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Letter to the Editor

Generic substitution of itraconazole resulting in sub-therapeutic levels and resistance

Sir,

Itraconazole is a widely used oral antifungal drug for aspergillosis and superficial fungal infection (2004 UK community expenditure £4.4 million). However, the itraconazole capsule formulation is well known for its unpredictable bioavailability, hence the widespread adoption of drug-level monitoring in vulnerable and non-compliant patients [1]. Variation in PK profiles is due not only to variable bioavailability but also to individual variation of cytochrome P450 activity. Extensive drug interactions can occur with itraconazole because it is both an inhibitor and substrate of the CYP3A4 enzyme and P-glycoprotein transporter systems [2]. Although the use of generic drugs is encouraged in order to minimise health expenditure, here we report that three patients had significant problems after substitution of the generic formulation of itraconazole (Sandoz), including the development of antifungal resistance (Table 1). None of these problems was attributable to drug interactions. All itraconazole levels were performed with bioassay with a therapeutic range of 5.0–15.0 mg/L. It should be noted that the results obtained with bioassay are 2–10 times higher than the results obtained for HPLC, mainly because microbiological assay methods detect an active metabolite in addition to the drug itself [3] (Table 1).

Patient 1 was a 41-year-old asthmatic man who was diagnosed with allergic bronchopulmonary aspergillosis (ABPA) in 1997 and became corticosteroid-dependent. Itraconazole capsules were started in 2001 (200 mg bd). He had a dramatic

response to this with complete cessation of oral steroids. For 4 years, itraconazole levels remained in the therapeutic range. However, 2 months after substitution to generic itraconazole the patient noticed an erythematous rash, and his peak flow deteriorated, suggesting active disease. Itraconazole levels fell from 6.9 mg/L to 4.6 mg/L, and the therapy Sporanox™ 400 mg daily was substituted. Two months later the patient was clinically very well. His last itraconazole level was 14.7 mg/L.

The second patient was a 51-year-old man who deteriorated while on treatment for *Mycobacterium malmoeense* infection, when chronic cavitary pulmonary aspergillosis (CCPA) was diagnosed. He was started on 400 mg daily itraconazole in October 2004. Substantial clinical improvement was observed, and itraconazole levels were in the expected range. When Sporanox™ was shifted to generic itraconazole, levels fell to 3.4 mg/L. Brand medication was restarted, and levels of 5.2 mg/L were obtained 3 months later.

Patient 3 was a 47-year-old woman with CCPA and mannose binding protein deficiency who was in treatment with itraconazole since 1999, with stable disease (patient 8 in Ref. [4]). In April 2005, her GP substituted generic itraconazole, at the same dosage. Itraconazole levels were undetectable in June 2005 and were 4.2 mg/L 5 months later. Raised precipitins and IgE levels indicated ongoing active disease. Culture from sputum performed in December 2005 revealed *A. fumigatus* resistant to itraconazole (MIC > 8.0 mg/L), whereas multiple specimens had been culture-negative for years before this.

Theoretically, a generic pharmaceutical product is the bioequivalent of a brand name (innovator) pharmaceutical.

Table 1
Characteristics of patients switched from Sporanox™ to generic itraconazole (Sandoz)

Age, sex	Diagnosis	Summary
41, M	ABPA	Levels dropped 66% after switching to generic itraconazole and rose again 69% after reverting to Sporanox™. Levels had been in the therapeutic range for 4 years with brand medication
51, M	CCPA	Levels decreased 44% after changing to generic itraconazole and increased by 53% after returning to brand medication
47, F	CCPA, MBP deficiency	Low (0–4.2 mg/L) itraconazole levels after substitution with generic itraconazole. Development of an isolate of <i>A. fumigatus</i> resistance to itraconazole (MIC > 8.0 mg/L).

F, female; M, male; ABPA, allergic bronchopulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; MBP, mannose binding protein.

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59 Registration of a generic requires bioequivalence studies
60 in humans, and in order to have pharmaceutical equiva-
61 lence a medicinal product needs to contain the same amount
62 of the same active substance(s) in the same dosage forms
63 that meet the same or comparable standards [5]. To date,
64 most bioequivalence studies are designed to evaluate average
65 bioequivalence, and experience with population and individ-
66 ual bioequivalence is still very limited. These studies are
67 usually performed on a limited number of healthy individ-
68 uals, which might be problematic for some compounds with
69 poor bioavailability in particular patient groups. Accord-
70 ingly, post-marketing surveillance importantly adds to the
71 knowledge about drugs in current use. Our data suggest
72 that more stringent criteria for bioequivalence seem to be
73 required for itraconazole. Consideration of the size of the
74 studies, the population in which they are conducted and
75 their power, particularly for ‘difficult to formulate’ drugs
76 with well-recognised limitations in bioavailability such as
77 itraconazole, would be appropriate.

78 Conflict of interest

79 The authors declare no potential conflicts of interest.

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References

- 82
- [1] Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for
83 diseases caused by *Aspergillus*. Clin Infect Dis 2000;30:6696–
84 709. 85
- [2] Prentice AG, Glasmacher A. Making sense of itraconazole phar-
86 macokinetics. J Antimicrob Chemother 2005;56(Suppl. 1):i17–
87 22. 88
- [3] British Society for Antimicrobial Chemotherapy Working Party. Lab-
89 oratory monitoring of antifungal chemotherapy. Lancet 1991;337:
90 1577–80. 91
- [4] Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cav-
92 itary and fibrosing pulmonary and pleural aspergillosis: case series,
93 proposed nomenclature and review. Clin Infect Dis 2003;37(Suppl.
94 3):S265–80. 95
- [5] European Agency for the Evaluation of Medicinal Products (EMA).
96 Guidance on the investigation of bioavailability and bioequivalence.
97 Available at: <http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf>
98 [accessed 21st November 2006]. 99

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