Comment on

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Comment on: Utility of voriconazole therapeutic drug monitoring: a meta-analysis

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Sir,

With great interest we have read the recently published paper of Luong *et al.*[1] In this systematic review an exposure–response relationship was observed between voriconazole serum concentrations and clinical success. Supratherapeutic voriconazole serum concentrations were associated with the development of toxicity. However, in clinical practice highly variable voriconazole concentrations are commonly observed when performing therapeutic drug monitoring (TDM) and it remains difficult to interpret these highly variable concentrations.[2] In addition, the non-linear pharmacokinetics of voriconazole complicates correct dosing of this drug.[3]

Voriconazole is extensively metabolized to its main metabolite, voriconazole-*N*-oxide, by several CYP450 iso-enzymes.[4] For better understanding of the variability in voriconazole serum concentration, the metabolite of voriconazole, which is not routinely measured, can give clarification. Extensive metabolizers seem to have a metabolic ratio (voriconazole-*N*-oxide concentration divided by voriconazole concentration) of ∼0.85.[5] Altered metabolism caused by several clinical conditions, as summarized in Table 1, can be easily detected by determining voriconazole and voriconazole-*N*-oxide concentrations[6] and can be helpful to guide dosing with voriconazole.

If a low voriconazole concentration is observed, non-compliance can be distinguished from a CYP2C19 ultra-rapid metabolizer by measuring the metabolite of voriconazole. A very low voriconazole-*N*-oxide concentration is expected in non-compliance,[7] while high metabolite concentrations point to ultra-rapid metabolism.[5]

Drug–drug interactions seem unavoidable in clinical practice.[2] Drugs that induce CYP450 iso-enzymes can result in low voriconazole concentrations, while voriconazole-*N*-oxide concentrations are expected to be high. This was indeed observed for rifampicin, a CYP450-inducing drug.[8]

Liver toxicity is commonly seen as an adverse event in patients treated with voriconazole.[3] Since voriconazole is extensively metabolized in the liver, hepatic dysfunction can result in reduced metabolism of voriconazole and hence higher voriconazole concentrations.[9] If a patient develops hepatic abnormalities during treatment with voriconazole, early detection of a reduced metabolism can be observed as a decreased metabolic ratio compared with previous measurements. If this is observed, the voriconazole dose may be adjusted in a timely manner and thus prevent toxic voriconazole concentrations.

Severe inflammation also seems to reduce voriconazole metabolism.[10] Prior to toxic voriconazole concentrations, the metabolic ratio will be decreased compared with previous measurements and dose adjustments can be made to prevent toxic voriconazole concentrations. In addition, the metabolic ratio will increase again when inflammation subsides and low voriconazole concentrations can be avoided by adjustment of the voriconazole dose.

In conclusion, voriconazole-*N*-oxide concentrations can provide information on the metabolic capacity of the liver and are therefore helpful to optimize voriconazole treatment.

Table 1. Voriconazole/voriconazole-*N*-oxide concentrations in relation to typical clinical situations

	Low voriconazole	High voriconazole
Low voriconazole-*N*-oxide	non-compliance malabsorption	poor metabolizer/ intermediate metabolizer hepatic impairment DDI: CYP450 inhibitor inflammation
High voriconazole-*N*-oxide	DDI: CYP450 inducer ultra-rapid metabolizer	overdose

DDI, drug–drug interaction.

Transparency declarations

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Comment on: Pristinamycin in the treatment of MSSA bone and joint infection

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Sir,

We read with interest the outcomes reported by Valour *et al.*[1] when using pristinamycin therapeutically for MSSA bone and joint infections. Pristinamycin is a synergistic antimicrobial combination of streptogramin A and B that remains unlicensed in the UK. Valour *et al.*[1] surmise that the three treatment failures described might have been predicted by the MLS_B resistance phenotype—this is not supported by the evidence. Cocito *et al.*[2] reported that the MLS_B phenotype in solitude is not sufficient to cause pristinamycin resistance; instead, a mixture of resistance mechanisms (e.g. MLS_B in conjunction with enzymatic degradation) is required to inactivate both group A and group B streptogramins and achieve high-level resistance to pristinamycin. In support of this, we found that despite 11 of 16 isolates of *Staphylococcus* spp. (15 CoNS and 1 *Staphylococcus aureus*) being resistant to erythromycin (which is indicative of the MLS_B resistance phenotype), all 16 isolates remained susceptible to pristinamycin (as determined by the Kirby–Bauer disc diffusion method against the surrogate marker streptogramin quinupristin/dalfopristin).

Moreover, clinical studies have reported good outcomes with pristinamycin treatment in erythromycin-resistant staphylococcal infections. Ng and Gosbell[3] used pristinamycin for MRSA osteoarticular infections: of 18 evaluated cases, 13 were cured, 3 were chronically suppressed and only 2 failed therapy. Of these, all but one were macrolide- and lincosamide-resistant MRSA, inferring the MLS_B phenotype. Dancer *et al.*[4] reported an 87% success rate in treating predominantly skin and soft tissue MRSA infections with pristinamycin, despite 55% of isolates being either resistant to lincosamides, or having inducible resistance, suggestive of MLS_B. Likewise, of the 26 patients with predominantly osteoarticular infections treated with pristinamycin by Reid *et al.*[5] caused by 31 strains of *Staphylococcus* spp. (9 MRSA, 5 MSSA, 13 methicillin-resistant CoNS and 4 methicillin-susceptible CoNS), 8 were successfully cured and 15 suppressed. Three patients that 'failed' therapy were due to drug intolerance, rather than uncontrolled infection. Valour *et al.*[1] might consider whether the three patients with unfavourable outcomes on pristinamycin therapy who were culture-positive with MSSA isolates harbouring the MLS_B resistance phenotype were related to the suboptimal source control rather than antimicrobial treatment failure.

The *in vitro* MLS_B phenotype of macrolide and lincosamide resistance does not seem to be associated with pristinamycin resistance.[3] Likewise, clinical studies report good outcomes with pristinamycin use in presumed MLS_B staphylococcal infections. Rather than discourage the use of pristinamycin in the presence of a likely MLS_B resistance phenotype, we would welcome further prospective randomized controlled trials to assess further the efficacy of this antimicrobial for treating staphylococcal bone and joint infections.

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Transparency declarations

None to declare.

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