# Reduced moxifloxacin exposure in patients with tuberculosis and diabetes

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# Reduced moxifloxacin exposure in patients with tuberculosis and diabetes

*To the Editor:*

Prevalence of diabetes mellitus (DM) in patients with tuberculosis (TB) is increasing and may negatively impact TB outcomes in patients with active disease [1]. Gastrointestinal problems, including gastroparesis, may result in delayed drug absorption or malabsorption in patients with DM, which may cause suboptimal drug exposure and poor outcome [2]. Studies on the pharmacokinetics of the first-line anti-TB drugs in patients with DM yielded conflicting results on low drug exposure [3–7]. Moxifloxacin is a potent bactericidal drug against *Mycobacterium tuberculosis* and is key for the treatment of multidrug-resistant tuberculosis (MDR)-TB [8]. Moreover, moxifloxacin can be recommended for TB treatment in patients with monoresistance or intolerance to first-line drugs [9]. Recently, we reported on a patient with TB and DM in whom moxifloxacin exposure was reduced [10].

In this study, we aimed to evaluate moxifloxacin drug exposure in patients with TB and DM. We retrospectively identified all patients aged ⩾16 years who underwent routine therapeutic drug monitoring (TDM) using at least three time-points for moxifloxacin as part of their TB treatment at our centre in the period 2006–2018. For this study, the Medical Ethical Committee of the University Medical Center Groningen (Groningen, the Netherlands) waived the need for written informed consent due to the retrospective nature of the study (reference 2013/492). Patient data were processed according to the Declaration of Helsinki. Controls were TB patients without DM matched for age, sex and rifampicin use (cases/controls 1/1). Patient characteristics were extracted from the electronic health record. DM was excluded from control patients by routine blood glucose measurements once weekly, according to national guidelines. Plasma moxifloxacin concentrations were determined using a validated liquid chromatography–tandem mass spectrometry method [11]. Pharmacokinetic parameters were calculated using two models for moxifloxacin (in the absence and presence of rifampicin) [12]. For continuous variables, data are expressed as medians with interquartile ranges (IQRs). For categorical variables, percentages of the total group are presented. Comparisons between both groups were performed using a Mann–Whitney U-test and differences were considered statistically significant at $p<0.05$. All statistical evaluations were performed using SPSS version 23.0 (IBM, Armonk, NY, USA).

In total, 126 TB patients having been subjected to moxifloxacin TDM were eligible for evaluation. For the DM group, 16 patients with DM treated orally with moxifloxacin 400 mg once daily were identified and selected, of whom 69% were male, one of whom had DM type 1, 12 had DM type 2 and three had steroid-induced DM. Glycated haemoglobin (HbA1c) results were available for nine patients and was a median of 8.3% (IQR 6.2–11.3%). 14 patients were treated with insulin, three patients were treated with metformin and three patients were treated with sulfonylurea derivatives. Fasting blood glucose results determined within 1 week of TDM sampling were available for 12 patients and were a median of 8.2 $mmol{\cdot}L^{-1}$ (IQR 6.1–10.9 $mmol{\cdot}L^{-1}$). The median age of the patients with DM was 52 years (IQR 42–55 years) and median body mass index (BMI) was 21.9 $kg{\cdot}m^{-2}$ (IQR 20.1–25.5 $kg{\cdot}m^{-2}$). Eight (50%) patients were diagnosed with pulmonary TB. Five patients were diagnosed with MDR-TB, seven patients with drug-susceptible TB, two patients with monoresistant TB and for two patients, susceptibility data were not available. Nine (56%) patients used rifampicin. For the control group, 16 matched patients were selected, of whom 63% were male, with a median age of 49 years (IQR 40–62 years) and median BMI of 20.7 $kg{\cdot}m^{-2}$ (IQR 18.2–23.3 $kg{\cdot}m^{-2}$). In the control group, pulmonary TB was the most common

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**Exposure to moxifloxacin is low in patients with tuberculosis and diabetes comorbidity due to increased clearance of the drug. As low exposure may result in poor treatment outcomes, higher moxifloxacin doses may be required for treatment success.** http://bit.ly/2Ynxdf7

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diagnosis (75%). Six patients were diagnosed with MDR-TB, six patients with drug-susceptible TB and four patients with monoresistant TB. Seven (44%) patients used rifampicin. No differences in creatinine clearance or estimated glomerular filtration rate were observed between DM and control patients (data not shown). No differences for demographics were observed either.

Median moxifloxacin dose was 6.6 mg·kg$^{-1}$ (IQR 4.7–7.2 mg·kg$^{-1}$) for patients with DM and 6.5 mg·kg$^{-1}$ (IQR 5.1–7.2 mg·kg$^{-1}$) for control patients (p>0.05). The median time between the start of treatment and TDM was 17 days (IQR 7–38 days) and 22 days (IQR 10–35 days), respectively. The median number of samples was 6 (IQR 6–7) for the DM group and 7 (IQR 6–7) for the control group. Most frequently used time points (>90%) included $t$=0, 1, 2, 3 and 4 h. In addition, at least one sample was obtained between $t$=4 and 8 h.

Exposure to moxifloxacin, expressed as the area under the concentration–time curve from 0 to 24 h ($AUC_{0-24}$), was significantly lower in patients with DM compared to control patients (17.4 mg·h·L$^{-1}$ (IQR 12.5–21.8 mg·h·L$^{-1}$) *versus* 23.2 mg·h·L$^{-1}$ (IQR 16.8–32.1 mg·h·L$^{-1}$), respectively; p<0.05) (figure 1a). In line with the exposure, the maximum concentration ($C_{max}$) (1.7 mg·L$^{-1}$ (IQR 1.3–2.6 mg·L$^{-1}$) *versus* 2.4 mg·L$^{-1}$ (IQR 2.0–3.0 mg·L$^{-1}$), respectively; p<0.05) (figure 1b) and trough concentration (0.13 mg·L$^{-1}$ (IQR 0.04–0.24 mg·L$^{-1}$) *versus* 0.30 mg·L$^{-1}$ (IQR 0.10–0.51 mg·L$^{-1}$), respectively; p<0.05) (figure 1c) were also lower in patients with DM. Notably, only seven patients (three DM and four controls) had $C_{max}$ concentrations within the expected range [10]. Clearance (CL/F) of moxifloxacin was increased in DM patients (25.2 L·h$^{-1}$ per 1.85 m$^2$ (IQR 20.9–32.5 L·h$^{-1}$ per 1.85 m$^2$) *versus* 18.3 L·h$^{-1}$ per 1.85 m$^2$ (IQR 13.3–26.4 L·h$^{-1}$ per 1.85 m$^2$), respectively; p<0.05) (figure 1d). Due to the limited number of patients with HbA1c values available, no correlation could be performed between moxifloxacin CL/F and HbA1c. No differences were observed between the groups for time to $C_{max}$, lag time ($t_{lag}$), volume of distribution or absorption rate constant (data not shown).

In line with previous studies [12], rifampicin significantly reduced moxifloxacin exposure (23.8 mg·h·L$^{-1}$ (IQR 17.8–27.6 mg·h·L$^{-1}$) *versus* 16.9 mg·h·L$^{-1}$ (IQR 12.5–20.7 mg·h·L$^{-1}$), p<0.01). Conversely, aminoglycosides (kanamycin and amikacin) appeared to significantly increase exposure (15.7 mg·h·L$^{-1}$ (IQR 12.7–17.6 mg·h·L$^{-1}$) *versus* 23.8 mg·h·L$^{-1}$ (IQR 18.4–27.6 mg·h·L$^{-1}$), p<0.05), which is in line with the fact that these patients were not treated with rifampicin. No apparent interactions were observed with other comedications. When considering only the patients treated with regimens without rifampicin, DM comorbidity still reduced moxifloxacin exposure *via* increased clearance of the drug (data not shown). Collectively, these data indicate that in addition to rifampicin, DM comorbidity may increase moxifloxacin clearance in patients with TB.

To establish clinical relevance of the reduced exposure, area under the unbound drug concentration–time curve ($fAUC_{0-24}$)/minimal inhibitory concentration (MIC) ratios were calculated. From hollow-fibre models mimicking human pharmacokinetics, a $fAUC_{0-24h}$/MIC ratio >53 has been suggested to be optimal for treatment efficacy [13]. MICs were available for 12 control patients (0.125 mg·L$^{-1}$ for nine patients and 0.25 mg·L$^{-1}$ for three patients) and seven patients with DM (0.125 mg·L$^{-1}$ for three patients, 0.25 mg·L$^{-1}$ for three patients and 0.5 mg·L$^{-1}$ for one patient) resulting in adequate $fAUC_{0-24h}$/MIC ratios for 10 (77%) control patients and two (29%) patients with DM. When the breakpoint (0.25 mg·L$^{-1}$) [14] was used for all patients, $fAUC_{0-24h}$/MIC ratios were adequate for seven (44%) control patients, whereas no adequate exposure was observed in patients with DM (p=0.007 by Fisher's exact test).

Our study showed that patients with TB and DM comorbidity have a lower exposure of moxifloxacin compared to matched controls. Previous studies already established that the pharmacokinetics of moxifloxacin are highly variable and that reduced exposure may contribute to poor patient outcomes [9]. Reduced exposure to first-line anti-TB drugs in patients with DM has been attributed to gastrointestinal problems [3, 4]. Although not routinely reported, no absorption problems were found. Moreover, no effect was observed on the $t_{lag}$ or absorption rate constant for moxifloxacin, suggesting that the reduced exposure was independent of absorption problems. Indeed, moxifloxacin clearance was found to be increased in DM patients. Moxifloxacin is metabolised by uridine diphosphate glucuronosyltransferase (UGT)1A1, UGT1A3 and UGT1A9. Of these, genetic variants of *UGT1A1* with increased activity are positively associated with DM, providing a potential explanation for the increased clearance observed [15].

There are limitations to this study, including the retrospective nature and small number of patients. The analysis was complicated due to potential differences caused by cotreatment with rifampicin in some of the patients. Moreover, no matching was performed on kidney function or weight. Although TDM has become standard practice for moxifloxacin at our centre, this was not the case at the beginning of the analysis period and cases may have been missed. The patients included in this study had a relatively normal BMI; whether these results also apply to overweight or obese patients with DM remains to be determined. Data on the pharmacokinetics of moxifloxacin in patients with DM without TB compared to control patients are lacking.

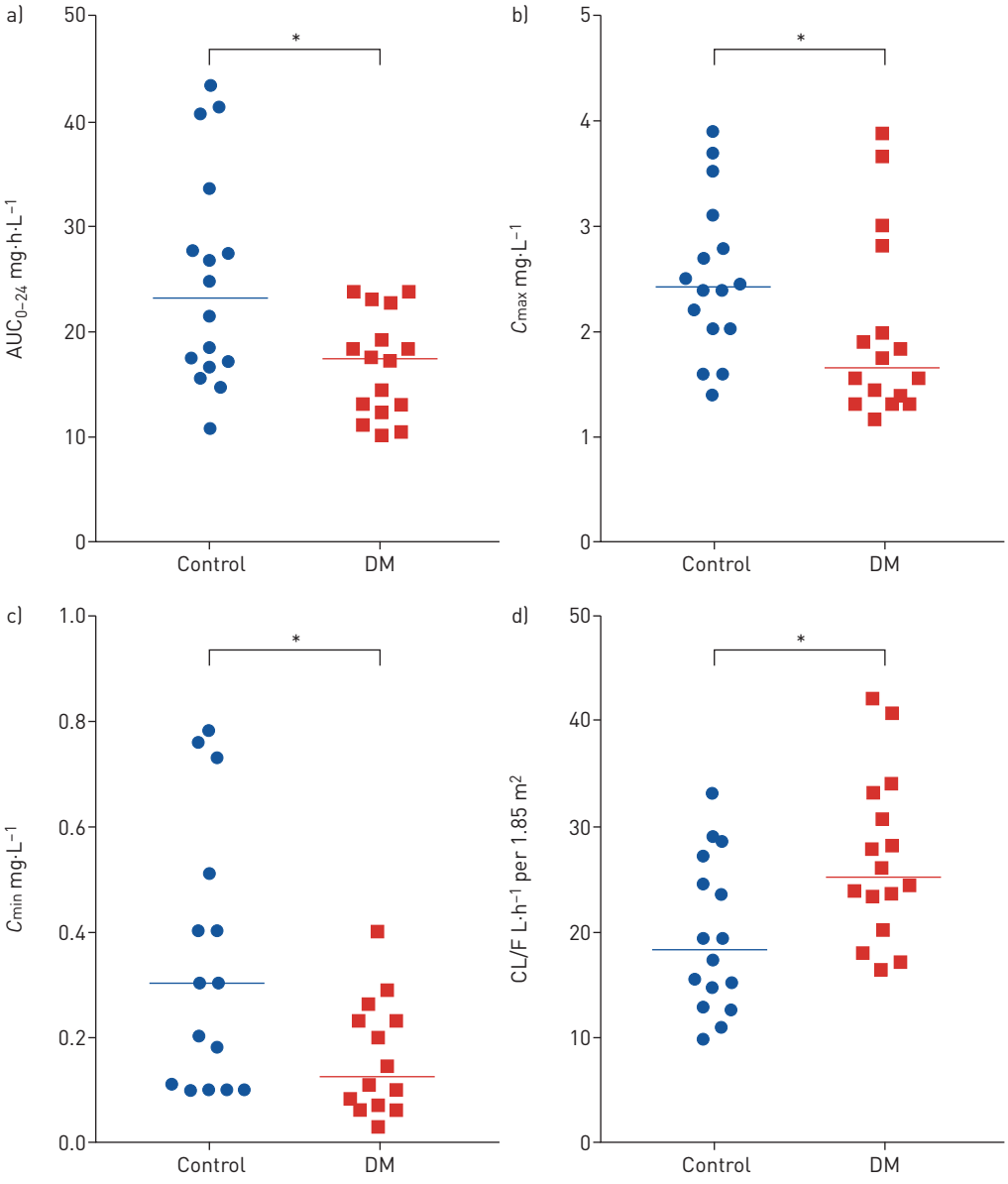


FIGURE 1 Moxifloxacin exposure is reduced in tuberculosis (TB) patients with diabetes mellitus (DM). a) Exposure, expressed as area under the concentration–time curve from 0 to 24 h ($AUC_{0-24}$), to moxifloxacin in TB patients without (control) and with DM. b) Observed maximum concentrations ($C_{max}$) and c) observed trough concentrations ($C_{min}$) for TB patients without (control) and with DM. d) Clearance (CL/F) of moxifloxacin in TB patients without (control) and with DM. *: p<0.05 compared to control patients.

In conclusion, our results indicate that exposure to moxifloxacin is reduced in patients with TB and DM. This reduction is clinically relevant, suggesting that, as for MDR-TB, higher doses of 600–800 mg may be necessary to improve treatment outcomes. Whether these doses result in adequate exposure and are safe, especially in the light of the recent European Medicines Agency and US Food and Drug Administration warnings for this drug, should be addressed in future studies.

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## References

1 Goletti D, Lindestam Arlehamn CS, Scriba TJ, *et al.* Can we predict tuberculosis cure? What tools are available? *Eur Respir J* 2018; 52: 1801089.
2 van der Burgt EPM, Sturkenboom MGG, Bolhuis MS, *et al.* End TB with precision treatment! *Eur Respir J* 2016; 47: 680–682.
3 Nijland HMJ, Ruslami R, Stalenhoef JE, *et al.* Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis* 2006; 43: 848–854.
4 Babalik A, Ulus IH, Bakirci N, *et al.* Plasma concentrations of isoniazid and rifampin are decreased in adult pulmonary tuberculosis patients with diabetes mellitus. *Antimicrob Agents Chemother* 2013; 57: 5740–5742.
5 Alfarisi O, Mave V, Gaikwad S, *et al.* The effect of diabetes mellitus on the pharmacokinetics and pharmacodynamics of tuberculosis treatment. *Antimicrob Agents Chemother* 2018; 62: e01383-18.
6 Ruslami R, Nijland HMJ, Adhiarta IGN, *et al.* Pharmacokinetics of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. *Antimicrob Agents Chemother* 2010; 54: 1068–1074.
7 Requena-Méndez A, Davies G, Ardrey A, *et al.* Pharmacokinetics of rifampin in Peruvian tuberculosis patients with and without comorbid diabetes or HIV. *Antimicrob Agents Chemother* 2012; 56: 2357–2363.
8 Falzon D, Schünemann HJ, Harausz E, *et al.* World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur Respir J* 2017; 49: 1602308.
9 Pranger AD, van Altena R, Aarnoutse RE, *et al.* Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J* 2011; 38: 888–894.
10 Dekkers BGJ, Akkerman OW, Alffenaar JWC. The role of therapeutic drug monitoring in treatment optimization in tuberculosis and diabetes mellitus co-morbidity. *Antimicrob Agents Chemother* 2018; 63: e02074-18.
11 Pranger AD, Alffenaar J-WC, Wessels AMA, *et al.* Determination of moxifloxacin in human plasma, plasma ultrafiltrate, and cerebrospinal fluid by a rapid and simple liquid chromatography–tandem mass spectrometry method. *J Anal Toxicol* 2010; 34: 135–141.
12 Elsen SHJ, Sturkenboom MGG, Akkerman OW, *et al.* Limited sampling strategies using linear regression and the Bayesian approach for therapeutic drug monitoring of moxifloxacin in tuberculosis patients. *Antimicrob Agents Chemother* 2019; 63: e00384-19.
13 Gumbo T, Louie A, Deziel MR, *et al.* Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an *in vitro* pharmacodynamic infection model and mathematical modeling. *J Infect Dis* 2004; 190: 1642–1651.
14 World Health Organization. Technical Report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva, WHO, 2018.
15 Abbasi A, Deetman PE, Corpeleijn E, *et al.* Bilirubin as a potential causal factor in type 2 diabetes risk: a Mendelian randomization study. *Diabetes* 2015; 64: 1459–1469.