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Published in:
British Journal of Clinical Pharmacology

DOI:
10.1111/bcp.13151

Publication date:
2017

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 678–680 678

LETTER TO THE EDITOR

The effect of inflammation on voriconazole trough concentrations in children

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Received 18 August 2016; **Revised** 1 October 2016; **Accepted** 5 October 2016

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Table of Links

TARGETS
Enzymes [2]
CYP2C19
CYP2C9
CYP3A4

This Table lists key protein targets in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Voriconazole is a first-line antifungal agent for the treatment of invasive aspergillosis. The major metabolic pathway is by cytochrome P450 (CYP) 2C19, 3 A4 and 2C9. Pharmacokinetics of voriconazole appear to be near linear in children <12 years and nonlinear in children ≥12 years and adults [3].

Therapeutic drug monitoring (TDM) of voriconazole has been recommended because of the large variability in drug exposure and relative narrow therapeutic window [4].

Recently, in adults, it was shown that severe inflammation, reflected by C-reactive protein (CRP) value, was associated with elevated voriconazole trough concentrations [5–8]. This was explained by inflammatory stimuli leading to downregulation of CYP isoenzymes, resulting in reduced metabolism of voriconazole [9].

The aim of this study was to investigate if routinely measured voriconazole concentrations in children were also associated with inflammation, reflected by CRP value [6, 7].

In this retrospective study, paediatric patients treated with voriconazole between January 2005 and January 2015 at the University Medical Centre, Groningen, the Netherlands, were eligible for inclusion. Patients with a steady-state voriconazole trough concentration and a CRP value measured on the same day were included. Exclusion criteria were concomitant use of CYP inducers/inhibitors and relatively low (<7.5 mg/kg/day) or high (>12.5 mg/kg/day) voriconazole dosage to avoid bias due to extreme dosing. Only the first eligible data set was selected from each patient to ensure that each patient contributed equally to the final data set.

TDM of voriconazole is routinely performed for all children in our hospital using a validated assay (within-run coefficient of variation 1.9–2.3%, between-run coefficient of variation 0.0–3.1%, limit of quantification 0.1 mg/l) [10]. This assay is routinely evaluated by international proficiency testing [11].

Medical data were collected from the medical chart. This study was evaluated by the local ethics committee and the need for written informed consent was waived due to its retrospective nature (IRB-2013-491).

Patients were divided in two groups based on their age [3]: group 1 (<12 years) and group 2 (≥12 years). To investigate

DOI:10.1111/bcp.13151

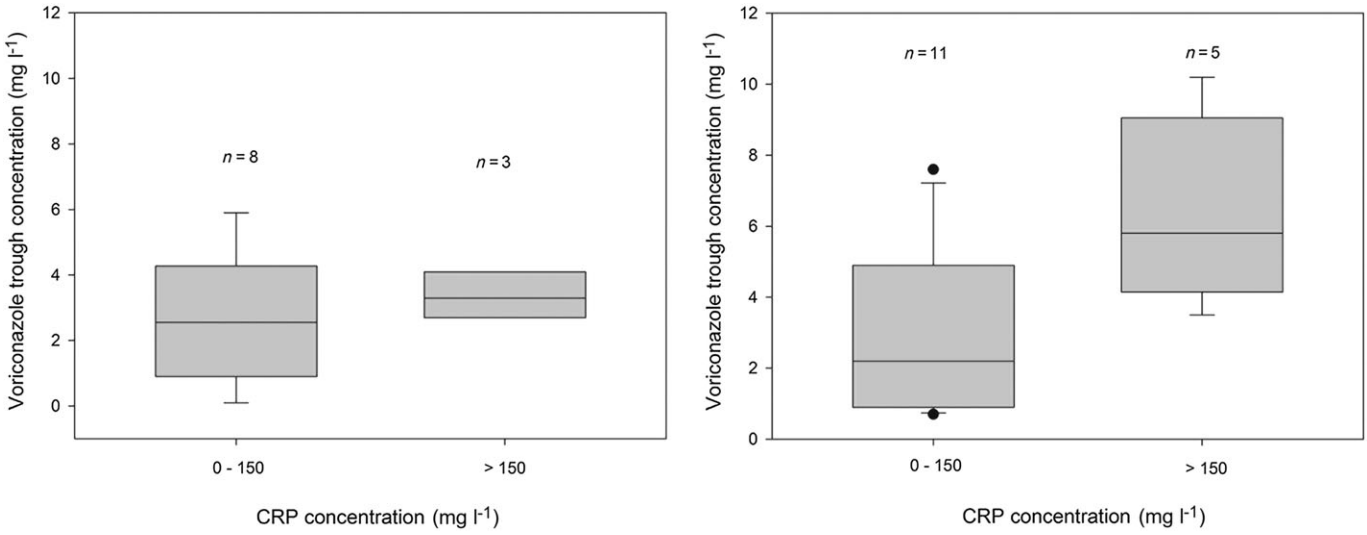

Figure 1

Difference in voriconazole trough concentration in relation to C-reactive protein (CRP_. Box (median and 25th and 75th percentiles) and whisker (5th and 95th percentiles) plots of voriconazole trough concentrations in children aged <12 years (left panel) and children aged ≥12 years (right panel) with no to moderate inflammation and with severe inflammation. For children aged ≥12 years a significant difference in voriconazole trough concentration was found between children with low to moderately high CRP concentration and high CRP concentration (P = 0.027)

the influence of inflammation on voriconazole trough concentrations a Mann–Whitney U test and a box and whisker plot were performed with CRP values categorized in low to moderately high (0–150 mg/l) and high (>150 mg/l) concentrations [12].

Statistical tests were performed using SPSS, version 20.0 (IBM Corporation, Armonk, New York).

Twenty-seven paediatric patients were included in this study, of which 11 children in group 1 (median age 4 years, interquartile range [IQR]: 2–6 years) and 16 children in group 2 (median age 15 years, IQR: 13–17 years). Patient characteristics, including underlying disease, voriconazole trough concentration and CRP value were similar between both groups.

In Group 1, no significant difference (P = 0.682) in voriconazole trough concentration was observed between children with CRP values 0–150 mg/l (2.6 mg/l, IQR: 0.9–4.3 mg/l; n = 8) and children with CRP values >150 mg/l (3.3 mg/l, IQR: 2.7–3.3 mg/l; n = 3). In Group 2, a significantly higher (P = 0.027) voriconazole trough concentration was found in children with CRP values >150 mg/l (5.8, IQR: 4.2–9.1 mg/l; n = 5) compared to children with CRP values 0–150 mg/l (2.2 mg/l, IQR: 0.9–4.9 mg/l; n = 11). See Figure 1.

All groups received similar voriconazole doses based on mg/kg body weight (Group 1: P = 0.470 and Group 2: P = 0.817).

This retrospective analysis showed that inflammation, reflected by CRP value, seems associated with higher voriconazole trough concentrations in children ≥12 years; however, the effect is less distinct compared to adult patients [5]. For children <12 years no effect of inflammation on voriconazole trough concentrations was observed.

Dote and colleagues [8] showed that coadministration of glucocorticoids an inflammation, reflected by CRP and hypoalbuminaemia, were associated with voriconazole clearance. Due to limited use of glucocorticoids and limited determination of albumin in our population, we were not able to investigate these other covariables in our study.

Spriet and colleagues [4] were not able to demonstrate an association between voriconazole trough concentrations and CRP in children. However, their results should be interpreted prudently, because of the smaller patient cohort (n = 10). Furthermore, no distinction was made between younger and older children [4].

A potential explanation could be the difference in liver microsomes, CYP2C19, CYP3A4 and flavin-containing mono-oxygenase 3 (FMO3), between children aged 2–10 years and adults. The main metabolite of voriconazole, voriconazole N-oxide, was formed three-fold quicker in liver microsomes from children. It thus seems that FMO3 and CY2C19 have a higher metabolic activity in young children as compared to adults, since expression is not significantly different in both populations [13]. As the metabolic activity of CYP2C19 is probably higher in younger children, a decrease in expression due to inflammation will be less likely to have impact on voriconazole metabolism.

The main limitation of our study is its retrospective nature. However, we used strict inclusion criteria to avoid bias by other factors that could have a significant impact on voriconazole trough concentrations, such as non-steady-state concentrations and extreme dosages.

In conclusion, inflammation as reflected by CRP values, is associated with higher voriconazole trough concentrations in children ≥12 years but not in children <12 years. The CRP value may be helpful in TDM of voriconazole during severe infection.

Competing Interests

There are no competing interests to declare.

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