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Comment on: Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and *Aspergillus fumigatus* in an *in vitro* pharmacokinetic/pharmacodynamic model

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Sir,

Siopi *et al.*[1] are to be congratulated on a superb paper with convincing results using a combination of resistant isolates and sophisticated pharmacodynamic modelling to demonstrate the strong relationship between voriconazole serum concentrations and outcome. Three different MIC determinations yielded similar although numerically slightly different results. The authors propose slightly different breakpoints for resistance using the EUCAST method and breakpoints can now be set for *Aspergillus fumigatus* for the other two methods.

The model assumed a short half-life for voriconazole, of only 6 h; in many patients (but not most children) the half-life is longer than this. The key pharmacodynamic parameter for response appears to be the $fAUC_{0-12}$ value (Figures 4 and 6 and Table 1), which is closely associated with the 50% effective concentration (EC_{50}). This indicates that in *A. fumigatus* it is time over MIC that matters, in contrast to much of the pharmacokinetic/pharmacodynamic work with *Candida* spp. and bacteria, in which peak or total AUC concentrations best correlated with outcome. From a modelling perspective it is often difficult to separate out the time over MIC from the AUC over MIC, and additional study groups are required with different dosing intervals but similar total drug exposures. By back calculating, Siopi *et al.*[1] probably can definitively confirm that it is indeed time over MIC rather than total AUC that matters for therapeutic success in *A. fumigatus* infections; or they may conclude that it is a combination of AUC *and* time over MIC that is important. They have not provided any data on the duration of the post-antifungal effect, which could be crucial to interpretation. The post-antifungal effect in *A. fumigatus* after voriconazole exposure appears to be time dependent.[2]

This matters a lot in clinical practice with a drug with huge interpersonal variation in metabolic rates and exposures.[3] In those patients with short half-lives of voriconazole, simply increasing the dose twice daily may accentuate exposure-related toxicity, but do little to improve the anti-*Aspergillus* effect of the drug. This may be particularly so in children, in which much larger doses are used (8–9 mg/kg, 12 hourly) than in adults. It may be that splitting the same daily paediatric dose (16–18 mg/kg/day) into three or four doses may yield better outcomes. If time over MIC is the most reliable parameter governing response, this also raises the prospect of superior efficacy using continuous infusion rather than intermittent dosing.

Can the authors confirm that their data confirm that it is time over MIC that is the key determinant of outcome in their model? Would they like to comment on the implications of this for the clinical use of voriconazole and future experimental modelling of *A. fumigatus* infection? Given the increasing reliance on pharmacodynamic modelling of new antimicrobials by drug developers and regulatory authorities,[4] confirmation of the optimal parameter to study voriconazole's effect has many implications for comparative work.

Transparency declarations

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