

# Voriconazole, a new wide-spectrum antifungal triazole: Activity *in vitro* and *in vivo*

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Voriconazole, also known in early reports as UK-109,496, was developed by Pfizer Central Research, UK. In 1995 at the 35 th Interscience Conference Antimicrobial Agents Chemotherapy (ICAAC) in San Francisco, California, USA 18 abstracts about Voriconazole were presented. The subjects of these abstracts ranged from voriconazole synthesis [1], favorable pharmacokinetics in man, guinea pigs, and dogs [2,3], to antifungal activity against opportunistic and pathogenic fungi *in vitro* and *in vivo*. Results from phase II clinical trials of voriconazole against candidiasis and aspergillosis were also reported [4]. A comprehensive review of this body of information was published in 1996 by Fromtling and Castaner [5].

During the ensuing years several reports have been published on the *in vitro* efficacy of voriconazole against *Candida* species [6,7], *Cryptococcus neoformans* [8-10], and opportunistic filamentous and dimorphic fungi [11,12]. By contrast, there has been very few published papers about the efficacy of voriconazole against fungal infections in animal models. These studies have been limited due to the pharmacokinetics of voriconazole, which has rapid clearance in mice, rats, and rabbits, but not guinea pigs, dogs, and humans [2]. Nevertheless, there are efficacy data on voriconazole against systemic candidiasis [13], aspergillosis [14] and cryptococcosis [15] in the guinea pig.

In phase II clinical trials in AIDS patients with CD<sub>4</sub> cells < 50 to 60 per mm<sup>3</sup> and oropharyngeal candidiasis, oral voriconazole daily at 200 mg for 7 days produ-

ced clinical efficacy of 80 to 100 % [5]. In another study, a group of immunocompromised patients with acute invasive aspergillosis, 72% of whom had failed prior therapy with itraconazole or amphotericin B, had favorable responses to a voriconazole regimen (27 of 36). The regimen consisted of 6 mg/kg of voriconazole i.v. every 12 h, then 3 mg/kg every 12 h for 6 to 27 days. This initial regimen was followed by oral voriconazole 200 mg twice daily for 4 to 24 weeks [5,16]. Six patients (8%) experienced enhanced perception of light, a mild visual disturbance that was drug-related.

In a study with 25 non-neutropenic patients with chronic invasive aspergillosis, 50% of whom had failed prior therapy, oral voriconazole at 200 mg twice daily for 4 to 24 weeks also showed efficacy. However, with this regimen drug-related visual disturbance was reported in 11 of 25 patients [4,5].

In a recent case study, a patient with chronic granulomatous disease (CGD) and invasive micromodular aspergillosis, oral voriconazole at 200 mg twice daily for 2 weeks gave a favorable response and abnormalities disappeared within 3 months. Regular prophylaxis of the patient with interferon-gamma and cotrimoxazole was continued during voriconazole treatment [17].

Phase III clinical trials have been ongoing during the past few years, however the results have not been released or published. Approval of voriconazole for treatment of certain fungal infections in humans is anticipated to be promulgated in the near future.

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