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Early View

Research letter

Treatment of MDR-TB using therapeutic drug monitoring: first experiences with sub-300 mg linezolid dosages using in-house made capsules

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Research letter ERJ

Treatment of MDR-TB using therapeutic drug monitoring: first experiences with sub-300 mg linezolid dosages using in-house made capsules

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Take home message: Therapeutic drug monitoring allows for sub-300 mg linezolid dosages once daily to successfully achieve PK/PD targets. Let's confirm these retrospective data in a prospective study using dried blood spots.

Despite all our efforts, the disease burden of tuberculosis (TB) is not falling fast enough to reach the 2030 milestone of the End TB strategy [1]. Multidrug-resistant tuberculosis (MDR-TB) remains a public health crisis, with low treatment success rates [1]. The repurposed drug linezolid has emerged as a core drug in MDR-TB treatment regimens [2,3], despite its toxicity, e.g. anemia, peripheral neuropathy and gastrointestinal disorders, optic neuritis, and thrombocytopenia [4,5]. Currently, linezolid is used off-label, as part of Group A “Medicines to be prioritised” of the World Health Organization MDR-TB treatment guideline [2] and in several large trials [6], such as the NIX- TB and END-TB trials.

We use a holistic approach to treat MDR-TB, focusing multidisciplinary on optimizing treatment using pharmacokinetics (PK) and pharmacodynamics, assessing and optimizing nutritional status, providing physical therapy and social care [7]. Treatment regimens are based on the WHO guidelines, but are individualized based on drug susceptibility testing (DST) combined with TDM if the regimen consists of second-line drugs or if patients are at risk for PK variability [8]. DST is performed at Dutch National Mycobacterial Reference Laboratory (RIVM, Bilthoven, The Netherlands).

Most patients start on a dose of 600 mg linezolid once daily. After two weeks, a full pharmacokinetic curve is obtained for all patients that receive linezolid, after which the dosage is lowered to 300 mg once daily. At steady state, the lowered dosage is again checked with TDM. Based on limited available literature, we strive for an area under the time – total fraction concentration curve (AUC_{0-24h}) / minimum inhibitory concentration (MIC) ratio >100 [9]. If TDM allows, the dose of linezolid is reduced further to an optimal, lowest dose, with the aim to reduce toxicity of linezolid [4,5,10]. If the AUC_{0-24h}/MIC ratio of linezolid is high enough, a dose reduction to 200 or even 150 mg of linezolid once daily is considered. In this study, we describe the first experiences of the treatment of MDR-TB using sub-300 mg dosages.

We retrospectively searched for inpatients for whom linezolid PK data was collected between 2015-2018. As routine treatment data were collected retrospectively and anonymously, the Institutional Ethical Review Board waived the requirement to obtain informed consent (METc 2013/492). Patients that received a sub-300 mg dose of linezolid were included. Baseline characteristics co-morbidities (HIV/HBV/HCV/diabetes), MIC for linezolid, treatment regimen, and treatment outcome, were obtained from the electronic hospital record and the discharge letter from the treating lung physician.

Twenty-seven patients with linezolid pharmacokinetic data were identified. Of these patients, 18 (66%) had a final dose ≥ 300 mg linezolid once daily. Nine (34%) patients received a sub-300 mg dose of linezolid and were included in our study (see Table 1). These patients had a median (range) weight

of 55 (43-77) kg. At admission, patients had a median (range) leucocyte count 6.6 (4.6-10.8) $\times 10^9/L$, thrombocytes 324 (238-461) $\times 10^9/L$, and hemoglobin 13.2 (11.8-16.3) g/dL. At admission, one of the patients was 32 weeks pregnant. Based on local policy, the individual patient and her preferences, it was decided – in contrast with standard practice – that the start of treatment of MDR-TB could be postponed until the patient gave birth to a healthy child.

Four patients had pulmonary TB, two had extra-pulmonary TB, one had miliary TB, one had pleural TB, and one had a combination of pulmonary and extra-pulmonary TB. DST revealed that eight patients had MDR-TB and one had rifampin resistant TB. The MIC for linezolid of the *Mycobacterium tuberculosis* isolate was 0.25 mg/L for seven patients and 0.5 mg/L for two patients. Based on the available $\text{totalAUC}_{0-24h}/\text{MIC}$ ratios, dosages were lowered to 200 mg once daily in four (15%) patients and 150 mg in five (19%) patients.

The sub-300 mg dosages of linezolid are prepared as capsules at the compounding department of our pharmacy. Commercially available linezolid tablets are pulverized and sieved. Lactose-1-water is used to create the correct volume of the homogenized powder mixture, after which transparent empty capsules are filled. All capsules are checked visually and ten capsules are checked for the correct weight and percentage of deviation ($\leq 3\%$) from the correct weight. The capsules are kept at room temperature for a maximum of one year.

With the sub-300 mg dosages of linezolid, the patients had a median (range) totalAUC_{0-24h} of 50 (49-57) $\text{mg}\cdot\text{h}/L$. In three cases, there was no AUC_{0-24h} available for the lowest dose due to logistical issues. In these cases, the totalAUC_{0-24h} of the lowest dose was calculated using our linezolid pharmacokinetic model [11] in MWPharm++ (Mediware, Groningen, the Netherlands). The median (range) $\text{totalAUC}/\text{MIC}$ ratio was 196 (98-276), with all except one patient attaining the target of 100 that is used in our clinic, based on a systematic review of literature [12]. Since the AUC/MIC ratio of that patient was 98, we did not increase the dose.

As soon as the patients received and tolerated their tailor-made regimen, treatment was continued at home. The included patients finished their treatment as outpatients under supervision of the staff of our center. At discharge, patients had a median (range) leucocyte count 4.7 (3.7-7.3) $\times 10^9/L$, thrombocytes 270 (159-327) $\times 10^9/L$, and hemoglobin 13.7 (11.1-16.4) g/dL. None of the patients had significant adverse events or toxicity from the linezolid dosages they received. Despite the fact that we cannot draw any conclusions about the safety or efficacy of our approach, after discharge, all except one patient (lost to follow-up) finished their treatment regimens successfully.

This study describes the treatment of TB with linezolid dosages lower than 300 mg. Linezolid is known for its side effects, with a meta-analysis showing adverse events in 58.9% of patients with linezolid containing regimens to treat MDR-TB [4]. Higher dosages of linezolid (i.e. >600mg) show more side effects than lower dosages (i.e. between 300-600mg) [4,5]. In our study, in nine out of 27 patients, TDM combined with DST allowed for lowering the linezolid dosage to 200 mg or 150 mg once daily, thereby possibly limiting the number of side effects even further.

Obviously, there are limitations to this study, such as the small number of patients, missing data, and the retrospective character of the study. We do not yet have long term follow-up data, although so far no relapses occurred. We only performed PK analysis of blood samples, not of the affected tissue [13,14]. Also, the applicability of this study to low-income countries, where MDR-TB is most prevalent, might be limited. For instance, a compounding unit in a pharmacy that is able to produce linezolid capsules might not be readily available. In these cases, one could perhaps consider using quarter tablets of 600 mg linezolid (or 300 mg every two days) to administer 150 mg once daily, however one must then make sure splitting is done in a correct and safe manner. We have not studied the bioequivalence of our capsules. However, since the absorption of linezolid is usually fast and complete, PK of linezolid is non-linear, and we performed TDM, we do not expect this to impact the treatment outcome. Furthermore, TDM is not available everywhere, but dried blood spots (DBS) [15] combined with limited sampling methods [11] might allow for this strategy to be implemented in other settings. There is still an ongoing discussion on the most appropriate PK/PD target for linezolid. In our clinic, we use an AUC/MIC target of > 100 using the total fraction concentration of linezolid, based on a recent manuscript as a part of a WHO initiative to systematically review the current recommended dose for second-line TB drugs [12]. In future research, besides applicability and implementation of TDM in low-income countries, cost-benefit should also be studied. By administering lower dosages of linezolid in patients if the AUC_{0-24h} and MIC allows, drug costs per patient of this rather expensive drug is reduced. Finally, lower dosing might reduce dose-related toxicity allowing treatment for a prolonged period of time [16].

In conclusion, sub-300 mg doses of linezolid can achieve putative PK/PD targets in certain patients. A large prospective study with DBS might provide us with valuable information on the possibilities to implement this strategy in other settings.

Table 1 baseline characteristics and pharmacokinetic/pharmacodynamic results patients receiving sub-300mg dosages of linezolid as a part of their tuberculosis treatment regimens

Parameter	Value
Subjects	9
Age (years)	27 (17-55)
Male	4 (44%)
Weight (kg)	55 (43-77)
Height (m)	1.65 (1.55-1.88)
Body mass index (kg/m ²)	20.5 (16.2-24.1)
Continent of origin	
Asia	4 (44%)
Europe	4 (44%)
Africa	1 (12%)
HIV, Hepatitis B or C positive	0/7
Drug susceptibility	
Multidrug-resistant	8
Rifampicin-resistant	1
Treatment regimen	
Linezolid	9/9
Moxifloxacin	9/9
Amikacin	8/9
Ethambutol	8/9
Clofazimine	6/9
Pyrazinamide	5/9
Protionamide	2/9
(High dose) isoniazid	2/9
Cycloserin	1/9
Linezolid	
Lowest dose (once daily)	
200 mg	4 (44%)
150 mg	5 (56%)
Dose per kg body weight (mg/kg)	3.1 (2.0-4.7)
$totalAUC_{0-24h}$ (mg*h/L)	50 (35-73)
C_{min} (mg/L)	0.5 (0.3-1.2)
$MIC_{linezolid}$	
0.25 mg/L	7 (78%)
0.5 mg/L	2 (22%)
$totalAUC_{0-24h}/MIC$	196 (98-276)

All data are presented as median (range) or number (percentage); linezolid concentrations are presented as total fraction concentrations (e.g. $totalAUC$); HIV: human immunodeficiency virus; weight, height, and body mass index were collected at admission; MIC: minimum inhibitory concentration; $totalAUC$: area under the time concentration curve.

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