Fluconazole penetration into the prostatic fluid of patients with AIDS-associated cryptococcal meningitis

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Sir,

Cryptococcus neoformans causes progressive meningitis in up to 10% of patients with AIDS. The prostate gland is thought to be a common site for persistent C. neoformans infection following amphotericin B therapy for cryptococcal meningitis in patients with AIDS. Furthermore, positive cultures of post-prostatic massage urine have been found in 29% of patients in whom cryptococcal meningitis relapsed despite additional fluconazole therapy, presently considered elective in consolidation and suppressive therapy of AIDS-associated cryptococcal meningitis. Therapeutic concentrations of fluconazole have been demonstrated in a number of body compartments including the cerebrospinal fluid, but limited data are available concerning diffusion into the prostatic fluid. Most antimicrobial agents do not achieve therapeutic levels in this body fluid, the exceptions being un-ionized, lipid-soluble drugs, which are not firmly bound to plasma proteins, and a few water-soluble compounds of small molecular size and specific spatial configurations.

The aim of the present study was to investigate fluconazole concentrations in the prostatic fluid from patients with AIDS-associated cryptococcal meningitis and no signs of severe renal failure or evidence of acute prostatitis. Seven HIV-infected patients (mean age 38.7 years, range 32–45; mean body weight 62.3 kg, range 49.2–70.5) were studied. Written informed consent was obtained from all. Patients received oral fluconazole 400 mg once daily after 2-week induction therapy with amphotericin B. Steady-state fluconazole concentrations were measured in prostatic fluid obtained by prostate massage 8–14 days after the start of treatment. To exclude urinary contamination, samples were collected just before the first morning voiding. Blood for determination of serum fluconazole levels was drawn immediately before the prostatic massage. Fluconazole concentrations were determined in serum and prostatic secretion according to the high performance liquid chromatography assay of Kok et al. The prostatic distribution of fluconazole, based on a simple ratio method, was obtained by dividing the concentration in prostatic fluid by the concentration in serum.

Characteristics of patients and pharmacokinetic parameters are given in the Table. Serum concentrations of fluconazole, obtained between 24 and 27 h following administration, were in the range 16.67–28.64 mg/L with a mean ± S.D. of 21.96 ±4.84 mg/L. Fluconazole concentrations in the prostatic fluid were 12.30–18.35 mg/L with a mean of 16.31 ±2.97 mg/L. As a result, fluconazole distribution in the prostatic fluid exhibited little variation, ranging between 0.59 and 0.89 with a mean ratio of 0.75 ±0.12.

Despite its weakly basic nature and the low degree of lipid solubility, fluconazole concentrations achieved in the prostatic fluid appear to correlate significantly with the serum concentrations in individual patients, perhaps due to the low molecular weight and plasma protein binding. Our results are in agreement with those obtained in a study on healthy volunteers which showed that steady-state mean concentrations of fluconazole in the prostatic and seminal vesicle fluid from split ejaculate were 7.51, 9.17, 11.48, and 9.56 mg/L, sampling respectively 2, 3, 4, and 6 h after administration of the last dose. These levels closely approximated those measured in serum (ratio of first fraction of ejaculate to serum, 0.99), although urinary contamination was not excluded. In contrast, low fluconazole concentrations were found by other authors in the prostatic tissue of healthy volunteers undergoing

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transurethral resection for benign prostatic hypertrophy.\textsuperscript{6}

Steady-state mean total concentration of prostatic fluconazole 12 to 15 h after the last dose was 1.93 mg/L, or 29\% of the concurrent serum levels. However, the degree of antimicrobial penetration into the prostatic fluid may be more important than the prostatic tissue concentration because \textit{C. neoformans} resides predominantly in the prostatic secretions and not merely within the interstitium and stroma of the prostate gland.

Since MICs of fluconazole for \textit{C. neoformans} isolates from primary cases on initial presentation range from 0.37 to 6.25 mg/L, the concentrations found in the prostatic fluid of our patients on 400 mg daily dosage clearly exceed fluconazole MICs against most \textit{C. neoformans} isolates for at least 24 h after the last drug administration. Controlled clinical investigations are needed to evaluate this therapeutic regimen for suppression of post-prostatic massage cryptococcuia in HIV-infected patients.

### References


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\textbf{An open, non-comparative evaluation of the efficacy and safety of amphotericin B lipid complex as treatment of neutropenic patients with presumed or confirmed pulmonary fungal infections}

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Sir,

Amphotericin B is the ‘gold standard’ for the treatment of immunocompromised patients with invasive fungal infections. However, administration of this drug is frequently associated with severe adverse reactions, including nephrotoxicity, which undermine its efficacy and restrict its use. Lipid formulations of amphotericin B enable higher dosages to be administered with lower incidences of side-effects. We describe here our experience with one such formulation, amphotericin B lipid complex (ABLC) (Abelcet, The Liposome Company, London, UK), as treatment of patients with presumed or proven pulmonary fungal infections.

Between March 1995 and February 1997, 15 patients with pulmonary infiltrates highly suggestive of fungal infection received 18 courses of ABLC at the Royal Bournemouth Hospital; three patients each received two courses during separate neutropenic episodes. The characteristics of the patients are shown in the Table. In all cases, the decision to initiate antifungal treatment was based on both persistence of fever in a neutropenic patient who failed to respond to broad-spectrum antibiotics and characteristic radiological features. All but one patient received ABLC at a dosage of 5 mg/kg/day as a 2 h