Moxifloxacin in multidrug-resistant tuberculosis: is there any indication for therapeutic drug monitoring?

To the Editors:

Fluoroquinolones are rapidly emerging as important drugs in the treatment of tuberculosis (TB) worldwide [1]. In drug-susceptible TB, their use is currently under investigation and, according to the American Thoracic Society/Centers for Disease Control guidelines, fluoroquinolones are indicated only in patients receiving the conventional regimen who present severe adverse reactions [2]. However, in drug-resistant (DR) and, more specifically, in multidrug-resistant (MDR)-TB, the role of fluoroquinolones is much better established. Later-generation fluoroquinolones are included even in extensively drug resistant (XDR)-TB regimens since they may have some efficacy against ofloxacin-resistant strains [3].

The area under the concentration–time curve up to 24 h post-dosage (AUC_{24}) is generally considered as the best predictor of fluoroquinolone efficacy [1]. Among fluoroquinolones, moxifloxacin is considered the most bactericidal, with potency comparable to that of isoniazid, and also seems to have some sterilising activity [1]. The maximal concentration (C_{max}) of moxifloxacin exceeds mutant prevention concentration [1] and the currently recommended dose of 400 mg is likely to suppress the emergence of resistance in 60% of patients [4]. However, pharmacokinetic data on moxifloxacin in patients with TB are scarce, especially in the setting of an MDR-TB regimen.

In this report of a pilot prospective study, we present preliminary data on pharmacokinetic parameters in patients with MDR- or XDR-TB receiving second-line treatment. Patients were receiving moxifloxacin (Avelox®; Bayer, Leverkusen, Germany) *p.o.* for $\geqslant$4 days, in order to achieve a steady state, as part of their anti-TB treatment, which was based on drug susceptibility test results. Quinolone resistance was determined by ofloxacin susceptibility testing. All patients gave informed written consent and the study was approved by the hospital's ethical committee.

Plasma samples were collected *via* a peripheral venous catheter immediately before and 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 h after the moxifloxacin dose. Samples were stored at -20°C until they were analysed. Moxifloxacin concentration was determined by high-performance liquid chromatography with fluorescence detection as previously described [5]. The AUC_{24} was calculated according to the trapezoidal rule.

Seven patients (five males and two females, mean$\pm$SD age 40.1$\pm$15.7 yrs) were included in the study. All patients were HIV negative, suffered from extensive pulmonary TB, and had normal renal and hepatic function. Patients received 400 mg of moxifloxacin daily, a mean dose of 5.5 mg·kg^{-1}. None of the patients was on treatment with antacids, sucralfate, drugs containing metal cations, multivitamins containing iron or zinc, nonsteroidal anti-inflammatory drugs, or class IA and III antiarrhythmics. Moxifloxacin was well tolerated and no adverse effects were reported. The mean period of treatment until sample collection was 244.1$\pm$257.3 days. Patients' characteristics, comorbidities, anti-TB drugs, pharmacokinetic parameters and outcomes are presented in table 1. Mean C_{max} was 4.59$\pm$2.06 mg·L^{-1} and was reached after 2.36$\pm$0.56 h (T_{max}). Mean AUC_{24} was 37.96$\pm$16.52 mg·h·L^{-1}. Both C_{max} and AUC_{24} showed a high variability.

To our knowledge, this is the first pharmacokinetic analysis of moxifloxacin in a series of patients with MDR-TB. Concerning C_{max} and AUC_{24}, our results are in agreement with previous reports on moxifloxacin pharmacokinetics in healthy volunteers [6]. In addition, PELOQUIN *et al.* [7] and NIJLAND *et al.* [8], in two interesting studies administered moxifloxacin in patients with drug-susceptible TB either before or after the end of standard treatment, observed similar results. However, in the only study evaluating pharmacokinetic parameters in the setting of an anti-TB regimen, significantly lower values were detected (C_{max} 2.5 mg·L^{-1}, AUC_{24} 24.8 mg·h·L^{-1}) [9]. The reasons for this discrepancy are not clear. One possible explanation might be the co-administration of rifampicin in 10 out of 16 patients for whom pharmacokinetic analysis was available, although the moxifloxacin AUC_{24} was not statistically significantly different between patients who received rifampicin and those who did not [9]. As shown by NIJLAND *et al.* [8], rifampicin reduces moxifloxacin C_{max} and AUC_{24} by ~30%. The percentage of 30% corresponds to the difference between our results and those of PRANGER *et al.* [9]. Rifampicin, like all absorbable rifamycins, is a well-known inducer of cytochrome P450 isoenzymes, and induces phase II metabolic processes of glucuronidation and sulfation. Since cytochrome P450 is not involved in moxifloxacin metabolism, the rifampicin–moxifloxacin interaction is expected to result from the induction of phase II metabolism. It is noteworthy that three of our patients were receiving rifabutin. To our knowledge, no trials examining the effect of rifabutin on moxifloxacin metabolism have been conducted. However, the possibility of an interaction between these two drugs cannot be excluded, although, according to our results, it would probably be weaker than the rifampicin–moxifloxacin interaction. It is known that rifabutin is a less potent enzyme inducer than rifampicin. Isoniazid, which was also administered in the study by NIJLAND *et al.* [8], is only known to affect cytochrome P450 metabolism and, thus, it is not expected to alter moxifloxacin levels. Therefore, considering moxifloxacin levels, patients with MDR-TB receiving moxifloxacin (but not rifampicin) have an advantage in comparison with patients with DR-TB receiving both drugs. Interactions between moxifloxacin and pyrazinamide or second-line agents have not been clearly established in the literature.

In contradiction to previous data, in the present study, mean T_{max} was more than double the value usually observed. This discrepancy may be attributed to co-administered drugs the impact of which on the pharmacokinetics of moxifloxacin has not been investigated yet. Interestingly, T_{max} reached its higher value (3 h) in the two patients with the lowest C_{max} and AUC_{24}.

In accordance with the study by PRANGER *et al.* [9], a high variability of C_{max} and AUC_{24} values was observed. As shown

TABLE 1 Patients' characteristics, comorbidities, medication, pharmacokinetic parameters and outcomes

Patient	Age yrs	Sex	Weight kg	BMI kg·m^{-2}	TB	Comorbidity	Anti-TB drugs	Treatment time days	C_{max} mg·L^{-1}	T_{max} h	AUC_{24} mg·h·L^{-1}	Final outcome
1	41	M	105	33.5	MDR	Diabetes	Rfb, Z, Cm, Mfx, Eto, Cs	696	6.94	2.5	51.14	Cured
2	58	M	61	21.6	XDR	COPD	Cm, Mfx, Eto, Cs, PAS	83	6.44	2.5	52.79	Died while on treatment (COPD exacerbation)
3	39	M	92	30	MDR	Diabetes	Z, Cm, Mfx, Eto, Cs	425	5.77	2	52.78	Cured
4	29	M	86	26	XDR		Rfb, Z, Cm, Mfx, Eto, Cs	365	2.49	3	24.04	Failed
5	26	F	52	20.6	XDR		E, Cm, Mfx, Eto, Cs	8	1.32	3	9.17	Died while on treatment (suicide)
6	64	M	69	23.9	MDR	Peptic cancer	E, Cm, Mfx, Eto, Cs	81	4.38	2	37.29	Still on treatment, improved
7	24	F	44	17.6	MDR	CF	Rfb, Am, Mfx, Eto, Lzd, Ipm/Cln	51	4.81	1.5	38.54	Still on treatment, improved

BMI: body mass index; TB: tuberculosis; C_{max}: maximal concentration; T_{max}: time at which C_{max} reached; AUC_{24}: area under the concentration–time curve up to 24 h post-dosage; M: male; F: female; MDR: multidrug-resistant; XDR: extensively drug-resistant; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis; Rfb: rifabutin; Z: pyrazinamide; Cm: capreomycin; Mfx: moxifloxacin; Eto: ethionamide; Cs: cycloserine; PAS: para-aminosalicylic acid; E: ethambutol; Am: amikacin; Lzd: linezolid; Ipm/Cln: imipenem/cilastatin.

in table 1, two groups of patients can be recognized, those with a C_{max} of ~6 mg·L^{-1} and an AUC_{24} >50 mg·h·L^{-1}, and those with significantly lower values. In the first group, the AUC_{24}/minimum inhibitory concentration (MIC) ratio would exceed 100 for an MIC of 0.5 mg·L^{-1}. These differences are hard to explain since patients were repeatedly instructed not to use medications with known effects on moxifloxacin metabolism. Additionally, none of the patients was underweight at the time of the pharmacokinetic analysis or during the whole anti-TB treatment, with the exception of patient 7, a patient with cystic fibrosis. In the case of patient 5, low values may be explained by poor compliance. The case of patient 4 with ofloxacin-resistant TB is more intriguing, since there were no compliance issues and low AUC_{24} may actually have deprived this patient of a possible cure. Surprisingly, the clinical condition of this patient remained exceptionally good despite treatment failure. However, given the complexity of the second-line regimens, it is difficult to attribute this treatment failure strictly to the low levels of moxifloxacin. It has been suggested that moxifloxacin may be effective in ofloxacin-resistant TB when MIC is $\leqslant$2 mg·L^{-1} [10]. Therefore, in agreement with PRANGER *et al.* [9], we conclude that the standard dose of 400 mg of moxifloxacin is not sufficient for all patients and this is especially true for XDR-TB cases.

In this setting, monitoring of therapeutic concentrations of moxifloxacin, particularly in patients with XDR-TB, could have a significant impact on clinical decisions. However, it is noteworthy that the pharmacodynamic target for *Mycobacterium tuberculosis* has not been defined, *i.e.* it is not clear whether the AUC_{24}/MIC ratio should exceed 40 (as in the case of Gram-positive bacteria) or 100 (as is generally indicated in the case of Gram-negative bacterial infections). Given the complexity of anti-TB regimens and the variability of moxifloxacin concentrations among patients receiving the same regimen, it is imperative that specific pharmacodynamic targets should be determined through properly designed clinical trials and, hence, appropriate adjustments of dosage may be attempted in clinical practice.

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An uncommon reason for dyspnoea: phrenic paresis secondary to alveolar echinococcosis

To the Editors:

We describe the presentation of an *Echinococcus multilocularis* (EM) infection (alveolar echinococcosis (AE)) with progressive massive orthopnoea and progressive dyspnoea on exertion due to infiltration of the diaphragm and phrenic nerves. Diagnosis was proved using a combination of computed tomography (CT), lung function in the supine and sitting position, sniff test during radioscopy and AE serology. Because of diffuse infiltration of the retroperitoneal and mediastinal space a surgical intervention was inapplicable. Thus, medical treatment was initiated using albendazole. Noninvasive ventilation (NIV) resolved orthopnoea and the patient was discharged.

AE occurs in the northern hemisphere but in Switzerland it is classified as a rare disease. To our knowledge this is the first described case of this rare infection with a consecutive bilateral paresis of the diaphragm. But despite its unique entity, this case report demonstrates that clinical findings and routine diagnostic methods may lead to the correct diagnosis.

Progressive phrenic paresis is a rare cause of orthopnoea and dyspnoea on exertion [1]. Relevant paresis is often overseen and diagnosed late in the course of the disease. The main reasons for bilateral phrenic paresis are traumatic, inflammatory, neuropathic, idiopathic or tumour related [1]. We present a case of a non-malignant compression caused by AE leading to bilateral phrenic paresis.

A 60-yr-old farmer's wife presented to a district hospital with progressive dyspnoea on exertion for 2 yrs. A cardiologic consultation at that time including echocardiography and exercise testing was unremarkable. Within the last year, the patient complained about weight loss of 10 kg and postprandial epigastric pain. During the final 2 months before presentation, the patient developed orthopnoea, panicking in the supine position. Clinical examination revealed extenuated breathing sounds on the left basal side, but no signs for left or right heart failure. Respiration showed a paradoxical breathing pattern in the supine position. Laboratory testing was unremarkable and showed normal brain natriuretic peptide and D-dimer-values. The chest radiograph depicted an elevation of the left side of the diaphragm but otherwise was unremarkable. Further investigations (echocardiography and gastroscopy) revealed no relevant pathology. Finally, a CT scan showed a multifocal, cystoid and hypodense mass in the retrocardial, transdiaphragmal and retrocaval space (fig. 1). Because of the rapid progression of symptoms the patient was brought to our tertiary care hospital (Cantonal Hospital St Gallen, St Gallen, Switzerland) for further diagnostics and therapy.

The reason for dyspnoea and orthopnoea was considered to be either phrenic paresis or inferior vena cava syndrome due to a cystic process of unknown origin, most likely malignant or by AE.

Based on the cystoid growth a screening test for Echinococcus species (Cellognost; Dade Behring Marburg GmbH, Marburg, Germany) was performed, which showed a highly positive result. AE was confirmed by the more specific antigen test for EM (Em2plus-ELISA; Bordier Affinity Products, Crissier, Switzerland).

Inferior vena cava syndrome was ruled out using angiography and manometry. By contrast, vital capacity dropped from 47% (sitting) to 26% in the supine position (fig. 2) and orthopnoea resolved when using noninvasive positive pressure ventilation despite the normocapnic blood gases. Finally radioscopy (sniff test) confirmed functional bilateral paresis of the diaphragm.

We concluded that the dyspnoea of the patient was due to a bilateral paresis of the diaphragm caused by the infiltration of the echinococcal mass.

Because of mediastinal and retroperitoneal infiltration the infection was not considered to be surgically curable and treatment using albendazole (400 mg *b.i.d.*) was initiated. Treatment will continue for many years or even for life. After initiation of nocturnal noninvasive home ventilation,