Oral Voriconazole Dose in Children: One Size Does Not Fit All

To the Editor—We read with interest the article by Neely et al [1], who reported their clinical pharmacokinetic and pharmacodynamic experience with voriconazole in pediatric patients. The article raises interesting issues about the pharmacologic rationale for the approved oral dose of voriconazole in children.

According to European recommendations, a fixed 200-mg oral dose should be given twice daily in all children 2–12 years old, irrespective of age or weight. As a consequence, children with a low weight would receive a higher dose on a milligram per kilogram basis than those with a high weight. This is bewildering given that voriconazole dosing on the basis of body weight is recommended for the intravenous route, because previous results showed that weight significantly influenced the pharmacokinetics of intravenous voriconazole in children [2].

Because the pediatric reference study [3] found that oral bioavailability in children was markedly reduced relative to that in adults (44.6% vs 96%), a possible justification for a fixed dose could lie in a correlation between bioavailability and age or weight. However, this study did not demonstrate any significant influence of weight or age on oral bioavailability, and no covariate was included in the final model. In fact, the fixed 200-mg dose of oral voriconazole was based on a single pharmacokinetic study that did not include a pharmacodynamic end point [3]. In the study by Neely and colleagues, an effect of age or weight on bioavailability was not observed either. The estimated oral bioavailability was higher (~80%), with no significant difference between children aged <12 years and those aged ≥12 years [1].

Neely and colleagues state that use of the fixed 200-mg dose may result in many concentrations considerably above or below a target trough of 1 μg/mL, and they question the tolerability of such a dose in the youngest children. The fixed dose also raises concerns about possible underdos- ing in the oldest children.

We examined 35 trough concentrations obtained from routine therapeutic drug monitoring in 21 hospitalized pediatric patients (age range, 7–18 years; mean age, 13.3 years) who received 200 mg of oral voriconazole twice daily between 2002 and 2008 (unpublished data from a multicenter French and Swiss database). Concentrations were measured at least 4 days after the dose was changed to 200 mg given twice daily or after therapy with this regimen was initiated. Trough concentration data were as follows: mean ± standard deviation, 1.66 ± 1.62 μg/mL; median, 1.29 μg/mL; range, <0.2 to 5.7 μg/mL. Seventeen levels (48.6%) were ⩾1 μg/mL and may be considered suboptimal [4, 5]. Two levels were >5.5 μg/mL. Although limited, these data suggest that the fixed 200-mg dose is likely to expose a significant proportion of children to suboptimal voriconazole concentrations.

There is increasing evidence for exposure-effect relationships in patients treated with voriconazole [1, 4, 6]. Because voriconazole pharmacokinetics is highly variable, we agree with Neely and colleagues’ support of the need for therapeutic drug monitoring in children. We also believe that optimal dosage regimens of voriconazole, based on pharmacokinetic and pharmacodynamic end points, are still to be developed.

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