Clinical pharmacology and therapeutic drug monitoring of voriconazole

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

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To the editor

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, noncompliance 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 noncompliance [7], while high metabolite concentrations point to ultrarapid metabolism [8].

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

<table>
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<tr>
<th>Table 1. Voriconazole/voriconazole-N-oxide concentrations in relation to typical clinical situations.</th>
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<td>Low voriconazole-N-oxide</td>
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<td>Low voriconazole-N-oxide</td>
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DDI: drug-drug interaction
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.
References


