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EDITORIAL COMMENTARY

Hypoalbuminemia and Posaconazole Therapeutic Drug Monitoring

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A recent report in *Open Forum Infectious Diseases* linked hypoalbuminemia with the occurrence of subtherapeutic posaconazole concentrations. Specifically, 22.7% failed to achieve the trough concentrations desired for prophylaxis, and 50% failed to achieve concentrations of at least 1.25 µg/mL for therapy. Using logistic regression, albumin concentrations <3 g/dL were associated with subtherapeutic posaconazole concentrations. The authors suggested higher initial dosing of posaconazole and therapeutic drug monitoring (TDM) to ensure achievement of "therapeutic concentrations" [1]. Posaconazole is highly protein bound (>98%), mostly to albumin. Many patients at risk for fungal infections have hypoalbuminemia. There is no doubt that the extent of protein binding can affect pharmacokinetics, but the implications of these changes are not simple [2]. There has been 1 report in which total and unbound concentrations were measured. Low serum albumin was associated with reduced probability of attaining target total, but not unbound posaconazole concentrations. The authors recommended TDM of unbound concentrations where available [3]; however, availability is likely limited to research. Measurement of unbound concentrations for drugs that are highly bound is difficult due to sample separation variables and sensitivity requirements.

Distribution into tissues and pharmacologic activity are governed by free (unbound) concentration as the unbound drug is able to diffuse across membranes and interact with transporters, metabolic enzymes, and receptors. In plasma, only about 1% of posaconazole is represented by the unbound drug. Unbound drug (D) is in equilibrium with the other 99%, which exists as a protein–drug complex (P-D). This binding has a relatively low affinity and is readily reversible. When the drug is bound, it is kept in a "reservoir," and drug from the P-D pool can easily replenish the pool of unbound drug. The ratio of P-D:D is determined by the affinity of the drug for albumin. To simplify matters, we will assume that all protein binding is to albumin. The normal albumin concentration averages about 4.4 g/dL. When the albumin concentration is low (eg, 2.2 g/dL) and there is no change in drug affinity for albumin, the capacity to hold the drug in plasma is reduced. The intuitive way to think of this scenario is to consider a concentration of 1 µg/mL in plasma. It is logical that if drug binding is reduced, then the free concentration should increase. What really happens is that the unbound concentration stays the same because this is governed by intrinsic clearance and unbound volume of distribution. For low-clearance drugs such as posaconazole, only the unbound drug is cleared by the liver. Unbound drug remains in equilibrium with bound drug, but the capacity to bind the drug is reduced proportionally to the reduction in albumin concentration. The greater the extent of protein binding, the larger the impact on pharmacokinetics (total clearance and volume of distribution) from the perspective of total drug. When TDM is performed, one expects the same unbound concentration but a markedly reduced total concentration. Total concentration is much easier and less expensive to measure, so total concentration is typically available.

From a theoretical perspective, we can predict how changes in albumin concentration will affect total concentration. For posaconazole TDM, the treatment therapeutic trough range is typically 1 to 3.75 µg/mL [4, 5]. The associated free concentration is approximately 0.01 to 0.0375 µg/mL with 99% percent bound. In theory, the unbound drug concentration best reflects the antifungal activity. As an example, a person receiving posaconazole has an albumin concentration of 2.2 g/dL, and the observed total posaconazole concentration (C_{obs}) is 0.7 µg/mL. Compared with a case with normal albumin, total concentration (C_{obs}) would be decreased, unbound concentration would be the same, and percent unbound would increase ~2-fold. An equation can be derived to provide a

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corrected total concentration in the setting of hypoalbuminemia [6].

$$C_{corr} = C_{obs} \frac{1}{\left(0.01 + 0.99 \frac{Alb}{4.4}\right)}$$

In this case, $C_{corr} = 1.39$ μg/mL. The unbound fraction (f_U) is 0.01, and the bound fraction is 0.99. Given the extreme degree of protein binding for posaconazole, this equation can be simplified to provide an approximate result as f_U is negligible in the denominator.

$$C_{corr} = C_{obs} \frac{4.4}{Alb}$$

The corrected concentration of 1.4 μg/mL should be used to interpret the result vs the therapeutic range. This correction approach has been used with phenytoin for TDM [6]; however, posaconazole and itraconazole are particularly highly protein bound.

The elephant in the room is defining the concentration that best predicts pharmacologic activity. In theory, free (unbound) concentration is most relevant for antifungal activity and toxicity. Killing of *Candida lusitaniae* studied in serum vs growth media was greater in serum than expected based only on unbound concentration. A static effect was noted in RPMI media at a posaconazole concentration of 0.1 μg/mL, and no killing and only slightly reduced growth were noted with a serum concentration of 1 μg/mL; however, the growth of yeast in these 2 media was not comparable [7]. Serum affected the growth pattern, and a full response–concentration profile was not provided. Therefore, it is important to ensure that serum by itself does not result in killing or inhibition of yeast growth. The antifungal effect of 5 to 20 times greater than the unbound concentration was attributed to flux of drug from the protein-bound pool to the higher affinity binding in yeast cells. Unbound drug rather than drug–protein complex still diffuses to and binds to the lanosterol 14α-demethylase. Albumin only serves as a reservoir for drug available in close proximity as a source to replenish drug.

The pharmacodynamics of posaconazole were studied in a neutropenic mouse model using 12 strains of *Candida albicans*. The free 24-hour area under the curve (AUC) is most predictive of EC_{50} in this model, and free AUC/minimum inhibitory concentration (MIC) averaged 16.9 [8]. Based on an f_U of 0.01 and MIC range of test isolates, this translates to a 24-hour AUC (total) of 25–202 mg h/L being required for treatment. The average 24-hour AUC achieved by posaconazole delayed-release tablets, 300 mg daily, is 51.6 for healthy subjects and 37.9 mg h/L for patients with fungal infections. It is possible that the difference in exposure (24-hour AUC) is due to hypoalbuminemia in a portion of the patients, which would result in lower total, but similar free 24-hour AUC. The expected free 24-hour AUC is sufficient to treat infections due to most *Candida* spp. (except *C. glabrata*) with MICs at or below the epidemiological cutoff value (ECV) [9]. Only this 1 study has characterized the pharmacodynamics of posaconazole on *Candida* spp. Another highly bound antifungal azole, ravuconazole, was studied using a neutropenic mouse model. The 24-hour AUC/MIC ratio was best correlated with efficacy; however, a much higher value of 24-hour AUC/MIC was required for rosuvaconazole (96% bound) compared with fluconazole (10% bound). Adjustment for free drug AUC/MIC resulted in superimposed results for both drugs, indicating that activity is best gauged by unbound drug concentrations [10].

For *Aspergillus* spp., the target 24-hour AUC/MIC has been proposed to be 167, which corresponds to a half-maximal antifungal effect in a murine model of pulmonary aspergillosis. The effect measured was galactomannan index, which correlates with fungal burden [11]. Given the MIC of the infecting strain (0.125 mg/L), a total 24-hour AUC of 12 mg h/L would be sufficient to achieve the EC_{50}, and EC_{90} would be achieved with a 24-hour AUC of 30 mg h/L. Lewis et al. [12] published a provisional target 24-hour AUC/MIC of 100 and showed that this value is applicable to *A. fumigatus* and *Rhizopus oryzae* in a neutropenic murine model of invasive pulmonary aspergillus and mucormycosis. One report found that the serum galactomannan end point reached an asymptote with doses of posaconazole that provided a 24-hour AUC >30 mg h/L. Given that the infecting organism MIC was 0.125 mg/L, this equates to an AUC/MIC of >240, and if 50% of the maximal effect is desired, then the AUC target would be 94 mg h/L [13]. Given the mortality associated with invasive mold infections, using an end point of 80%–90% of the maximal effect seems reasonable. Determined using the Emax equation [11, 13], going from 50% of the maximal effect to 90% of the maximal effect requires a 2.5× dose (or AUC) increase. One study presented targets as free AUC/MIC, with end points of static (no kill or growth) and 1-log kill in a model of invasive pulmonary aspergillosis in neutropenic mice. The dose required for 1-log kill averaged 2.7 times the dose required for static effect. Free 24-hour AUC associated with 1-log kill averaged 2.07 (total AUC/MIC ~207). One-log kill in this model is slightly more than half the maximal effect [14].

The target 24-hour AUC/MIC for molds has ranged from 94 to >167 based on achieving 50% of the maximal effect. If 90% of the maximal effect is desired, the dose and target AUC/MIC would need to be increased by 2.5 (24-hour AUC/MIC of 235 to 417), These values have been presented in terms of total concentration. If the target range is converted to free 24-hour AUC/MIC, the range would be ~2.35 to 4.17, which is lower than the 16.9 noted for *Candida* spp. When using TDM for posaconazole, it is important to realize that total concentration is measured, but we are really interested in the free concentration. Pharmacodynamic targets have been presented both in terms of free and total concentrations in different publications. We recommend adjustment of any measured concentration for albumin concentration in patients with hypoalbuminemia as a means to properly interpret

the data and use of target exposures specified in terms of total concentration.

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