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].

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2. Courtney R, Radwanski E, Lim J, Laughlin M.


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

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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

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2. Courtney R, Radwanski E, Lim J, Laughlin M.


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group and 16 (5%) in the fluconazole or itraconazole group (P=0.01) [1, p. 353].

The resultant absolute risk reduction of 3% yields a number needed to treat of 33.3.

We do agree that the numbers alone do not tell us of the value of 1 life. Furthermore, that assessment cannot be made in the abstract but must be considered in relation to each individual and his or her circumstances and, especially, his or her personal wishes.

In response to Jain and Pottinger [4], who raised the issue of gastric acidity affecting posaconazole absorption, we requested further information from Schering-Plough, the sponsor of posaconazole [5]. Per the sponsor, “concomitant use of posaconazole and cimetidine should be avoided. The effects of other histamine-2 receptor antagonists that may suppress gastric acidity for several hours on plasma levels of posaconazole have not been studied, but a reduction in bioavailability may occur so that coadministration should be avoided, if possible” [5].

Acknowledgment

Potential conflicts of interest. S.D. is an advisory board member of Schering-Plough and Ortho-McNeil (Johnson & Johnson) and serves on the speakers’ bureau for Merck, Ortho-McNeil (Johnson & Johnson), Schering-Plough, Pfizer, Wyeth, and Cubist. V.N.: no conflicts.

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References


Antiviral Therapy and Outcomes in Hospitalized Patients with Influenza

To the Editor—It can be difficult to design studies that involve patients who are hospitalized with influenza; challenges include definition of the patient population, determination of the primary study endpoint, study design, and efficacy evaluation. McGeer et al. [1] should be commended for accumulating the largest prospective cohort of hospitalized patients with laboratory-confirmed influenza. During the period January 2005–May 2006, researchers identified 541 patients at acute care hospitals in the Toronto Invasive Bacterial Diseases Network. Their study corroborates other findings of substantial morbidity and mortality associated with influenza [2]. Study limitations include its observational design, sample size, diagnostic methods used, inability to compare antiviral treatment effects in different patient subgroups, insufficient power to identify effect of time to first treatment relative to symptoms, lack of generalizability, and potential confounders, such as potential bias associated with a lack of randomization.

Although the authors suggest that antiviral treatment might reduce mortality among hospitalized patients, these conclusions should be considered in the context of the study’s limitations and the scientific challenges involved in studying patients who have been hospitalized with influenza. First, detailed data on clinicians’ rationale for antiviral treatment was not obtained. Patients who received antivirals (106 [32%] of 327 adults) may represent an enriched subpopulation. Patients with prolonged symptom duration, poor gastrointestinal absorption, or other factors may have been excluded from treatment on the basis of a low clinical likelihood of benefit. Second, the study did not include a randomized control arm and was underpowered to distinguish efficacy differences between patients who received antivirals and those who did not. Third, there is no evidence-based, standard-of-care antiviral treatment for hospitalized patients with influenza. Although this challenge could be addressed using superiority study design, no such studies (to our knowledge) have been performed to date. An additional challenge to demonstrating the efficacy of drugs against serious influenza is the observation that patients may present for medical care several days after the onset of symptoms. Randomized, prospective studies evaluating the treatment effect of antivirals initiated ≥48 h after the onset of influenza symptoms have not been performed. Therefore, any study design considerations are complicated by the absence of evidence of benefit—or of the magnitude of benefit—that might be used in hospitalized patients with influenza. Fourth, the most appropriate primary end point for patients who are hospitalized with influenza is unknown. In this study, the primary end point was defined as mortality within 15 days after symptom onset [1]. Although mortality could be a reasonable end point, larger sample sizes would likely be needed to demonstrate a treatment effect. No surrogate marker has been identified as reasonably likely to predict important clinical outcomes. It is possible that a combined clinical end point may need to be determined for future studies. Such a primary end point could be derived from other studies of hospitalized patients with acute, serious, or potentially life-threatening respiratory illnesses [3, 4].

Despite the challenges discussed above, McGeer et al. [1] show that studies of patients hospitalized with influenza are feasible and can provide useful data, and they have demonstrated that studies with sample sizes in the range of several hundred patients may be able to detect differences in important clinical end points. Addi-