



Voriconazole Film-Coated Tablets: To Split Them or Not?

Zahra Sahraei^{1,2}, Saghar Barati^{1*}

¹Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: 2020-07-15, Revised: 2020-07-23, Accept: 2020-07-28, Published: 2020-09-30

ARTICLE INFO

Article type:

Letter to the Editor

J Pharm Care 2020; 8(3): 148-149.

► Please cite this paper as:

Sahraei Z, Barati S. Voriconazole Film-Coated Tablets: To Split Them or Not? J Pharm Care 2020; 8(3): 148-149.

Voriconazole is a broad-spectrum triazole antifungal agent used to treat invasive Aspergillosis and Candidiasis (1). The intravenous (IV) dosing of voriconazole is 6 mg/kg for two doses given 12 hours apart (loading dose) which then, is reduced to the maintenance dose of 4 mg/kg as an IV route or 200 mg BD as an oral route (1). Although the dosing of 200 mg BD in the oral route has been approved by the food and drug administration (FDA), however, studies have reported that this dose is approximately equivalent to a 3mg/kg of the IV route and to achieve similar exposure to a 4mg/kg of the IV route, approximately 300 mg BD of the oral formulation should be administered (2, 3). Voriconazole is available as 50 and 200mg film-coated tablets (2). Lack of access to oral suspensions in some countries such as Iran and recommendation of the manufacturer on the fact that patients should swallow the whole tablets has made the physicians to administer, the standard dose of 200 mg BD by the oral route in tablet forms to almost all patients regardless of their weight. This approach may lead to treatment failure since the dose probably will not achieve steady-state concentrations, higher than the minimum inhibitory concentrations (MIC) of aspergillus species in some patients (3).

Voriconazole has nonlinear pharmacokinetics and polymorphism of CYP2C19, which is responsible for the metabolism of voriconazole (1), makes it necessary to measure trough plasma concentrations of voriconazole for efficacy and toxicity about 5-7 days after administering the maintenance dose (when the blood levels of the drug reach the steady-state concentration) (1). Many patients may develop the ultra-rapid metabolizer phenotype of

CYP2C19, which may lead to treatment failure (1). Trough concentrations of voriconazole should be between 1 mg/L (MIC of most Aspergillus species) and 6 mg/L (1). Voriconazole dosing must be adjusted when encountering a sub or supratherapeutic levels. For example, If the trough concentration is less than 1 mg/L, the oral 200 BD dose may be increased to 300 mg BD. Hence again, the need for splitting voriconazole tablets appears essential here. Another option is to administer a 200 mg tablet with two 50 mg tablets which puts an economic burden on the patients and their families. The high number of tablets that has to be consumed daily must also be considered.

The primary aim of film-coating tablets is to enhance the appearance of the tablets or to mask their smell and taste (4). It seems that film-coating voriconazole tablet does not affect the extent and rate of its absorption, as the manufacturer does not mention this. In addition, there is a study that has concluded that voriconazole tablet if crushed, has the same bioavailability as the whole tablet (5). The Overall development of side effects was also similar (5). Although voriconazole film-coated tablets are not that easy to divide in half, as they are not scored, and also the manufacturer has mentioned that the tablets should be swallowed whole, it seems that dividing voriconazole tablets will not change the bioavailability and the clinical exposure is almost the same (5). It is also safe and well-tolerated (5). Another point is that voriconazole is not on the list of tablets that should not be crushed (6). It means that crushing voriconazole tablet probably does not affect the absorption rate or its efficacy.

As a conclusion, it is suggested that physicians consider

*Corresponding Author: Dr Saghar Barati

Address: Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +989124236623, Fax: +982188200087.

Email: sgh_brt68@yahoo.com

splitting voriconazole tablets when encountering the need for administering 300 or 150 BD of oral-formulations when the oral suspension is not available. This approach may lead to high rates of treatment success. Splitting voriconazole tablets may also be considered in patients with renal failure who are not candidates for receiving the IV formulation, based on the extent of cyclodextrin in it and the possible development of renal toxicity.

References

1. Mangal N, Hamadeh IS, Arwood MJ, et al. Optimization of voriconazole therapy for the treatment of invasive fungal infections in adults. *Clin Pharmacol Ther* 2018;104(5):957-65.
2. Vfend (Voriconazole) Tablets, Oral Suspension, and IV [package insert]. New York: Pfizer, 2011.
3. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob Agents Chemother* 2002;46(8):2546-53.
4. Eldar D. Design, formulation and manufacture of film-coated drug products [2017]. Available from: <https://www.europeanpharmaceuticalreview.com/article/68115/design-formulation-manufacture/>.
5. Dodds Ashley ES, Zaas AK, Fang AF, Damle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. *Antimicrob Agents Chemother* 2007;51(3):877-80.
6. Practice Ifsm. oral dosage forms that should not be crushed [2020] [Available from: <https://www.ismp.org/recommendations/do-not-crush>].