Correspondence

Numbers Needed to Treat with Posaconazole Prophylaxis to Prevent Invasive Fungal Infection and Death

To the Editor—Nagappan and Deresinski [1] are to be commended for their highly interesting and timely review of posaconazole. However, there is a miscalculation on the numbers needed to treat (NNTs) to prevent 1 fungal infection or death.

NNTs are of utmost importance when deciding on the relevance of incidence rates reported in clinical trials. They are calculated on the inverse of the absolute risk reduction of a clinical trial (table 1) [4]. In addition to the evaluation of the clinical effect, cost-benefit approaches play an important role for every prophylactic measure. Those approaches frequently rely on NNTs; therefore, the discrepancy between these essential data derived from the original publications and those given in the review needs to be addressed. When weighing cost and benefit, NNTs are used to determine the appropriateness of initiating prophylaxis. This is especially suitable when addressing the prevention of invasive fungal infection. NNTs > 20 have been proposed as being too high to support prophylaxis [5]. However, there is no threshold NNT generally agreed on by the scientific community. Others, however, attempted a more reasonable approach. Sinclair et al. [6] made an effort to calculate a threshold NNT that enables a clinician to assume that a given medical intervention is acceptable. But the NNT for preventing the permanent outcome of death is even more challenging and was not adequately addressed in the review by Nagappan and Deresinski [1]. It would require a mathematically predefined value for saving a life and is subject to ethical discussions, not determined by personal statements [5].

Table 1. Numbers needed to treat (NNTs) with posaconazole prophylaxis to prevent invasive fungal infection and death.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Incidence rates, %</th>
<th>Neutropeniaa</th>
<th>Graft-versus-host diseaseb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Posaconazole (200 mg TID)</td>
<td>Fluconazole (400 mg QD) or (itraconazole (200 mg BID)</td>
<td>Relative risk reductionc</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>2.3</td>
<td>9.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>0.7</td>
<td>6.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Death due to fungal infection</td>
<td>1.6</td>
<td>5.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Death due to any cause</td>
<td>14.5</td>
<td>21.5</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**NOTE.** BID, 2 times per day; OD, 1 time per day; TID, 3 times per day.

a Exposure period for fungal infection rates and 100 days after randomization for death rates. Data on neutropenia are derived from Cornely et al. [2].

b Fixed time period of 112 days for fungal infection and 168 days after randomization for death rates. Data on graft-versus-host disease are derived from Ullmann et al. [3].

c Calculated as 1/(Ps – Pp), where Ps is fluconazole or itraconazole and Pp is posaconazole.
d Calculated as Ps – Pp, where Ps is fluconazole or itraconazole and Pp is posaconazole.
e Calculated as 1/(Ps – Pp), where Ps is fluconazole or itraconazole and Pp is posaconazole.
f Calculated as 1/(Pf – Pf), where Pf is fluconazole and Pp is posaconazole.
g Calculated as Pf – Pp, where Pf is fluconazole and Pp is posaconazole.
h Calculated as 1/(Pf – Pp), where Pf is fluconazole and Pp is posaconazole.
i Not significant.

Acknowledgments

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References

The Effect of Gastric Acid on the Absorption of Posaconazole

To the Editor—In the article entitled “Posaconazole: A Broad Spectrum Triazole Antifungal Agent,” there is a statement that is misleading with regard to the effect of gastric acid on the absorption of posaconazole [1]. In the pharmacology section, the authors state, “Unlike itraconazole, the absorption of posaconazole is not affected by changes in gastric acidity” [1, p. 1611]. However, in paragraph 4 of that same section, the authors state, “Cimetidine reduces posaconazole exposure” [1, p. 1612]. We understand that, in the first statement, the authors refer to a pharmacokinetic study involving antacids and posaconazole in which no clinically significant alteration in absorption was found [2]. The second statement thus contradicts the first statement, because cimetidine is a histamine-2 receptor antagonist that reduces gastric acidity. In statement 2, the authors cite the prescribing information of posaconazole, but this reference clearly explains that the reason for this interaction is attributable to an alteration of gastric pH [3].

The manufacturer, as stated in the prescribing information, proclaimed that no other acid suppressants—such as proton pump inhibitors or other histamine-2 antagonists—affect the absorption of posaconazole, but, in theory, this interaction could occur if the mechanism of the cimetidine interaction is attributable to an alteration in gastric pH. The mechanism for this interaction is unknown and not thought to be related to cytochrome P450 inhibition, because posaconazole is not a substrate of the cytochrome 450 system [3]. The prescribing information provides a blanket statement that other agents that reduce gastric acidity do not interact with posaconazole, but it does not provide the data behind this claim. Cimetidine reduces the Cmax and area under the curve of posaconazole by 39%, which led the manufacturer to recommend avoiding this combination. Because studies have indicated that patients with lower posaconazole levels may be at higher risk of refractory or breakthrough invasive fungal infections [4, 5], it is essential to understand which agents (i.e., proton pump inhibitors and other histamine-2 receptor antagonists) reduce posaconazole concentrations and to what extent this reduction occurs. We urge the manufacturer and our pharmacology colleagues to assist with the understanding of this interaction so that clinicians can use this agent in the most efficacious manner.

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References


Reply to Cornely and Ullmann and to Jain and Pottinger

To the Editor—Our statement with regard to the numbers needed to treat in the study by Cornely et al. [1] was somewhat poorly worded, and we apologize for that. The stated numbers, however, are quite similar to those calculated by Cornely and Ullmann [2] (in this issue). Our calculations [3] indicate that the numbers needed to treat to prevent 1 invasive fungal infection, 1 case of aspergillosis, and 1 death were similar to each other (16.4, 16.7, and 14.5, respectively). A more significant discrepancy between our calculations and those indicated by Cornely et al. [1] is in the number needed to treat to prevent 1 death due to invasive fungal infection, which they calculate to be 26, on the basis of an absolute risk reduction that they indicate to be 3.7%. Their result is likely to be more precise than ours, because our calculation was, necessarily, based only on the data presented in the text of the article, which states, “Of the 116 deaths that occurred during the study, 21 were considered to be related to fungal infection: 5 (2%) that occurred in the posaconazole