VORICONAZOLE-INDUCED HEPATOTOXICITY

Siti Rahmatul Aini

Faculty of Medicine, Mataram University

Abstract

Voriconazole, a triazole antifungal, is widely used as the first line treatment of invasive aspergillosis in patients with haematological malignancies and hematopoietic stem cell recipients. Like other triazole antifungals, voriconazole is potentially hepatotoxic. Repeated dose oral studies in rats, mice and dogs have shown the liver to be the main target organ, with a range of adaptive and functional changes such as increasing liver weight, centrilobular hypertrophy, smooth endoplasmic reticulum proliferation and cytochrome P450 induction. Based on the Infectious Diseases society of America (IDSA)'s guidelines for the treatment of invasive aspergillosis, monitoring voriconazole levels and adjusting the dosage are recommended instead of switching to alternative antifungal drugs because of better survival and improved responses on initial therapy with voriconazole. However, if hepatotoxicity occurs, voriconazole will often be discontinued. Considering this, we try to investigate the voriconazole-induced hepatotoxicity mechanism by reviewing the literature. Based on the similarity of metabolism pathway between ketoconazole and voriconazole, we assume that the mechanism of voriconazole induced hepatotoxicity is mediated probably through N-oxide voriconazole. N-oxide voriconazole is oxidized by flavin-containing monooxygenase (FMO) on the fluoropyrimidine ring. It produces further metabolites showing toxic consequences that produces hepatic injury.

Keywords : Voriconazole, hepatotoxic, invasive aspergillosis

I. Introduction

Voriconazole is a triazole antifungal that is used as first line treatment of invasive aspergillosis in patients with haematological malignancies and hematopoietic stem cell recipients[1].Discovered in the late 1980s, voriconazole is indicated as treatment of invasive aspergillosis, fluconazole-resistant invasive *Candida* infections (including *C. Krusei*), serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp[2,3,4]. Voriconazole is a derivative of fluconazole, differing by the addition of a methyl group on the propanol backbone and by the replacement of a triazole moiety by a fluoropyrimidine ring[5]. The mechanism of action is the selective inhibition of the fungal cytochrome P450-dependent enzyme, 14a-sterol demethylase and terminating the biosynthesis of ergosterol[2,3].

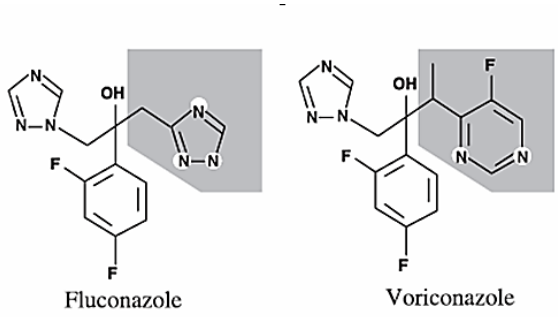

Fig. 1. Structural relationship between voriconazole and fluconazole[2]

Like other triazole antifungals, voriconazole is potentially hepatotoxic. Repeated dose oral studies in rats, mice and dogs have shown the liver to be the main target organ, with a range of adaptive and functional changes such as increasing liver weight, centrilobular hypertrophy, smooth endoplasmic reticulum proliferation and cytochrome P450 induction[4].

Several cohort studies found a large fluctuation of voriconazole levels[3-6]. High voriconazole levels are related with side