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Research Article

# INFLUENCE OF STORAGE TEMPERATURE ON THE DOSE UNIFORMITY OF VORICONAZOLE POWDER FOR ORAL SUSPENSION

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**ABSTRACT**

Objective: Voriconazole, the first line agent in the treatment of invasive aspergillosis, is known to have non-linear pharmacokinetics, causing large variability in plasma concentrations. We recently observed extremely high voriconazole plasma concentrations of 20.4 and 16.8 mg/L in a 22-year-old cystic fibrosis lung transplant recipient treated with voriconazole powder for oral suspension. Because the dispersed voriconazole suspension was incorrectly stored at 2-8°C, the influence of aberrant storage conditions of the dispersed voriconazole suspension on dose uniformity was investigated.

Methods: While storing a bottle of reconstituted voriconazole oral suspension in the refrigerator, a standard volume of 7ml (=280mg) was systematically removed from the bottle every 12 hours, without shaking the bottle to simulate a worst-case scenario. Voriconazole concentrations were determined using LC-MSMS analysis.

Results: The concentrations of voriconazole in the suspension decreased from 39.8 mg/ml on day 1 to 32.8 mg/ml on day 3. From that moment on, concentrations increased again day by day until a concentration of 37.6 mg/ml in the bottle remnant.

Conclusion: Dose uniformity of the voriconazole powder for oral suspension, when stored at 2-8°C, is not guaranteed. This experiment demonstrates the variability in voriconazole concentration of the sampled volumes, as days go by. This may eventually result in underdosing and ultimately treatment failure of invasive fungal infections.

**Keywords:** Voriconazole; Powder for oral suspension; Redispersibility; Dose uniformity; Supratherapeutic plasma concentration; Therapeutic Drug Monitoring.

**RUNNING TEXT**

Voriconazole, one of the newer triazole antifungal agents, is active against several clinically relevant fungal pathogens and is currently the first choice in the treatment of invasive aspergillosis (IA) (loading dose 6 mg/kg bid, maintenance dose 4 mg/kg bid) [1].

In our hospital, therapeutic drug monitoring (TDM) of voriconazole is routinely performed using a validated LC-MSMS method [2], because of the wide Inter and intraindividual variability of voriconazole plasma trough concentrations (VTCs) [3,4]. A therapeutic interval for VTCs of 1-5.5 mg/L [4] is applied and the dose adjustment scheme in our hospital advises a dose increase of +50% in case of a subtherapeutic VTC and a dose reduction of -50% in case of a supratherapeutic VTC [4-6]. A switch from intravenous (IV) to oral administration of voriconazole can easily be realized, controlled via TDM. Tablets or oral suspension are used when patients are clinically improving and able to swallow.

Recently, we observed an extremely elevated VTC of 20.4 mg/L and a second confirmatory plasma concentration of 16.8 mg/L, on the same day, in a 22-year-old patient known with cystic fibrosis (40 kg), admitted to the intensive care unit (ICU). After bilateral lung transplantation, voriconazole 200 mg bid (i.e. 5 mg/kg) was started intravenously to prevent IA because of pre-transplant colonization with *Aspergillus* spp.. After a few days, voriconazole was changed from IV to oral administration, using the powder for oral suspension (POS). After gradual dose increases of +50% because of persistent undetectable VTCs (< 0.2 mg/L), a dose of 15 mg/kg bid was given for seven days. On day 7, the above mentioned extremely elevated VTCs were detected. Despite the unusual high dose of voriconazole, and despite the fact that follow-up VTCs were only determined after seven days of therapy with 15 mg/kg bid, instead of the recommended interval of four days needed to reach steady-state VTCs (7), such high VTCs were unexpected because voriconazole was still undetectable in plasma with a dose of 10 mg/kg bid at steady state. No other influencing factors, such as co-medication interacting with CYP2C19, CYP2C9, CYP3A4 [8], recent (< four days) IV-PO switch [9,10], interaction with simultaneously administered food or enteral feeding [11-13], CYP2C19 polymorphism [14] or liver disease [15,16] were found, which could explain the undetectable VTCs at 10 mg/kg bid followed by the highly supratherapeutic VTCs associated with 15 mg/kg bid. The voriconazole POS was correctly reconstituted with 46 ml of water [16]. However, the reconstituted POS was incorrectly stored at 2-8°C. The objective of this project was to investigate whether aberrant storage conditions of the voriconazole POS, could have led to disturbed dose uniformity, which could explain the extreme VTCs observed in this case. According to the summary of product characteristics (SmPC) [16], dispersed voriconazole POS needs to be stored at room temperature. When stored at 2-8°C, low temperature might induce caking of the suspended powder. This can lead to poor redispersibility and an increase in concentration of the suspension towards reaching the end of the bottle, especially when the POS is not shaken thoroughly before administration (Pfizer Medical Information: EUMedInfo@Pfizer.com. Consulted April, 2012). Due to cake formation, the suspension would not be dispersed properly by turning the bottle upside down when sampling and diluted 'supernatant fluid' would be sampled in the beginning, with a lower voriconazole concentration, followed by more concentrated samples towards reaching the end of the bottle.

This hypothesis was tested by reconstituting a voriconazole POS with 46 mL of water to reach a final concentration of 40 mg/mL and storing it in the refrigerator. Every 12 hours, a standard volume (7 mL, corresponding to 280 mg voriconazole) was removed with an oral dispensing syringe, until the bottle was empty. The first sample was taken before storing the bottle at 2-8°C. To simulate a worst-case scenario, we did not shake the

bottle before sampling. Although, according to the SmPC, the bottle was turned upside down to remove the suspension out of the bottle. All samples were stored at -20°C until analysis.

This resulted in 10 samples, equally spread over 5 consecutive days, plus one sample from the bottle remnant. The morning sample from the first 4 days (sample numbers 1-4), both samples of day 5 (sample number 5-6) and the bottle remnant (sample number 7) were all determined in duplicate by LC-MSMS [2] and the mean concentration was calculated for every time point of sampling. A 95% confidence interval (C.I.) was calculated around the first concentration of 39.8 mg/ml, based on the analytical coefficient of variation (CV) of 3.1% [38.6-41.0] and a scatterplot was constructed. As shown in Figure 1, voriconazole concentrations of the suspension did not rise above the standard concentration of 40 mg/mL, implicating that storage conditions and sampling of the suspension without shaking, could not have led to an overdose causing the supratherapeutic VTCs in this case. In contrast to the postulated rise in concentration for the later samples, caused by the hypothetical decrease in dispersibility due to storage at low temperature, a decrease in concentration was observed, which could not be explained by the between-run analytical variance of the LC-MSMS method (C.I. [38.6-41.0]) [2].

Hypothesis: caking induced by low temperature, resulting in lower voriconazole concentrations in the supernatant (1), followed by an increase in concentrations towards the end of the bottle (2).

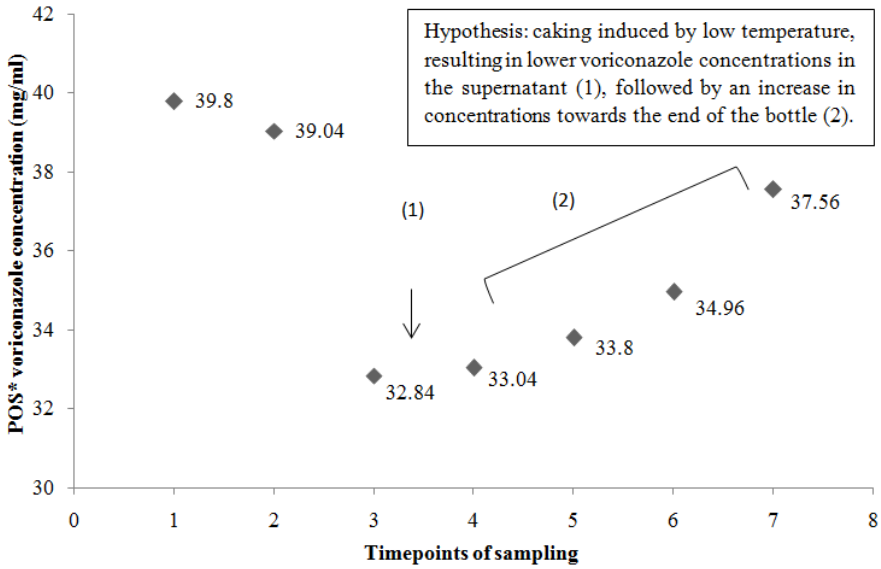


**Fig. 1: It shows the voriconazole concentration of the POS* in mg/ml as determined by LC-MSMS [2]. Each point of the graph represents the mean voriconazole concentration of a duplicate measurement.**

1. Sample 2-5: 08:00 am, respectively at day 2-5.
2. Sample 6: 08:00 pm day 5, the last sample of 7ml from the bottle
3. Sample 7: the bottle remnant.
4. *POS = powder for oral suspension
5. Sample 1: 08:00 am day 1, before storage at 2-8°C

To our knowledge, this is the first report that investigates the influence of storage temperature on dose uniformity of the commercialized powder for oral voriconazole suspension [17].

Some remarks have to be made. It seems that the hypothesis about the cake formation did not cause elevated VTCs. On the contrary, lower voriconazole concentrations of the POS were observed, when stored at 2-8°C, potentially accompanied by inadequate dosing and treatment failure. In the presented case, the extremely elevated VTCs were probably caused by a set of circumstances like improved clinical status of the patient with better absorption of the POS in the gastrointestinal tract, combined with the unusual high voriconazole dose.

Although a control experiment at room temperature is lacking, we can assume that dose uniformity is guaranteed when storing the reconstituted POS at room temperature, based on the manufacturer's storage recommendations. Although the reproducibility of this experiment has to be confirmed, it indicates that inadequate storage conditions can result in insufficient dose uniformity with a great risk of under dosing and failure of the antifungal treatment.

**Conflicts of interest**

All the authors declare that no conflict of interest exists. All the authors state that they have a full control of data and that they agree to allow the journal to review their data if requested.

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