Commentary

Minimum inhibitory concentration, pharmacokinetics/pharmacodynamics and therapeutic drug monitoring: An integrated approach for multidrug-resistant tuberculosis

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Development of drug resistance in *Mycobacterium tuberculosis* (*Mtb*) has been ascribed to inadequate treatment, insufficient dose or dosing frequency, non-adherence to the regimen, and pharmacokinetic (PK) variability.[1] PK variability becomes even more important given that emergence of drug resistance during the course of therapy is a major problem and sub therapeutic drug exposure may further select the drug resistant mutants. Timely intervention to adjust the doses based on the PKs derived as a result of therapeutic drug monitoring (TDM) has been shown to benefit the patients, especially those with multidrug-resistant tuberculosis (MDR-TB).[2] While antibiotic susceptibility testing (AST) is already in practice and provides valuable information, TDM has not been used to its full potential for the management of tuberculosis.

As a clinical standpoint it is important to know the minimum inhibitory concentration (MIC) of a drug toward the infecting bacteria as well as the drug concentration achieved in patients after administration of the standard doses of anti-tuberculosis drugs (i.e. therapeutic drug monitoring (TDM)). The critical concentration or the susceptibility breakpoint is the lowest concentration of drug inhibiting 95% of the wild type strains of *Mtb*, never been exposed to drug in question, and those clinical strains not inhibited at this concentration labeled as drug resistant.[3] There is a surge in number of reports/cases with MDR-TB and extremely-drug resistant tuberculosis (XDR-TB), and recent reports of totally drug resistant tuberculosis further stress on the importance of the susceptibility testing for *Mtb*.[4,5] In this context it's a gloomy fact that selection of these critical concentration for anti-tuberculosis drugs lack scientific evidence.[6,7] Thus, it becomes imperative to design new susceptibility breakpoint for anti-tuberculosis drugs in the background of scientific evidences and available relevant data.

To address this problem Gumbo[7] interrogated the anti-tuberculosis drug susceptibility breakpoints in the year 2010. Computer-aided clinical trial simulations applied to *in vitro* PK/PD data along with the patient data and new susceptibility breakpoints were derived. For low and high-level isoniazid resistance the breakpoints were proposed to be 0.0312 mg/L and 0.125 mg/L, respectively. The susceptibility breakpoint for rifampin was proposed to be 0.0625 mg/L, for pyrazinamide 50 mg/L, for ethambutol 4.0 mg/L, and for moxifloxacin was projected as 1.0 mg/L.[7] This was followed by another study from South Africa projecting the susceptibility breakpoint for ofloxacin as 0.5 mg/L[8] using the same methods applied by Gumbo.[7] These PK/PD derived susceptibility breakpoints are now backed by clinical studies. In one such study Gene-Xpert technology demonstrated that some rifampin resistance isolates with *rpoB* mutations had MICs below the standard 1.0 mg/L and these MIC values were as low as 0.125 mg/L.[9] Interestingly this observed lower MIC was very close to the one derived from PK/PD and simulation studies (0.0625 mg/L).[7] As predicted by simulation[7] these patients failed to improve on rifampin-containing standard combination therapy.[9] Second supporting evidence comes from the study done in the Netherlands reporting isolates with a rifampin MIC of 0.25-1.0 mg/L harboring mutation at Asp516Tyr of *rpoB* gene.[10]

Toxicity of the anti-TB drugs poses another problem in the effective treatment of TB (both drug sensitive and drug-resistant). Many drugs which have good efficacy against *Mtb* are equally toxic at the standard doses administered. Therefore, PK/PD based dose selection becomes very important. In this context two recent reports calls for attention towards equally effective and less toxic dose selection of linezolid.[2,11] The first report is a PK drug-drug interaction study between linezolid (300 mg twice daily) and clarithromycin.[2] Co-administration of 500 mg clarithromycin was found to significantly increase the peak serum concentration (C_{max}) of linezolid from 6.0 to 9.4 mg/L and the area under the curve ($AUC_{0\text{-}12h}$) from 36.3 mg*h/L to 67.2 mg*h/L and was well tolerated by the patients. The second study addresses the drug penetration issue and measured the concentration of linezolid in the serum and lung tissue simultaneously from a patient with MDR-TB who underwent surgery.[11] Trough drug concentration in serum was 0.5 mg/L which was still above the minimal inhibitory concentration (MIC) 0.25 mg/L of the isolate.

Linezolid concentration was measured 3.87 μg/g in the left upper lobe, the most infected part, and 3.1 μg/g in the left lower lobe following surgery. It is important to note that by the time pulmonary resection was performed there was a 36 hours lapse after the last oral dose of linezolid and the concentrations were still measurable.

To summarize, MICs for nearly all major first- and second-line anti-tuberculosis drugs are now available[6] and these should be combined with the PK/PD data[12] to predict the clinical outcome of a regimen. The above mentioned studies are good illustration of integration of MIC, TDM, and PK/PD to significantly impact the decision making on the dose selection and dosing regimen, with the reference of linezolid for which cost and toxicity are major concern. While TDM provides the benefit of timely intervention to adjust the doses which could help overcome the toxicity issues with the more expensive second-line drugs, does add cost of therapy and methods to measure the drug concentration still need to be developed for many drugs. But given the very high overall cost to treat MDR/XDR-TB,[13,14] TDM will ultimately prove to be cost effective. Also early therapeutic interventions with adjusted doses may further shorten the duration of therapy.

To conclude, there are PK/PD and simulations tools available for clinically predictive susceptibility breakpoints and dose and dosing regimen should be developed in accordance with PK/PD parameters to suppress emergence of drug resistance in *M. tuberculosis*.

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