What Should Be the First-Choice Strategy To Maximize Posaconazole Exposure in Daily Clinical Practice?

We read with interest the study by Krishna et al. (2) describing the pharmacokinetics and absorption of posaconazole oral solution under various gastric conditions in healthy volunteers. In this four-part, randomized crossover study, a large interindividual variability in plasma drug exposure was documented according to the effects of gastric pH, dose frequency and prandial state, food consumption timing, and gastric motility. On the basis of the findings, the authors suggested a hierarchy of strategies that should be used to maximize posaconazole oral absorption. The most desirable approach should be the administration during or immediately after a high-fat meal or, alternatively, in decreasing order, with any meal, with nutritional supplement, or with an acidic carbonated beverage, whereas the least desirable choices should be dose fractioning or avoidance of proton pump inhibitors (PPIs). These conclusions were supported by the fact that the highest ratio estimate for the area under the concentration-time curve (AUC), in comparison with the 400-mg single dose alone, was observed when the same dose was administered during a high-fat meal (ratio of 482) or immediately after a high-fat meal (ratio of 487).

Although we fully agree on the necessity of identifying useful strategies to improve posaconazole oral absorption, we believe that this hierarchy should be modified. Indeed, the administration of posaconazole in association with meals results in an important variability in the dosing interval, which may alter the drug exposure. Conversely, we believe that the splitting of the 800-mg daily dose into four doses given 6 h apart could be the most relevant strategy to maximize posaconazole exposure in clinical practice.

Our contention is based on two major considerations. First, if one looks at absolute values rather than at ratio estimates, the highest AUC (132,000 ng/ml · h) was observed when posaconazole at 200 mg four times a day (QID) was administered alone under fasting conditions for 7 days. Interestingly, no significant increase in drug exposure was obtained when a nutritional supplement was coadministered with this dosage (112,000 ng/ml · h), whereas only lower values were observed with the 400-mg twice-a-day (BID) regimen, irrespective of the prandial state (52,300 ng/ml · h under fasting conditions and 80,600 ng/ml · h under nonfasting conditions). This seems to suggest that the influence of prandial state may be less relevant after administration of posaconazole in four divided doses. Second, there are some important clinical reasons to prefer this strategy in daily practice. Posaconazole is principally used in patients with hematological malignancies after myeloablative chemotherapy or allogeneic hematopoietic stem cell transplantation who cannot eat a high-fat meal or even tolerate food. In addition to anorexia, these patients often experience major gastrointestinal tract dysfunction due to severe gastrointestinal mucositis and/or intestinal graft-versus-host disease, which may theoretically alter posaconazole absorption and plasma exposure. Certainly, definitive evidence might have been obtained only if the influence of gastric pH, meal timing, and gastric motility on posaconazole exposure after single administration would have been comparatively tested using both doses (200 mg versus 400 mg).

Besides, in a clinical trial of posaconazole as salvage therapy for patients with invasive fungal infections it was shown that the response rate was as high as 75% in the subset of patients with invasive aspergillosis who had a mean average posaconazole concentration of 1,250 ng/ml (4). Consistently, in a recent review on therapeutic drug monitoring of azole antifungals, an average plasma concentration of >1,500 ng/ml was recommended as the optimal goal during posaconazole therapy (3). Of note, these thresholds are lower than those observed at steady-state by Krishna et al. when using the 200-mg QID regimen under fasting conditions. Consistently, these data, although they originated from healthy volunteers, lead us to reasonably suppose that the first-choice strategy for optimizing posaconazole pharmacodynamics in severely ill patients should be to split the 800-mg daily dose into four divided doses given 6 h apart. Interestingly, this dosing schedule could be given at a regular dosing interval, and this is an additional practical advantage at the bedside or in the outpatient setting. Finally, since coadministration of omeprazole was recently shown to significantly reduce the posaconazole serum trough level in a patient with invasive aspergillosis (1), the avoidance of PPIs should be considered as a priority in all patients under posaconazole therapy in the absence of an established indication.

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REFERENCES

The authors appreciate the comments by Pea et al. Our study (5) was designed to delineate the effects of variables (pH, meal timing, and gastric motility) with the higher posaconazole dose strength of 400 mg under fasting conditions as one single reference treatment for various comparisons. Posaconazole is a biopharmaceutics class II drug with dissolution-limited absorption (4) and is a weak base that is relatively more soluble at acidic pH (Schering-Plough, data on file). Thus, any solubility-mediated absorption enhancement was postulated to be more pronounced at the higher dose.

In Fig. 5 in our study (5), strategies to optimize posaconazole absorption were presented without an attempt to imply any hierarchy. Although absolute AUC values to the final time points were presented for all treatments, our conclusions in terms of the degree of absorption-enhancing effect were based on the ratio estimate of the log-transformed data as AUC is log-normally distributed. Furthermore, the most appropriate pharmacokinetic and clinical comparisons are (i) the AUC to the final time point or to infinity for comparing treatments following a single dose and (ii) AUCt (AUC for a dosing interval at the steady state) for comparing treatments with repeated dosing to steady state. The log-transformed AUCt values for dosing to the steady state were used to calculate the ratio estimate. Steady-state AUC from 0 to 24 h (AUC0–24) values derived from AUCt values are presented here in the raw scale in Table 1. For comparison, the steady-state AUC0–24 from another study using posaconazole at 400 mg BID under fed conditions is also presented (6).

By comparing all treatments to the 400-mg dose under the fasting condition, our study (5) demonstrated that in subjects who can tolerate food, nutritional supplement, or fluid, posaconazole absorption is optimized when taken (i) with or immediately (within 20 min) after a high-fat meal, (ii) with a liquid nutritional supplement, and (iii) with an acidic carbonated beverage. A previous study demonstrated that compared with the fasting condition, nonfat food also enhanced posaconazole absorption (3), and as such, is also included in overall strategies to optimize absorption. The steady-state AUC0–24 demonstrates that compared with 200-mg QID dosing under the fasting condition, 400 mg BID with a high-fat meal results in higher exposure and lower variability (Table 1). In subjects under the fasting condition, however, posaconazole absorption is enhanced by dividing the dose from 400 mg BID to 200 mg QID after daily dosing (4) and after repeated dosing to the steady state (5). Therefore, the authors agree that in those patients who cannot tolerate food or nutritional supplement, 200 mg QID optimizes absorption under fasting conditions compared with 400 mg BID (Table 1). The authors also agree as noted (5) that the concomitant use of posaconazole and PPIs should be avoided unless benefits outweigh the risk because PPIs reduced posaconazole absorption in the present study (5), in a study where patients received 200 mg posaconazole three times a day (7), and in the study cited by Pea et al. (1).

Interestingly, as Pea et al. also pointed out, prandial status did not have a pronounced effect on posaconazole exposure after administration in four divided doses (Table 1). The effect of food was pronounced only at 400 mg BID, presumably because of solubility enhancement. As noted earlier, this appears consistent with the biopharmaceutics class II properties of posaconazole.

The authors do question 1,500 ng/ml as the proposed plasma concentration goal for posaconazole (8) based on the following data. In patients with refractory invasive aspergillosis, a posaconazole mean plasma average concentration (Cavg) in the 2nd quartile of ~410 ng/ml was associated with an acceptable response rate of 53% (10). For comparison in a similar disease setting, the response rate is approximately 40% for other antifungals (2, 9), such as voriconazole and caspofungin. The authors do recognize, however, that higher posaconazole plasma concentrations were associated with greater response rates, further reinforcing the recommendation to optimize absorption by various strategies whenever possible and so long as the benefit outweighs the risk.

In conclusion, when considering posaconazole dosing strategies, a choice between the 400-mg BID regimen and the 200-mg QID regimen should be made by clinicians based on whether or not a patient can take posaconazole with food or nutritional supplement. BID dosing may furthermore offer better compliance by reducing dosing frequency and may fit better into a hospital dosing schedule.

The authors would also like to take this opportunity to correct an error in reference 5. On page 962, Table 3, last column, first row, AUC “170 (143–2,030)” should be “170 (143–203)”.

REFERENCES


