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Strategy To Limit Sampling of Antituberculosis Drugs Instead of Determining Concentrations at Two Hours Postingestion in Relation to Treatment Response

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We fully agree with Burhan et al. that "Numerous studies have reported low concentrations of antituberculosis drugs in tuberculosis (TB) patients, but few studies have examined whether low drug concentrations affect TB treatment response" (1). The current anti-TB drug regimen of 2HRZE-4HRE (2 months treatment with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months treatment with isoniazid, rifampin, and ethambutol) for drug-susceptible TB was based on numerous trials with similar favorable results, as this study shows (2). Fortunately, the majority of patients who receive and finish the treatment for drug-susceptible TB will respond completely to treatment (2). In cases of suspicion of inadequate exposure to anti-TB drugs and thereby a possibly suboptimal treatment response, indications for therapeutic drug monitoring (TDM) are those circumstances where the risk of treatment failure or toxicity is increased (3). Burhan et al. showed that first-line anti-TB drug concentrations in plasma at 2 h postingestion ($C_{2\ h}$) were often low but that culture results after 4 and 8 weeks of treatment were nevertheless favorable, i.e., negative (1). This raises the question of how much closer we are to predicting TB treatment response based on plasma concentrations of anti-TB drugs after this study.

One important limitation of Burhan et al.'s study is that the measurement of the anti-TB drug concentrations were done just once during treatment and that only a single sample at 2 h postdose to estimate the maximum concentration of a drug in serum (C_{max}) was used for the majority of patients. However, low 2-h concentrations do not rule out the possibility of delayed absorption. The relation between drug concentrations and efficacy has been determined in TB infection models, and it has been shown that the area under the concentration-time curve in relation to the MICs (AUC/MIC ratio) predicted efficacy best (4, 5). Therefore, we advocate measuring the AUC of each drug to evaluate a potential relationship between plasma concentrations of tuberculosis drugs and clinical outcome in TB patients. Besides, results of the MICs were lacking in the study of Burhan and coworkers. Not breakpoints but actual MICs are needed to calculate AUC/MIC values.

We are fully aware that full pharmacokinetic (PK) analysis is costly and difficult and that breakpoints are more frequently determined than actual MICs, but to be able to answer the question of whether TB drug concentrations influence clinical outcome, a strategy that assesses drug exposure (AUC) closely related to a full PK analysis should be considered. Limited-sampling strategies, using only 2 to 3 samples to predict AUC values with great accuracy and precision, may solve the problem of inadequate drug exposure assessment by $C_{2\ h}$ monitoring (6). Dried blood spot sampling, which is less expensive and more convenient for both patients and research teams, may help to collect the samples needed for predicting AUC values (7). The combination of limited-sampling strategies, dried blood spot analysis, and measuring actual MICs would give the information needed to determine the relation between TB drug concentrations and clinical outcome (8). In conclusion, we encourage investigators setting up clinical trials of TB patients to abandon classical $C_{2\ h}$ monitoring and replace it with full PK monitoring or limited sampling.

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REFERENCES

1. **Burhan E, Ruesen C, Ruslami R, Ginanjar A, Mangunnegoro H, Ascobat P, Donders R, van Crevel R, Aarnoutse R.** 2013. Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to treatment response in Indonesian pulmonary tuberculosis patients. Antimicrob. Agents Chemother. **57:**3614–3619. http://dx.doi.org/10.1128/AAC.02468-12.
2. **Fox W, Ellard GA, Mitchison DA.** 1999. Studies on the treatment of tuberculosis undertaken by the British medical research council tuberculosis units, 1946–1986, with relevant subsequent publications. Int. J. Tuberc. Lung Dis. **3**(10 Suppl 2)**:**S231–S279.
3. **Peloquin CA.** 2002. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs **62:**2169–2183. doi:http://dx.doi.org/10.2165/00003495-200262150-00001.
4. **Jayaram R, Gaonkar S, Kaur P, Suresh BL, Mahesh BN, Jayashree R, Nandi V, Bharat S, Shandil RK, Kantharaj E, Balasubramanian V.** 2003. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. Antimicrob. Agents Chemother. **47:**2118–2124. http://dx.doi.org/10.1128/AAC.47.7.2118-2124.2003.
5. **Jayaram R, Shandil RK, Gaonkar S, Kaur P, Suresh BL, Mahesh BN, Jayashree R, Nandi V, Bharath S, Kantharaj E, Balasubramanian V.** 2004. Isoniazid pharmacokinetics-pharmacodynamics in an aerosol infection model of tuberculosis. Antimicrob. Agents Chemother. **48:**2951–2957. http://dx.doi.org/10.1128/AAC.48.8.2951-2957.2004.
6. **Pranger AD, van Altena R, Aarnoutse RE, van Soolingen D, Uges DR, Kosterink JG, van der Werf TS, Alffenaar JW.** 2011. Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. Eur. Respir. J. **38:**888–894. http://dx.doi.org/10.1183/09031936.00176610.
7. **Vu DH, Alffenaar JW, Edelbroek PM, Brouwers JR, Uges DR.** 2011. Dried blood spots: a new tool for tuberculosis treatment optimization. Curr. Pharm. Des. **17:**2931–2939. http://dx.doi.org/10.2174/138161211797470174.
8. **Alffenaar JW.** 2012. Dried blood spot analysis combined with limited sampling models can advance therapeutic drug monitoring of tuberculosis drugs. J. Infect. Dis. **205:**1765–1766. http://dx.doi.org/10.1093/infdis/jis270. (Author reply, **205:**1766, http://dx.doi.org/10.1093/infdis/jis271.)

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