause a more pronounced variation in daily drug concentration. The aim of the study was to investigate the magnitude of variation in posaconazole drug concentrations at steady state. Therefore, patients were not enrolled before 7 days (mean, 31 days) of posaconazole administration, and patients with severe mucositis, gastrointestinal graft-versus-host disease (GVHD), or diarrhea (more than 3 times daily) were excluded.

For pharmacokinetic sampling, blood was drawn in the morning, 12 (11 to 13) h after the last evening dose and before the first daily dose (C_\text{trough} [C_{\text{on}}]), both at the time of maximum expected concentration (4 h after the morning dose [C_{\text{on}}]) and after another 4 h (C_{\text{on}}).

For pharmacokinetic analysis, PCs were determined using a previously validated high-performance liquid chromatography (HPLC) assay (9). Linearity ranged from 0.05 to 10.0 μg/ml. The intra- and interday coefficients of variation were <8.5%, with accuracy and precision of <10%.

Statistical analyses were performed with SPSS 18.0. The study was designed with 80% power at α = 0.1 to detect intraday variation of 20% or more, assuming a mean PC of 750 ng/ml and a standard deviation of 525 ng/ml (70%). The required sample size of 25 patients was calculated. A P value of <0.05 was considered to be significant. Comparisons of concentrations were performed by the Wilcoxon test for matched pairs.

A 1-day pharmacokinetic profile with three PCs was obtained from 25 hematological patients. The patients’ mean age was 56.7 years (range, 20 to 75 years), and characteristics are presented in Table 1. Patients received the broad range of concomitant medication typical for this clinical setting. Eighteen patients received either a proton pump inhibitor (pantoprazole) or an H2 antagonist (ranitidine), which might explain reduced absorption and low posaconazole drug levels.

Posaconazole median and mean concentrations showed no relevant differences for all time points, with a median (mean; range) of 362 ng/ml (645; 32 to 2,319) at 0 h, 374 ng/ml (678; 56 to 2,361) at 4 h, and 389 ng/ml (616; 64 to 3,081) at 8 h (Fig. 1).

To further analyze the variation of individual PC, absolute and relative changes were calculated for each patient and combination between the different time points. Here, concentra-
tions were lower at $C_{0h}$ and $C_{4h}$ than at $C_{8h}$ in 19 and 20 of 25 patients, respectively (Wilcoxon-Mann-Whitney test, $P < 0.05$). $C_{0h}$ and $C_{4h}$ had a mean difference of 17.8% (80 ng/ml).

In six cases, the 4-h drug level was below the concentration in the morning sample, and in only eight patients could a variation of more than 20% be detected. For the comparison of $C_{8h}$ to $C_{4h}$ and of $C_{8h}$ to $C_{0h}$, the mean differences were 19.3% (138 ng/ml) and 21.3% (131 ng/ml), with changes of more than 20% in 13 and 11 patients (Fig. 2).

Absolute deviation depended on drug concentration. For patients with a $C_{0h}$ below 500 ng/ml, the mean deviation was 33.4 ng/ml compared to $C_{4h}$ and 42.3 ng/ml compared to $C_{8h}$. For $C_{0h}$ in the range of 500 to 1,000 ng/ml ($C_{0h-4h}$ of 134.6 ng/ml and $C_{0h-8h}$ of 134.1 ng/ml) and above 1,000 ng/ml ($C_{0h-4h}$ of 125 ng/ml and $C_{0h-8h}$ of 357 ng/ml), the mean intraindividual variations were higher.

Maximal differences of PCs for an individual patient had a mean variation of 28%. Although for 72% of patients this maximum posaconazole change was above 20%, for most patients (60%) the trough level and the $C_{4h}$ showed a difference of less than 20% (Fig. 3).

There are some patients with a broader range of concentrations, compatible with an increased clearance of the compound. Here, no specific causal factor could be identified. Also whether patients received comedication of antacids resulted in no significant difference in variation.

PCs for all investigated time points were within the previously described broad range (10, 20). This variability of concentration is a major reason for the recommendation of

### TABLE 1. Baseline characteristics of study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>19</td>
</tr>
<tr>
<td>Other hematological malignancy(^{a})</td>
<td>6</td>
</tr>
<tr>
<td>Allogeneic SCT(^{b})</td>
<td>13</td>
</tr>
<tr>
<td>Autologous SCT</td>
<td>1</td>
</tr>
<tr>
<td>H2 blocking comedication</td>
<td></td>
</tr>
<tr>
<td>Ranitidin</td>
<td>3</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>15</td>
</tr>
</tbody>
</table>

\(^{a}\) Other malignancies include two cases of T-acute lymphatic leukemia and one case each of multiple myeloma, B-cell non-Hodgkin’s lymphoma (B-NHL), osteosarcoma, and aplastic anemia.

\(^{b}\) SCT, stem cell transplantation.

FIG. 1. Box plot of posaconazole concentrations (all patients) before and 4 and 8 h after medication (median, black bar; 50% interquartile range, white box).

FIG. 2. Individual course of posaconazole concentrations.
posaconazole drug monitoring (16). Although PC was higher 4 h after the morning dose, in the present study the intra-individual variation on a daily basis is rather small. For the majority of patients, $C_{3h}$ and $C_{4h}$ differed by no more than 20%. It should be taken into account that this deviation is even within the accepted range of interlaboratory comparisons (3).

Intraday variations of drug concentrations depend on numerous factors, including dose, half-life, volume of distribution, and also saturable absorption as typical for posaconazole, and drug interaction can influence bioavailability. Here, we show that after a steady state has been achieved, determination of posaconazole in a single, untimed blood sample yields reliable information about current drug plasma concentration.

A still low, arbitrary cutoff of 30% change in azole concentration results in a prognostic failure in only five of 25 patients, if maximum instead of trough concentration is taken into account. Major absolute differences are restricted to high PCs. We recommend here would the difference between trough level and maximum concentration change therapeutic recommendations (14), from our point of view, in none of the cases described here would the difference between trough level and maximum concentration change therapeutic recommendations.

For exclusion of broad intraday variation in an individual patient, a second determination 4 h later may be useful. By this method, patients not in steady state can be detected.

REFERENCES


