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Role of Therapeutic Drug Monitoring in Treatment Optimization in Tuberculosis and Diabetes Mellitus Comorbidity

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With great interest, we read the paper by Alfarisi et al. reporting the effects of diabetes mellitus (DM) on the pharmacokinetics and pharmacodynamics of tuberculosis treatment (1). The prevalence of DM in tuberculosis patients is increasing and may negatively impact disease outcome (2, 3). Here, we report a 47-year-old Caucasian man who was treated in our center for normal sensitive pulmonary tuberculosis. He had a history of alcohol abuse, chronic pancreatitis, and poorly controlled DM type 2 (hemoglobin A1c [HbA1c], 10.4%). At presentation, the patient was cachectic (body weight, 55 kg; body mass index [BMI], 18 kg/m^2). He started treatment with rifampin (600 mg), isoniazid (300 mg), pyrazinamide (1,500 mg), and ethambutol (1,000 mg) under directly observed therapy. Comedication consisted of vitamins (multivitamins and thiamine) and insulins (short-acting insulin thrice daily, 4 to 30 units, with additional insulin as needed and long-acting insulin, 22 units once daily). The subject had not been visiting a physician for his diabetes in the 5 years prior to his admission; therefore, insulin therapy had to be optimized during admission. No other medication was used, and the subject did not experience nausea, vomiting, or diarrhea during admission. After 2 weeks, isoniazid was replaced by moxifloxacin (400 mg) due to peripheral neuropathy. One month after the start of the treatment, azithromycin was added with a loading dose of 500 mg, followed by 250 mg once daily for 4 weeks, because of participation in a trial (ClinicalTrials registration no. NTC03160638). Therapeutic drug monitoring (TDM) for the antituberculosis drugs and azithromycin was performed 1 week after azithromycin initiation. Samples were obtained during a period of at least 8 h and analyzed by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The absorption of all drugs was reduced, with plasma concentrations below the reference ranges (Fig. 1, Table 1). To compensate, dosages of the rifampin and moxifloxacin were increased to 900 mg and 600 mg, respectively, and TDM was repeated. Although the exposure increased, the drug levels remained below the reference ranges (4). The dosage of moxifloxacin could not be further increased because of an already elongated corrected QT (QTc) interval, and moxifloxacin was stopped. The dosage of the rifampin was increased to 1,800 mg, which resulted in delayed but adequate exposure (Fig. 1). The patient did not report any adverse effects of this dosage of rifampin. For azithromycin, the drug concentrations remained below the detection level (0.1 mg/liter) at all time points. To confirm the malabsorption, the patient was rechallenged with 250 mg azithromycin, and the drug levels were determined 2, 4, and 6 h after administration of the drug. Again, drug concentrations remained below the detection limit.

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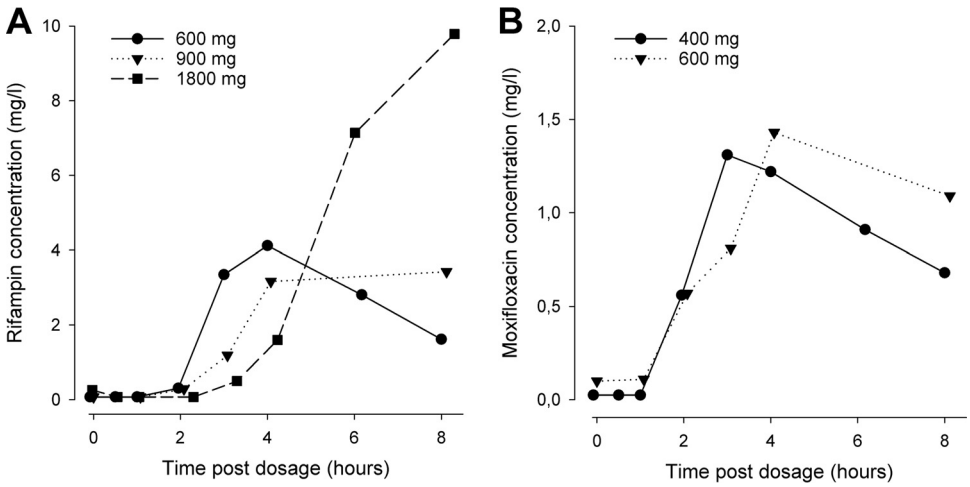

FIG 1 Serum concentrations over time for rifampin (A) and moxifloxacin (B).

Suboptimal exposure to tuberculosis drugs may contribute to poor outcome in patients with DM (4). Gastrointestinal problems, including gastroparesis, are often observed in DM patients and may result in delayed drug absorption or malabsorption (4). In our case, both problems appear to be observed. Studies on the pharmacokinetics of the first-line antituberculosis drugs have yielded conflicting results, showing reduced plasma levels in DM patients for rifampin, isoniazid, pyrazinamide in some but not all studies (1, 5–9). Our current findings indicate that the absorption of other antibiotics may also be reduced in DM patients. Our case strengthens the suggestion that TDM may be of added value in patients with DM, in particular, in patients with poorly controlled disease (1). These observations are of particular relevance, as subtherapeutic concentrations may contribute to treatment failure and acquired drug resistance (10). Moreover, in line with previous studies (11), we found that absorption may be delayed, emphasizing that not only the drug concentration levels at 2 h but intensive pharma-

TABLE 1 Pharmacokinetic parameters[a]

Drug dose (mg once daily [mg/kg])	C_{max} (mg/liter)	T_{max} (h)	AUC (h · mg/liter)
Rifampin			
600 (10.9)	4,12	4	31
900 (16.4)	3,43	≥8	44
1,800 (32.7)	9,79	≥8	107
Reference range[b]	8–24	0.75–2	
Pyrazinamide			
1,500 (27.3)	24.8	3	297
Reference range[b]	20–60	1–2	
Ethambutol			
1,000 (18.2)	1.2	4	10
Reference range[b]	2–6	2–3	
Moxifloxacin			
400 (7.3)	1.31	3	12
600 (10.9)	1.43	4	17
Reference range[b]	3–5	1–2	
Azithromycin			
250 (4.5)	<0.1	ND[c]	ND

[a]AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time at which C_{max} is observed.
[b]Ranges obtained from reference 4.
[c]ND, not determined.

cokinetic sampling is required to capture the maximum plasma concentration (C_{max}) and the area under the concentration-time curve (AUC).

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We have no conflicts of interest to declare.

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