Comment on: Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study

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Sir,

The era of individualized dosing in infectious diseases is upon us and TB therapy is not going to be an exception. Notwithstanding the paternalistic idea that this would be difficult to achieve in low- and middle-income countries, the idea will have to be implemented in high-burden countries, which often happen to be low- and middle-income countries. Several advances make this inevitable: evolution-mandated biological variability, greater understanding of pharmacokinetic/pharmacodynamic science and the emergence of the pharmacometrician. These have direct relevance to the therapeutic drug monitoring study of Prahl et al.,1 which we read with interest and would like to comment on.

There are three central dogmas of modern short-course chemotherapy for TB, all interrelated. Directly observed therapy (DOT), the practice of a healthcare worker watching patients swallow their pills, has been adopted universally. This approach is meant to reduce therapy failure and minimize the emergence of MDR-TB. A second and related concept is that if this is done, therapy success will be ≥95%. Thus, the higher therapy failure rates in low- and middle-income countries have been blamed on poor-quality DOT programmes. Third, current guidelines explicitly say that there is expected to be little pharmacokinetic variability for first-line drugs; thus, therapeutic drug administering is applied only in special situations and the use of recommended standard doses should suffice.3

The small but instructive prospective study by Prahl et al.1 among Danes explodes those myths. First, these Danish patients were in a good-quality DOT programme, yet 18% failed therapy despite the DOT. In fact, this is close to the average rate of failure for Europe in larger studies and is therefore typical.2 This simply illustrates that therapy failure is often high despite DOT and good quality TB programmes. In this regard, our question for the authors is to inform us of the outcomes of the patients they excluded from the analysis because of poor adherence. Did those patients fail therapy or were the outcomes no different from the adherent ones? Second, clearly there was pharmacokinetic variability encountered even in this small group of patients. By definition, if the number of patients increases to say the 9 million treated worldwide each year, there will be even more patients who achieve low drug concentrations. Between-patient pharmacokinetic variability is a fact of evolution: no two patients treated with the same dose are exactly the same and each will achieve a concentration–time profile different from the other. Third, the pharmacokinetic variability clearly drove important clinical outcomes, superseding effects of adherence, given that all patients studied by Prahl et al.1 were adherent to therapy. This aspect has been identified in hollow fibre system TB studies in tandem with in silico clinical trial simulations, a prospective study in Cape Town and results of two meta-analyses.4–7 This also applies to paediatrics, as illustrated by a recent report from South Africa of acquired drug resistance emerging on DOT.8 This makes sense; pharmacokinetic variability leads to different concentrations achieved in patients after standard dosing and there is a concentration–effect relationship for bactericidal and sterilizing effects. Restated, dose is a poor surrogate for concentrations achieved in patients because of pharmacokinetic variability.

While the study by Prahl et al.1 is, in our opinion, an excellent and illustrative study, we would like to quibble with their equating 2 h concentration and Cmax. Usually, 2 h concentrations differ from the true Cmax, while the Tmax for these drugs varies from 0.5 to 8.0 h. Thus, while there is some correlation, the correlation would be expected to be low in cases of high between-patient variability in systemic clearance. In addition, it is interesting that their concentration threshold cut-off for rifampicin of 6.5 mg/L is close to the 6.6 mg/L we identified in the past.6 We are curious as to how patients above and below this concentration performed as regards to 2 month sputum outcomes. In addition, how well do the threshold concentrations of 58.3 mg/L for pyrazinamide and 8.8 mg/L for isoniazid that we identified for 2 month sputum conversion perform for the same time period based on their data?9 Do the authors have data as to how well the 2 h concentration correlates with AUC in the Danish population for the standard drugs?

The authors should also comment on acquired drug resistance. It is wise not to decouple effects of different drug concentrations on microbial kill of Mycobacterium tuberculosis from those on acquired drug resistance.9 This is because subtherapeutic concentrations of first-line anti-TB drugs also initiate the antibiotic resistance arrow of time and are a powerful driver of acquired drug resistance.6,7,9,10 In this regard, what were the resistance patterns encountered in the patients who failed therapy? This information could strengthen their case for the utility of therapeutic drug monitoring.
Transparency declarations
None to declare.

References

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Clinical significance of 2 h plasma concentrations of first-line anti-tuberculosis drugs: a prospective observational study—authors’ response

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Sir,

We thank Pasipanodya et al.1 for their interest in our study.2 The study was the first in a series of clinical studies measuring all four anti-TB drugs (rifampicin, isoniazid, ethambutol and pyrazinamide) simultaneously in blood samples from TB patients after developing an LC-MS/MS method at Statens Serum Institut, Copenhagen, Denmark. Until then samples were shipped overseas for analysis, which naturally took some time. Now plasma drug concentrations can be determined and reported the same day.

In Denmark TB patients are managed at a relatively few centers by infectious disease or pulmonary medicine specialists. There has until now not been consensus on when and why the plasma concentrations of anti-TB drugs should be monitored. The currently used 2 h blood sampling strategy and the use of normal Cmax concentrations from healthy adults as normal 2 h values are based on studies of Peloquin.3 Due to the relatively scarce and somewhat confusing published data on the pharmacokinetics and pharmacodynamics of standard anti-TB drugs, we have also performed more detailed pharmacokinetic analyses of all four compounds at 1 week and 4 weeks after the initiation of treatment of TB and will correlate these with the treatment effects including Monte Carlo simulation in order to estimate the optimal doses of rifampicin and isoniazid (J. B. Prahl, K. Skovbo Jensen, N. Seershholm, T. Wilcke, Å. B. Andersen, A. S. Cohen and N. Frimodt-Møller, unpublished data).

Even though the sample size in our study2 is small, the 18% failure rate corresponds to the overall failure rate in Denmark.4 We fully agree on the problem of taking only a 2 h blood sample as a marker for peak drug concentrations and further explore this issue in the above-mentioned pharmacokinetic study of the four anti-TB drugs. Nevertheless, it is noteworthy that the CRP level at the time of sampling correlates inversely with the 2 h plasma concentration of isoniazid and that therapy failure occurs more frequently in patients with lower 2 h plasma concentration levels of isoniazid and/or rifampicin. However, in order to perform more relevant pharmacokinetic/pharmacodynamic analysis, e.g. estimates of AUC/MIC ratios, we recommend that at least two blood samples, drawn at 1 h and at 3–4 h after drug intake, should be analysed.

Only one patient was excluded from our study2 due to a suspicion of poor adherence to treatment. As no follow-up was performed, this patient could not contribute to the interesting discussion regarding the effect on treatment outcome of pharmacokinetic variability versus non-adherence.

We did not experience the development of resistance in any of the cases of TB, although control sputum samples for the culture of Mycobacterium tuberculosis were only available for those patients with persistent expectoration. Also, no association could be demonstrated between 2 month sputum conversion and plasma