Table 1. Analysis of factors associated with ofloxacin-resistant *M. tuberculosis* and MDR *M. tuberculosis* at a medical centre, 2005–10

Age category, years	Total no. of cases	No. of cases with ofloxacin-resistant *M. tuberculosis*	Resistance rate (%)	Odds ratio	95% CI	No. of cases with MDR *M. tuberculosis*	Resistance rate (%)	Odds ratio	95% CI
<24	179	3	1.68	0.28	0.08–1.00	11	6.15	0.64	0.30–1.37
24 to <34	195	3	1.54	0.26	0.07–0.92	15	7.69	0.82	0.41–1.63
34 to <44	227	13	5.73	reference		21	9.25	reference	
44 to <54	356	6	1.69	0.28	0.11–0.75	9	2.53	0.25	0.11–0.57
54 to <64	403	7	1.74	0.29	0.11–0.74	12	2.98	0.3	0.15–0.62
≥64	1333	4	0.30	0.05	0.02–0.15	21	1.58	0.16	0.08–0.29

Another interesting finding in this study is that ofloxacin resistance among MDR isolates was higher in adult patients aged 34 to <44 years than in patients in other age groups. Although previous studies conducted in the USA and Taiwan have demonstrated that isolates from adult patients have higher rates of isoniazid resistance,[2,6] our study, to the best of our knowledge, is the first to show that patients in that age group have higher rates of fluoroquinolone-resistant *M. tuberculosis* than patients in other age groups. Large-scale global surveillance studies are needed to establish the association between fluoroquinolone resistance and age.

In the study by van den Boogaard *et al.*[1] the two fluoroquinolone-resistant isolates were susceptible to rifampicin and isoniazid. Fluoroquinolone-resistant isolates were not found among the three MDR *M. tuberculosis* isolates.[1] In contrast to their findings, we found that about two-thirds of ofloxacin-resistant *M. tuberculosis* isolates were MDR and that only 8 of 36 isolates were susceptible to all first-line anti-TB agents. Based on our findings as well as those of previous studies that show that MDR *M. tuberculosis* isolates in Taiwan tend to be resistant to fluoroquinolones,[3,4] it is clear that the role of fluoroquinolones as second-line anti-TB agents is limited.

In conclusion, our study shows that the rate of fluoroquinolone-resistant *M. tuberculosis* remains low in northern Taiwan, and indicates that the rate of fluoroquinolone resistance is highest among adult patients and fluoroquinolone resistance is predominantly found among MDR *M. tuberculosis* isolates.

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Transparency declarations

None to declare.

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Pharmacokinetics of oral voriconazole in patients with cystic fibrosis

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Sir,

Aspergillus fumigatus may cause allergic bronchopulmonary aspergillosis (ABPA), aspergillomas or *Aspergillus* bronchitis in patients with cystic fibrosis (CF). Oral corticosteroids provide the mainstay of treatment for ABPA, but there are concerns about the side effects of long-term corticosteroid use.

Itraconazole has been used as a steroid-sparing agent, but absorption in people with CF is poor and unreliable.[1] Voriconazole, a broad-spectrum triazole antifungal agent, may be useful for the management of fungal infections in people with CF.

We undertook an open-label Phase IV pharmacokinetic study, which aimed to recruit 10 adults with CF, hospitalized for routine antibiotic therapy and with pancreatic insufficiency. Each subject received 400 mg of oral voriconazole (VFEND, Pfizer) 12 hourly on day 1, followed by 200 mg 12 hourly for the subsequent 13 days of the study. Venous blood samples were obtained for drug analysis pre-dose and at 1, 2, 4, 6, 8 and 12 h post-dose on days 1 and 14 of the study. Serum voriconazole levels were determined using liquid chromatography–tandem mass spectrometry. On days 1, 7 and 14, routine haematology, liver function tests and blood chemistry samples were taken. All suspected unexpected serious adverse reactions and serious adverse events were recorded. Data were expressed as the mean and standard deviation (SD). The maximum concentration (C_{max}) and the time of maximum concentration (T_{max}) were determined by visual inspection of the data. The area under the plasma concentration–time curve during the dosing interval (AUC_{0-12}) was determined using trapezoidal summation. Determination of the elimination constant (k_{el}) and half-life ($t_{\frac{1}{2}}$) were undertaken using least squares non-linear regression of the experimental data (GraphPad Prism 5.02, GraphPad Inc., USA). The clearance for the fraction of drug absorbed (CL/F) for voriconazole was calculated as the dose/AUC_{0-12} ratio. The volume of distribution for the fraction of drug absorbed (*V*/F) was estimated as dose/(k_{el}·AUC_{0-12}). This study was approved by the Leeds (East) Research Ethics Committee. Regulatory approval was obtained from the UK Medicines and Healthcare products Regulatory Agency. Informed written consent was obtained from all subjects.

Data were available from nine patients (seven males and two females). The study subjects had a mean percentage predicted forced expiratory volume in 1 s (FEV1%) (SD), percentage predicted forced vital capacity (FVC%) (SD) and weight (SD) of 38.7% (16.3%), 50.7% (17.1%) and 53.6 kg (7.1 kg), respectively. On day 1, the C_{max} (SD) was 3.8 mg/L (1.6 mg/L) and occurred at 2.3 h (1.2 h). At the end of the study, the C_{max} was 2.7 mg/L (0.8 mg/L) and occurred at 2.3 h (1.3 h) (see Figure 1). At day 14, all subjects achieved a peak serum voriconazole level of >1.0 mg/L and a trough level of >0.25 mg/L. The AUC_{0-12} (SD) was 24.0 h·mg/L (16.2 h·mg/L) and 15.5 h·mg/L (8.1 h·mg/L) on days 1 and 14, respectively. On days 1 and 14, the $t_{\frac{1}{2}}$ (SD) for oral voriconazole was 8.0 h (5.8 h) and 5.4 h (3.4 h), respectively. The *V*/F (SD) was 200.8 L (82.1 L) and 100.3 L (48.2 L) on days 1 and 14, respectively. The CL/F (SD) was 26.2 L/h (19.0 L/h) and 14.9 L/h (8.2 L/h) on days 1 and 14, respectively. Three subjects withdrew due to side effects; two subjects due to visual disturbance on days 1 and 3 (both had peak levels >5 mg/L), and one on day 7 due to liver function test derangement. All symptoms resolved on cessation of voriconazole.

Purkins *et al.*[2] reported the *V*/F and CL/F for 200 mg of voriconazole orally to be 160.2 L and 19.9 L/h, respectively. The data from the present study would suggest that voriconazole has a higher volume of distribution, but slower clearance in patients with CF. Patients with CF are almost always pancreatic insufficient, resulting in poor absorption from the gastrointestinal tract, and may have an increased volume of distribution and faster drug clearance.[3] Berge *et al.*[4] documented 14% and 30% of patients with CF developed neurological and hepatic side effects with oral voriconazole, respectively. The study of Berge *et al.*[4] may not be relevant to the pre-transplant patient with CF due to the complex nature of the post-transplant individual, particularly with regard to drug interactions.

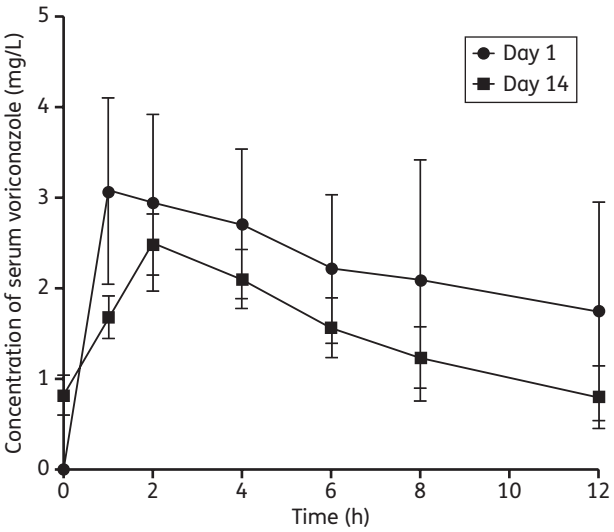

Figure 1. Mean serum concentration–time profile of voriconazole on days 1 and 14. Error bars represent 95% confidence intervals.

Voriconazole does not have an established standard therapeutic range, although a trough level of >0.25 mg/L has been suggested as being associated with a favourable outcome.[5] All the subjects in this study had trough levels >0.25 mg/L. This study supports a previously observed relationship between high serum voriconazole levels and the risk of visual disturbance. Therapeutic drug monitoring and dose adjustment may allow better tolerance of voriconazole and reduce the likelihood of side effects, such as visual disturbance, occurring.

The data from our study demonstrates that oral voriconazole is rapidly absorbed in patients with CF, with a peak concentration occurring 1–2 h after ingestion. In view of the controversy surrounding drug levels, we suggest that future interventional studies should incorporate the monitoring of trough and peak drug levels as part of the protocol to provide data that may relate serum drug levels with outcome.

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Transparency declarations

None to declare.

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