Effect of voriconazole on the pharmacokinetics and pharmacodynamics of zolpidem

Journal:	*British Journal of Clinical Pharmacology*
Manuscript ID:	draft
Manuscript Type:	Main Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Saari, Teijo; University of Turku, Anaesthesiology and Intensive Care Laine, Kari; University of Turku, Pharmacology and Clinical Pharmacology Leino, Kari; University of Turku, Anaesthesiology and Intensive Care Valtonen, Mika; University of Turku, Anaesthesiology and Intensive Care Neuvonen, Pertti; Dept of Clinical Pharmacology, Helsinki University Hospital, Univ. Helsinki Olkkola, Klaus; University of Turku, Anaesthesiology and Intensive Care
Key Words:	voriconazole, zolpidem, CYP3A4, cytochrome P450, drug interaction

Effect of voriconazole on the pharmacokinetics and pharmacodynamics of zolpidem

Teijo I. Saari, Kari Laine, Kari Leino, Mika Valtonen, Pertti J. Neuvonen & Klaus T. Olkkola

Department of Anaesthesiology and Intensive Care and the Department of Pharmacology and Clinical Pharmacology, University of Turku, Turku, Finland, and the Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

Correspondence: Teijo I. Saari, MD, Department of Anaesthesiology and Intensive Care, University of Turku, P.O. Box 52, Kiinamyllynkatu 4-8, 20520 Turku, Finland.

Tel. +358-2-313 0596 (work)

Fax +358-2-313 3960

E-mail: teijo.saari@tyks.fi

Keywords: voriconazole, zolpidem, CYP3A4, cytochrome P450, drug interaction

Short title: Interaction of voriconazole with zolpidem

18 pages, 3 figures, 1 table

Summary

Aims

To assess the effect of the antimycotic voriconazole on the pharmacokinetics and pharmacodynamics of oral zolpidem, a short-acting imidazopyridine hypnotic.

Methods

In an open, randomised crossover study with two phases, ten healthy volunteers were given either no pre-treatment (control phase) or voriconazole (voriconazole phase) orally 400 mg b.i.d. on the first day and 200 mg b.i.d. on the second day. A single oral dose of 10 mg zolpidem was given 1 hour after the last dose of voriconazole, and during the control phase. Plasma concentrations of zolpidem were determined for 24 hours and pharmacodynamic variables measured for 12 hours.

Results

Voriconazole increased the peak plasma concentration of zolpidem by 20% from 112 to 135 ng · ml^{-1} ($P < 0.05$; 95% CI of the difference 0.32 to 45.3) and the total area under the plasma zolpidem concentration-time curve by 41% from 528 to 743 ng · ml^{-1} · h ($P < 0.001$; 95% CI of the difference 119 to 310). The time to the peak plasma concentration of oral zolpidem was unchanged by voriconazole administration but the elimination half-life was prolonged from 3.2 to 4.1 hours ($P < 0.01$; 95% CI of the difference 0.27, 1.45). The pharmacodynamics of zolpidem were unaffected by voriconazole.

Conclusion

Voriconazole increased moderately the exposure to the orally administered zolpidem in healthy young volunteers but no pharmacodynamic changes were observed. Therefore, zolpidem can be used in normal doses together with voriconazole.

Introduction

Zolpidem is an imidazopyridine agent that is widely used for the treatment of insomnia. It is rapidly absorbed from the gastrointestinal tract and it has an oral bioavailability of approximately 70%. It displays linear pharmacokinetics at clinically used doses [1, 2]. In healthy volunteers zolpidem has an elimination half-life of 2.0 to 2.2 hours [3], but plasma concentrations of zolpidem are increased and elimination delayed in the elderly and in patients with liver or kidney disease [1]. Zolpidem is extensively metabolised in humans, predominantly by cytochrome P450 (CYP) 3A4, CYP2C9 and CYP1A2 [4].

Voriconazole is a novel triazole antifungal agent used for the treatment of severe fungal infections including *Aspergillus* and *Candida* species [5]. It is available both as oral and intravenous formulations. Voriconazole is rapidly and almost completely absorbed through the oral route and it has an extensive tissue distribution [6, 7]. Voriconazole undergoes extensive oxidative metabolism involving the cytochrome P450 enzyme isoforms CYP2C9, CYP2C19 and to a lesser extent CYP3A4 [8]. Voriconazole has been shown to inhibit several CYP enzymes, like 2C9 (e.g. warfarin), 2C19 (e.g. omeprazole) and 3A4 (e.g. sirolimus) [9, 10, 11]. We have previously shown that voriconazole has a strong pharmacokinetic interaction with both orally and intravenously administered midazolam [12]. After oral administration of midazolam, voriconazole increased the area under the plasma concentration-time curve (AUC) more than 10-fold.

The participation of multiple CYP-enzymes in the metabolism of zolpidem has implications for its susceptibility to possible metabolic drug interactions. Since zolpidem is only partially metabolised by CYP3A4, the inhibitors of CYP3A4 appear to have a smaller effect on the pharmacokinetics of zolpidem as compared to that of e.g. midazolam, which is metabolised almost completely by CYP3A4. In an earlier study, ketoconazole reduced the apparent oral clearance of zolpidem by 64 % and prolonged the elimination half-life by 30 % [13]. However, fluconazole and itraconazole had

only a minor effect on the pharmacokinetics of zolpidem and failed to enhance its sedative effects [13, 14]. On the other hand, ketoconazole, fluconazole and itraconazole all strongly affect the pharmacokinetics of midazolam [15, 16]. Because voriconazole inhibits multiple CYP-enzymes, which are involved in the metabolism of zolpidem, we found it important to study the possible effect of voriconazole on the pharmacokinetics of oral zolpidem.

Methods

The study protocol was approved by the Ethics committee of the Hospital District of Southwest Finland, as well as by the National Agency of Medicines, Finland. Written informed consent was obtained from all subjects prior to entry.

Subjects

Ten healthy volunteers, all men (age range 19 to 29 years; weight range 67 to 100 kg) were recruited from the students studying medicine at the University of Turku. Before entering the study, the volunteers were ascertained to be in good health by medical history, clinical examination and standard haematological and blood chemistry tests. None of the volunteers was receiving any continuous medication or was a smoker.

Study design

We used an open, randomised, two-phase crossover study design at intervals of one week. Before the administration of zolpidem, the volunteers were given in a randomised order either no pre-treatment (control phase) or oral voriconazole (voriconazole phase) for two days. The dose of voriconazole (Vfend tablet, Pfizer, Sandwich, Kent, UK) was 400 mg every 12 hours for one day and then 200 mg every 12 hours for one additional day. The last dose of voriconazole was given at 08:00 h with 150 ml of water by the investigators in the research facility, and those volunteers not receiving any pre-treatment were given 150 ml of water. One hour after the last dose of

voriconazole or the water intake all subjects received 10 mg of oral zolpidem (Stilnoct 10 mg tablet, Sanofi-Synthelabo, Bromma, Sweden) with 150 ml of water. The volunteers had been instructed to take the pre-treatment at home with meal and the adherence with the drug dosing schedule was assessed by using mobile phone short message service. The volunteers fasted for 12 hours before the administration of zolpidem. They were given standard meals 4 hours and 8 hours after zolpidem administration. The drinking of grapefruit juice, alcohol, coffee, tea or cola on the test days or for 2 days prior to the study was forbidden.

Blood sampling and drug analysis

On the test days, a forearm vein of each subject was cannulated and timed blood samples were drawn into ethylenediaminetetraacetic acid tubes immediately before the last voriconazole dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after zolpidem administration. Plasma was separated within 30 minutes and stored at -40 ºC until analysis.

Concentrations of zolpidem were determined after HPLC-separation with mass spectrometry and zopiclone was used as an internal standard [17]. The sensitivity of the method was 0.25 ng/ml and the interday coefficient of variation (CV) for zolpidem was 8.3%, 9.3% and 13.7% at a mean value of 1 ng/ml, 10 ng/ml and 100 ng/ml, respectively (n = 12 at each concentration). Concentrations of voriconazole were determined by HPLC [18, 19]. The quantitation limit was 20 ng/ml and the CV was 3.7%, 0.7% and 0.9% at a mean value of 51.1, 977 and 10047 ng/ml, respectively (n = 3 at each concentration).

Pharmacokinetic analysis

The peak plasma concentrations (C_{max}) and corresponding peak plasma concentration times (t_{max}) were observed directly from the data. The areas under the zolpidem plasma concentration-time curves AUC(0–∞) were estimated by means of the trapezoidal rule with extrapolation to infinity.

We used the linear trapezoidal rule while successive concentration values were increasing, and the logarithmic trapezoidal rule when successive concentration values were decreasing after the peak concentration value. For each subject, the terminal log-linear phase of the plasma zolpidem concentration-time curve was identified visually and the elimination rate constant (k_e) was determined by regression analysis. The elimination half-life ($t_{½}$) was then calculated from the equation: $t_{½} = \ln 2 / k_e$. The pharmacokinetic data was analysed with the use of pharmacokinetic program WinNonlin (version 3.0, Pharsight Corporation, California, USA).

Phamacodynamic measurements

The effects of zolpidem were assessed with three visual analog scales (VAS) and the Maddox wing test at the time of blood sampling up to 12 hours after zolpidem administration. Subjective effects (alert to drowsy, no drug effect to very strong drug effect, very good performance to very poor performance) were recorded on the 100-mm horizontal visual analog scales [20]. The Maddox wing test was used to measure the effect of zolpidem on the coordination of the extraocular muscles, and the result was given in diopters [21]. For each pharmacodynamic variable, the area under the response-time curve was determined by trapezoidal rule for 12 hours.

Statistical analysis

Student's paired t-test was used and differences were regarded significant if $P < 0.05$. We calculated also the 95% confidence intervals for the differences between the control and voriconazole phases. The possible relationship between the ratio of the AUC(0–∞) of zolpidem during the voriconazole phase to that during the control phase and the plasma concentration of voriconazole before the administration of last voriconazole dose (C_{trough}) was determined by Pearson's product-moment correlation coefficient. The results are expressed as mean values ± SD, except in illustrations in which, for clarity, mean values ± SEM are given. All data were analysed

with use of the statistical program SPSS for Windows, version 12.0 (SPSS Inc, Chicago, Illinois, USA).

Results

Voriconazole increased the mean C_{max} and AUC(0–∞) of oral zolpidem by 20% from 112 to 135 ng · ml^{-1} ($P < 0.05$; 95% CI of the difference 0.32 to 45.3) and 41% from 528 to 743 ng · ml^{-1} · h ($P < 0.001$; 95% CI of the difference 119 to 310), respectively (Fig. 1, Table 1). The AUC(0–∞) of oral zolpidem was increased in all subjects by voriconazole, the greatest increase being 188%. The $t_{½}$ of zolpidem was prolonged from 3.2 to 4.1 hours ($P < 0.01$; 95% confidence interval of the difference 0.27, 1.45). The values for t_{max} did not change (Fig. 2, Table 1).

Although voriconazole appeared to increase drowsiness in the immediate period following the administration of zolpidem, no statistically significant differences between the phases were seen in any of the pharmacodynamic variables (Fig. 3).

The mean value of C_{trough} of voriconazole was 596 ng/ml (range 249 to 1517) during the voriconazole phase. During the voriconazole phase, each of the volunteers had measurable voriconazole concentrations before the last dose of voriconazole. In the control phase, the plasma voriconazole concentrations were undetectable on the test days. There was no correlation between the ratio of the AUC(0–∞) of zolpidem during the voriconazole phase to that during the control phase and the C_{trough} of voriconazole ($r = -0.173$; $p = 0.63$).

All volunteers completed the study but visual adverse events were reported by all ten volunteers. Transient altered perception of light, chromatopsia and photophobia were experienced shortly after

taking voriconazole. One subject experienced transient headache after starting the pre-treatment with voriconazole. No other adverse effects were reported.

Discussion

Co-administration of voriconazole moderately affected the pharmacokinetics of oral zolpidem by increasing its C_{max} by 20% and AUC(0–∞) by 40%. Although voriconazole appeared to increase the sedative effects of zolpidem transiently in one of the pharmacodynamic variables, no statistically significant differences were seen.

The magnitude of the interaction between an orally administered substrate and an inhibitor of a CYP enzyme depends strongly on the pharmacokinetic properties of the substrate. We have previously shown that voriconazole increases the area under the oral midazolam plasma concentration-time curve more than 10-fold [12]. This occurrence is plausible because oral midazolam undergoes significant first-pass metabolism. Thus, the inhibition of first-pass metabolism causes a considerable increase of the midazolam concentrations. Another factor contributing to the magnitude of the interaction is the metabolic pattern of the substrate. The first-pass metabolism and elimination of midazolam are almost completely dependent on CYP3A4. The oral bioavailability of zolpidem is higher (70-80%) than that of midazolam (30%) and CYP3A4 is not the only cytochromal enzyme responsible for its elimination. Studies with human liver microsomes have shown that CYP3A4, CYP2C9 and CYP1A2 are likely to make a significant contribution to the elimination of zolpidem [2, 4]. Accordingly, an inhibited metabolic pathway of zolpidem may be compensated to some degree by another pathway [14].

Earlier studies with other azole-antifungals have shown that their interactions with zolpidem are clearly weaker than those with midazolam or triazolam [13-16, 22]. Both ketoconazole, itraconazole and voriconazole have caused at least a 10-fold increase in the mean AUC(0–∞) of oral midazolam

and increased greatly also the sedative effects [16, 12]. Correspondingly, itraconazole has increased the AUC(0–∞) of oral triazolam 27-fold [22]. However, ketoconazole, fluconazole and itraconazole do not increase the mean AUC(0–∞) of zolpidem more than 1.7-, 1.3- and 1.3-fold, respectively [13, 14]. In the present study, we observed a 1.4-fold increase of the zolpidem AUC(0–∞) by voriconazole.

Despite a statistically significant increase in the AUC(0–∞) and prolongation of the $t_{½}$ of zolpidem by voriconazole, the increased concentrations of zolpidem were not associated with increased psychomotor effects. This is understandable because of the log-linear relationship of the concentration versus response curves. Small differences in drug concentrations do not result in changes of drug effects. However, because no double-blind study design was used, the pharmacodynamic findings must be interpreted cautiously. There was a high rate of reversible visual disturbances following the administration of voriconazole. Since the volunteers were medical students who were well informed on the adverse-effects of voriconazole, even a double-blind study design would hardly have increased the validity of the pharmacodynamic results.

Because voriconazole caused only a minor increase in zolpidem concentrations after its oral administration, and because no pharmacodynamic changes were observed, our results suggest that zolpidem can most likely be used in normal doses in patients receiving voriconazole. Our study was done in young healthy male volunteers and the results cannot be extrapolated uncritically to elderly patients or patients having renal or liver dysfunction. It was shown recently in the elderly, that the clearance of zolpidem is substantially diminished, particularly in men. This may affect the clinical significance of the interaction between zolpidem and voriconazole [23]. There is also other evidence that gender may have an effect on zolpidem clearance. Women at all ages may have lower

oral clearance of zolpidem than men, which may change also the interpretation of the clinical significance of the voriconazole-zolpidem interaction [24,25].

In conclusion, voriconazole increased slightly the concentrations of orally administered zolpidem. Because no pharmacodynamic changes were observed, zolpidem can most likely be used in normal doses together with voriconazole. Further studies are needed to investigate whether our results can be extrapolated to patients having severe system diseases like renal or liver dysfunction.

The study was supported by the EVO grants #13821 and # 13390 of the Hospital District of Southwest Finland and the Sigrid Juselius Foundation

We thank Mrs. Elina Kahra, Mrs. Eija Mäkinen-Pulli and Mr. Jouko Laitila for skilful determinations of the drug plasma concentrations and technical assistance.

There are no conflicts of interest.

References

1. Langtry HD, Benfield P. Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1999; 40: 291-313.
2. Salva P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet 1995; 29: 142-53.
3. Greenblatt DJ, Harmatz JS, von Moltke LL, Ehrenberg BL, Harrel L, Corbett K, Counihan M, Graf JA, Darwish M, Mertzanis P, Martin PT, Cevallos WH, Shader RI. Comparative kinetics and dynamics of zaleplon, zolpidem and placebo. Clin Pharmacol Ther 1998; 64: 553-61.
4. Von Moltke LL, Greenblatt DJ, Granda BW, Duan SX, Grassi JM, Venkatakrishnan K, Harmatz JS, Shader RI. Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and in vivo correlations. Br J Clin Pharmacol 1999; 48: 89-97.
5. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents. Pharmacokinetics, safety and efficacy. Drugs 2004; 64: 1997-2020.
6. Purkins L, Wood N, Greenhalgh K, Eve MD, Oliver SD, Nichols D. The pharmacokinetics and safety of intravenous voriconazole – a novel wide-spectrum antifungal agent. Br J Clin Pharmacol 2003; 56: 2-9.
7. Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide spectrum triazole: oral pharmacokinetics and safety. Br J Clin Pharmacol 2003; 56: 10-6.
8. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metabol Dispos 2003; 31: 540-7.
9. Purkins L, Wood N, Kleinermans D, Nichols D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. Br J Clin Pharmacol 2003; 56: 24-9.
10. Wood N, Tan K, Purkins L, Layton G, Hamlin J, Kleinermans D, Nichols D. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. Br J Clin Pharmacol 2003; 56: 56-61.

11. Sádaba B, Campanero MA, Quetglas EG, Azanza JR. Clinical relevance of sirolimus drug interactions in transplant patients. Trans Proc 2004; 36: 3226-8.
12. Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Clin Pharmacol Ther 2006; in press.
13. Greenblatt DJ, von Moltke LL, Harmatz JS, Mertzanis P, Graf JA, Durol AL, Counihan M, Roth-Schechter B, Shader RI. Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. Clin Pharmacol Ther 1998; 64: 661-71.
14. Luurila H, Kivistö KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. Eur J Clin Pharmacol 1998; 54: 163-6.
15. Olkkola KT, Ahonen J, Neuvonen PJ. The effect of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analg 1996; 82: 511-516.
16. Olkkola KT, Backman JT, Neuvonen PJ. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 1994; 55: 481-85.
17. Stanke F, Jourdil N, Bessard J, Bessard G. Simultaneous determination of zolpidem and zopiclone in human plasma by gas chromatography-nitrogen-phosphorus detection. J Chromatogr B Biomed Appl 1996; 675: 43-51.
18. Gage R, Stopher DA. A rapid HPLC assay for voriconazole in human plasma. J Pharm Biomed Anal 1998; 17: 1449-53.
19. Pennick GJ, Clark M, Sutton DA, Rinaldi MG. Development and validation of HPLC assay for voriconazole. Antimicrobial Agents and Chemotherapy 2003; 7: 2348-50.
20. Bond A, Lader M. The use of analogue visual scales in rating subjective feelings. Br J Med Psychol 1974; 47: 211-8.

21. Hannington-Kiff JG. Measurements of recovery from outpatient general anaesthesia with a simple ocular test. Br Med J 1970; 3: 132-5.

22. Varhe A, Olkkola KT, Neuvonen PJ. Oral triazolam potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 1994; 56: 601-607.

23. Olubodum JO, Ochs HR, von Moltke LL, Roubenoff R, Hesse LM, Harmatz JS, Shader RI, Greenblatt DJ. Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men. Br J Clin Pharmacol 2003; 56: 297-304.

24. Greenblatt DJ, Harmatz JS, von Moltke LL, Wright CE, Durol ALB, Harrel-Joseph LM, Shader RI. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. J Pharmacol Exp Ther 2003; 293: 435-43.

25. Olubodum JO, Ochs HR, Trüten V, Klein A, von Moltke LL, Harmatz JS, Shader RI, Greenblatt DJ. Zolpidem pharmacokinetic properties in young females: influence of smoking and oral contraceptive use. J Clin Pharmacol 2002; 42: 1142-46.

Legends to the illustrations:

Figure 1. Plasma concentrations (mean ± SEM) of zolpidem in 10 healthy volunteers after an oral dose of 10 mg of zolpidem without pre-treatment (open circles) or following pre-treatment with oral voriconazole (400 mg b.i.d. on the first day and 200 mg b.i.d. on the second day; solid circles)

Figure 2. Individual values for the peak plasma concentration (C_{max}), area under the zolpidem plasma concentration-time curve (AUC(0–∞)), and elimination half-life ($t_{½}$) of zolpidem in 10 healthy volunteers after an oral dose of 10 mg of zolpidem without pre-treatment (control) or following pre-treatment with oral voriconazole (400 mg b.i.d. on the first day and 200 mg b.i.d. on the second day).

Figure 3. Results (mean ± SEM) of the recordings of drowsiness, performance and subjective drug effect from visual analog scales (VAS) and Maddox wing test after an oral dose of 10 mg of zolpidem without pre-treatment (open circles) or following pre-treatment with oral voriconazole (400 mg b.i.d. on the first day and 200 mg b.i.d. on the second day; solid circles) to 10 healthy volunteers.

Table 1. Pharmacokinetic parameters (mean ± SD; median (range) for t_{max}) of zolpidem after oral administration of 10 mg zolpidem without pre-treatment (control) or following pre-treatment with oral voriconazole (400 mg b.i.d. on the first day and 200 mg on the second day) to 10 healthy volunteers.

Parameter	Control phase	Voriconazole phase	95% confidence interval of the difference between voriconazole and control phases
Zolpidem			
C_{max} (ng · ml^{-1}) % of control (range)	112 ± 50 100	135 ± 47‡ 120 (90-147)	0.32, 45.3
t_{max} (h)	1 (0.5-4.0)	1.5 (0.5-3.0)	
AUC(0–∞) (ng · ml^{-1}· h) % of control (range)	528 ± 337 100	743 ± 412* 141 (117-288)	119, 310
$t_{½}$ (h) % of control (range)	3.2 ± 1.8 100	4.1 ± 1.6† 128 (100-270)	0.27, 1.45

C_{max} = peak plasma concentration; t_{max} = time to peak plasma concentration; AUC(0-∞) = area under the zolpidem plasma concentration-time curve; $t_{½}$ = elimination half-life.

*Significantly ($P < 0.001$) different from control.

†Significantly ($P < 0.01$) different from control.

‡Significantly ($P < 0.05$) different from control.

Fig. 1.

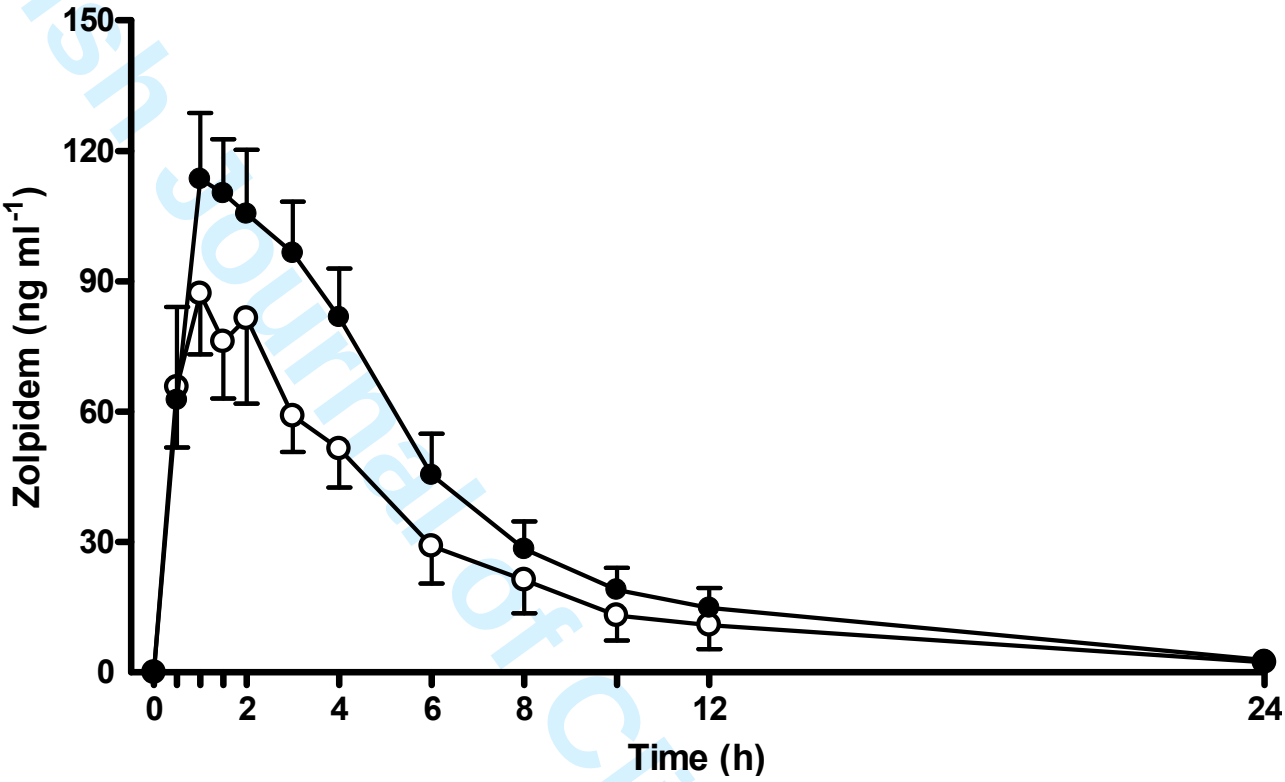

Fig 2.

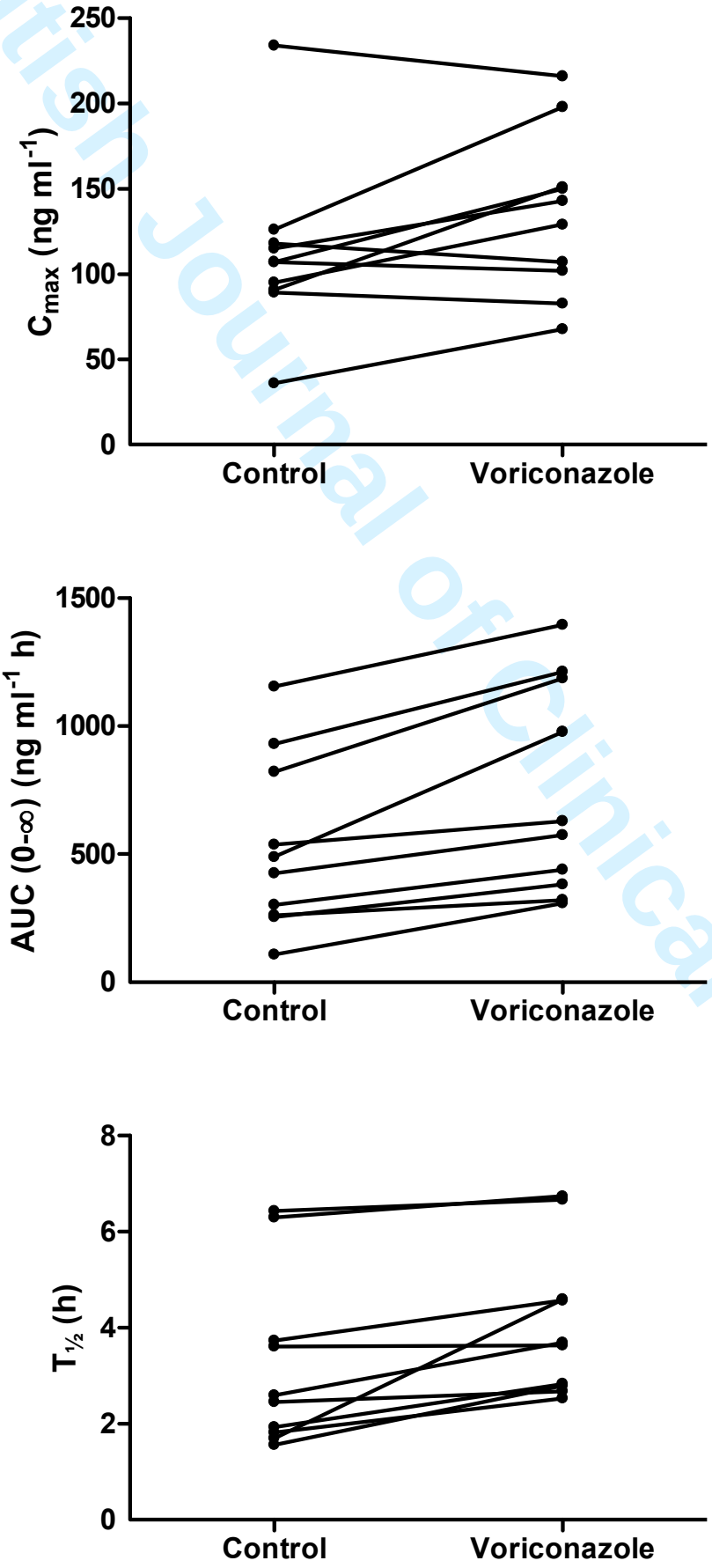

Fig 3.