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Letters to the Editor

Generic substitution of itraconazole resulting in subtherapeutic 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^{TM} 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 malmoense* 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 (6.1 to 21.3 mg/L). When Sporanox^{TM} 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. Registration of a generic requires bioequivalence studies

Table 1
Characteristics of patients switched from Sporanox^{TM} 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^{TM}. 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 *A. fumigatus* 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.

in humans, and in order to have pharmaceutical equivalence a medicinal product needs to contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards [5]. To date, most bioequivalence studies are designed to evaluate average bioequivalence, and experience with population and individual bioequivalence is still very limited. These studies are usually performed on a limited number of healthy individuals, which might be problematic for some compounds with poor bioavailability in particular patient groups. Accordingly, post-marketing surveillance importantly adds to the knowledge about drugs in current use. Our data suggest that more stringent criteria for bioequivalence seem to be required for itraconazole. Consideration of the size of the studies, the population in which they are conducted and their power, particularly for 'difficult to formulate' drugs with well-recognised limitations in bioavailability such as itraconazole, would be appropriate.

Conflict of interest

The authors declare no potential conflicts of interest.

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Alessandro Comarú Pasqualotto
David W Denning*
School of Medicine, The University of Manchester and Wythenshawe Hospital, Manchester, UK

* Corresponding author. Tel.: +44 161 2915811; fax: +44 161 291 5806.
E-mail address: ddenning@manchester.ac.uk (D.W. Denning)

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A blood isolate of *Neisseria meningitidis* showing reduced susceptibility to quinolones in Hong Kong

Sir,

In May 2006, an isolate of *Neisseria meningitidis* was obtained from the blood sample of a 50-year-old female patient suffering from fever, abdominal pain, diarrhoea and vomiting by a regional hospital in Hong Kong. The isolate was subsequently confirmed to be serogroup C by the Microbiology Division, Public Health Laboratory Services Branch, Centre for Health Protection. Susceptibility tests to penicillin, cefotaxime, rifampicin and ciprofloxacin were performed using Etest (AB BIODISK, Solna, Sweden) and interpreted according to the CLSI guidelines [1]. The isolate was sensitive to penicillin (MIC = 0.06 mg/L), cefotaxime (MIC $\leq$ 0.016 mg/L) and rifampicin (MIC = 0.047 mg/L) but showed resistance to ciprofloxacin (MIC = 0.125 mg/L).

In order to determine the mechanism behind the increased ciprofloxacin resistance, sequencing of the quinolone resistance determining regions (QRDR) of *gyrA*, *gyrB*, *parC* and *parE* were performed as previously described [2]. However, no mutation was seen in any of the QRDRs. In order to assess the involvement of active efflux, the isolate was then subjected to susceptibility testing by Etest to nalidixic acid and ciprofloxacin with and without the proton pump inhibitor reserpine (50 mg/L) supplemented to the 5% blood Mueller–Hinton agar base. Whilst MIC to nalidixic acid was greatly reduced from >256 to 24 mg/L, MIC to ciprofloxacin was only moderately affected (0.125–0.094 mg/L). Reserpine alone was shown to have effect on neither the colony morphology nor growth of the isolate. The decreased susceptibility was therefore thought to be due to active efflux and nalidixic acid appeared to be a better agent for detection of such a mechanism.

To the best of our knowledge, less than nine *N. meningitidis* isolates with reduced ciprofloxacin susceptibility have been reported in the literature [2,3]. The majority of the resistance was found to be due to mutations in the QRDR of the *gyrA* gene. Nevertheless, resistance due to active efflux has also been reported [2]. Although meningococcal infection, a notifiable disease, remains rare in Hong Kong [4,5], emergence of reduced quinolone susceptibility must be monitored as ciprofloxacin can be used as chemoprophylaxis to eradicate meningococci carriage. The adoption of the recently published CLSI zone diameter interpretive criteria for disk diffusion susceptibility testing of *N. meningitidis* [1] and inclusion of nalidixic acid in the test panel should effectively assist the detection of quinolone resistance. For our current patient, nine close contacts have been identified and