

University of Groningen

## The effect of inflammation on voriconazole trough concentrations in children

ter Avest, Mendy; Veringa, Anette; van den Heuvel, Edwin R.; Kosterink, Jos; Scholvinck, Elisabeth H.; Tissing, Wim J. E.; Alffenaar, Jan-Willem C.

*Published in:*  
British Journal of Clinical Pharmacology

*DOI:*  
[10.1111/bcp.13151](https://doi.org/10.1111/bcp.13151)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2017

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

ter Avest, M., Veringa, A., van den Heuvel, E. R., Kosterink, J., Scholvinck, E. H., Tissing, W. J. E., & Alffenaar, J-W. C. (2017). The effect of inflammation on voriconazole trough concentrations in children. *British Journal of Clinical Pharmacology*, 83(3), 678-680. <https://doi.org/10.1111/bcp.13151>

### **Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### **Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

## LETTER TO THE EDITOR

## The effect of inflammation on voriconazole trough concentrations in children

**Correspondence** Jan-Willem C. Alffenaar, PharmD, PhD, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, PO Box 30.001, 9700 RB Groningen, the Netherlands. Tel.: +31 5 0361 4070; Fax: +31 5 0361 4087; E-mail: j.w.c.alfenaar@umcg.nl

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

Mendy ter Avest<sup>1</sup>, Anette Veringa<sup>1</sup>, Edwin R. van den Heuvel<sup>2</sup>, Jos G. W. Kosterink<sup>1,3</sup>, Elisabeth H. Schölvinck<sup>4</sup>, Wim J. E. Tissing<sup>5</sup> and Jan-Willem C. Alffenaar<sup>1</sup>

<sup>1</sup>University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, the Netherlands,

<sup>2</sup>Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, the Netherlands, <sup>3</sup>Department of Pharmacy,

Section Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, the Netherlands, <sup>4</sup>University of Groningen, University

Medical Center Groningen, Department of Pediatrics (Infection/Immunology), Groningen, the Netherlands, and <sup>5</sup>University of Groningen, University

Medical Center Groningen, Department of Pediatrics (Oncology/Hematology), Groningen, the Netherlands

## Table of Links

TARGETS
<b>Enzymes [2]</b>
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, 3A4 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].

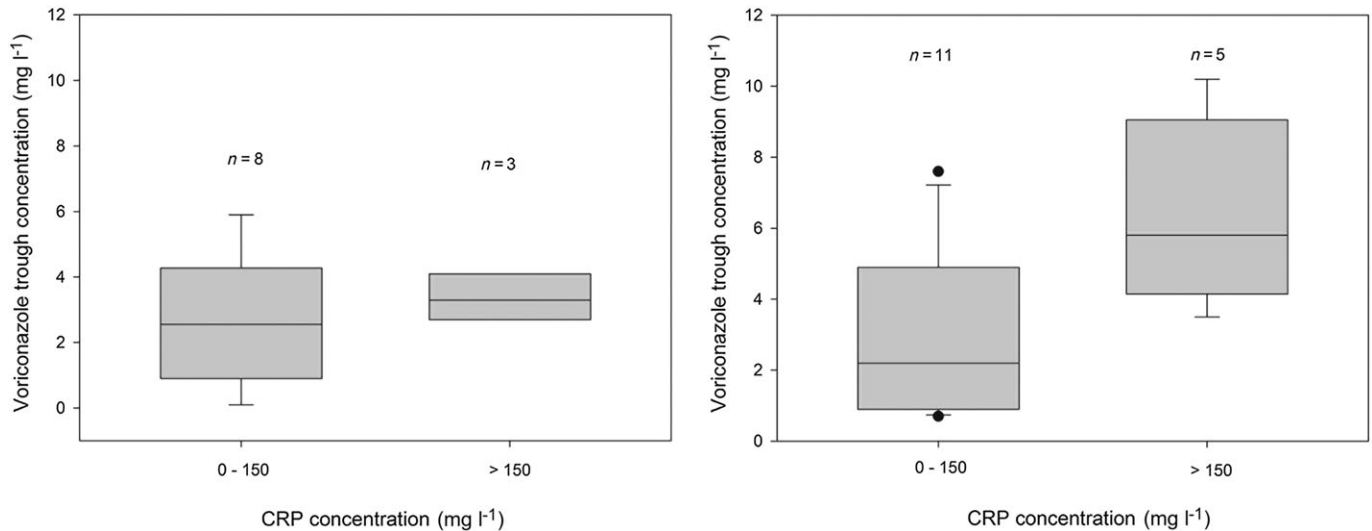
In this retrospective study, paediatric patients treated with voriconazole between January 2005 and January 2015 at the University Medical Centre, Groningen, the Netherlands, were

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



**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  $\geq 12$  years (right panel) with no to moderate inflammation and with severe inflammation. For children aged  $\geq 12$  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  $\geq 12$  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  $\geq 12$  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.

---

## References

- 1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al.* The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. *Nucl Acids Res* 2016; 44: D1054–D1068.
- 2 Alexander SPH, Fabbro D, Kelly E, Peters JA, Benson HE, Faccenda E, *et al.* The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. *Br J Pharmacol* 2015; 172: 6024–109.
- 3 Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother* 2009; 53: 935–44.
- 4 Spriet I, Cosaert K, Renard M, Uyttendroeck A, Meyts I, Proesmans M, *et al.* Voriconazole plasma levels in children are highly variable. *Eur J Clin Microbiol Infect Dis* 2011; 30: 283–7.
- 5 van Wanrooy MJ, Span LF, Rodgers MG, van den Heuvel ER, Uges DR, van der Werf TS, *et al.* Inflammation is associated with voriconazole trough concentrations. *Antimicrob Agents Chemother* 2014; 58: 7098–101.
- 6 Encalada Ventura MA, Span LF, van den Heuvel ER, Groothuis GM, Alffenaar JW. Influence of inflammation on voriconazole metabolism. *Antimicrob Agents Chemother* 2015; 59: 2942–3.
- 7 Encalada Ventura MA, van Wanrooy MJ, Span LF, Rodgers MG, van den Heuvel ER, Uges DR, *et al.* Longitudinal analysis of the effect of inflammation on voriconazole trough concentrations. *Antimicrob Agents Chemother* 2016; 60: 2727–31.
- 8 Dote S, Sawai M, Nozaki A, Naruhashi K, Kobayashi Y, Nakanishi H. A retrospective analysis of patient-specific factors on voriconazole clearance. *J Pharm Health Care Sci* 2016; 2: 10. doi: 10.1186/s40780-016-0044-9. eCollection 2016.
- 9 Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. *Clin Pharmacol Ther* 2009; 85: 434–8.
- 10 Alffenaar JW, Wessels AM, van Hateren K, Greijdanus B, Kosterink JG, Uges DR. Method for therapeutic drug monitoring of azole antifungal drugs in human serum using LC/MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010; 878: 39–44.
- 11 Lempers VJ, Alffenaar JW, Touw DJ, Burger DM, Uges DR, Aarnoutse RE, *et al.* Five year results of an international proficiency testing programme for measurement of antifungal drug concentrations. *J Antimicrob Chemother* 2014; 69: 2988–94.
- 12 Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. *Adv Neonatal Care* 2003; 3: 3–13.
- 13 Yanni SB, Annaert PP, Augustijns P, Ibrahim JG, Benjamin DK Jr, Thakker DR. *In vitro* hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. *Drug Metab Dispos* 2010; 38: 25–31.