Effect of tablet crushing on drug exposure in the treatment of multidrug-resistant tuberculosis

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Abstract

SETTING—Treatment outcomes in multidrug-resistant tuberculosis (MDR-TB) are poor. Due to drug toxicity and a long treatment duration, only approximately half of patients are successfully treated. Medication is often crushed for patients who have difficulty swallowing whole tablets. It is unknown whether crushing affects drug exposure in the treatment of MDR-TB.

OBJECTIVE AND DESIGN—We performed a sequential pharmacokinetic study in patients over 18 years of age on MDR-TB treatment at two hospitals in Cape Town. We compared the bioavailability of pyrazinamide, moxifloxacin, isoniazid, ethambutol, and terizidone when the tablets were crushed and mixed with water prior to administration versus swallowed whole. We sampled blood at six time points over 10 hours under each condition separated by two weeks. Non-compartmental analysis was used to derive the key pharmacokinetic measures.

RESULTS—Twenty participants completed the study: 15 were men, and median age was 31.5 years. There was a 42% reduction in the AUC₀–₁₀ of isoniazid when the tablets were crushed compared to whole (geometric mean ratio 58%; 90% CI: 47% to 73%). Crushing pyrazinamide, moxifloxacin, ethambutol, and terizidone did not significantly affect bioavailability.

CONCLUSIONS—We recommend that crushing of isoniazid tablets in the MDR-TB treatment regimen be avoided. Paediatric isoniazid formulations may be a viable alternative when the crushing of isoniazid is indicated.

Keywords

MDR-TB; crushed; pharmacokinetic; bioequivalence; bioavailability
INTRODUCTION
Outcomes in multidrug-resistant tuberculosis (MDR-TB) are poor with treatment completion rates at approximately 54%.\(^1\) A heavy pill burden, together with nausea and vomiting, which is reported to occur in up to 75% of patients,\(^2\)–\(^4\) contribute to poor regimen tolerability.\(^5\) It is regular practice in some centers to crush medication, mixing the crushed tablets with water to ease ingestion in the belief that this will reduce gastrointestinal upset. Crushing of tablets before administration is also common in young children as suitable formulations are frequently not available for those unable to swallow whole tablets. One qualitative study at a paediatric hospital in Cape Town reported that up to 69% of caregivers crush, dissolve, or mix TB medication with food prior to administration.\(^6\) Crushing tablets may also be necessary in critically ill patients with a depressed level of consciousness who are unable to swallow, and therefore require drug administration via a nasogastric tube. However, tablet crushing may alter bioavailability of the active ingredients within the drug.\(^7\) Studies comparing the bioavailability of crushed versus whole medication have shown that crushing decreases plasma concentrations of some drugs, including rifapentine, but not others.\(^8\)–\(^12\) Combining the crushed tablets of a multidrug regimen is common, moreover the tablets may be mixed into a vehicle-containing substance that reacts with the drugs.\(^12,\)\(^13\) Remnants may also adhere to the walls of the container in which the medication was crushed and thereby escape ingestion. Subtherapeutic plasma concentrations of some first and second line anti-TB drugs have been associated with poor clinical outcomes, including acquisition of drug resistance.\(^14\)–\(^16\) It is therefore important to understand whether crushing affects exposure of the drugs used to treat MDR-TB, many of which are key drugs in the recently updated WHO-recommended management guidelines.\(^17\)

STUDY POPULATION AND METHODS
We performed a sequential pharmacokinetic study, including two intensive pharmacokinetic blood sampling occasions in patients over 18 years of age on MDR-TB treatment at Brooklyn Chest Hospital and DP Marais Hospital in Cape Town. Between May 2016 and February 2017, we recruited participants with rifampicin-resistant TB who qualified for MDR-TB treatment. At the time of the study, the standard MDR treatment regimen consisted of pyrazinamide, moxifloxacin, kanamycin, cycloserine (dosed as terizidone), and either ethionamide or isoniazid depending on the results of the line-probe assay for katG and inhA mutations identified in the pretreatment sputum culture, indicating high-level resistance to isoniazid or low-level resistance to isoniazid and resistance to ethionamide, respectively.\(^18\) Ethambutol was added if there had been no ethambutol exposure in the month prior to treatment initiation, and the possibility of ethambutol resistance was considered low. We considered patients eligible for recruitment who were taking whole tablet MDR therapy, either for MDR-TB (defined as resistance to both rifampicin and isoniazid)\(^17\) or for rifampicin mono-resistant TB (resistance to rifampicin but sensitive to isoniazid). Two pharmacokinetic sampling occasions spaced approximately one to three weeks apart to allow as little inter-occasion variability as possible, were completed for each participant a minimum of two weeks after treatment initiation. Drug doses were in accordance with the national treatment guidelines during the study period and adjusted for toxicity prior to the first pharmacokinetic sampling occasion at the discretion of the treating clinician.\(^19\)
In the event of low level isoniazid resistance, participants were dosed with high dose isoniazid (10–15mg/kg); the standard dose of isoniazid (5mg/kg) was prescribed for participants with rifampicin mono-resistant TB. Participants were given the same drug doses on both pharmacokinetic sampling occasions, whole tablets on the first and crushed tablets on the second. Participants continued with whole tablet therapy until the second pharmacokinetic sampling occasion when they received crushed tablets, thereafter they continued on whole tablet therapy. Dosing was performed under fasting conditions and was strictly observed by the study doctor or nurse.

On the second pharmacokinetic sampling occasion, tablets were crushed with a standard-size mortar and pestle, terizidone capsules were carefully opened. All contents were mixed with 200mL of water in a mixing cup. After ingestion, tablet remnants adhering to the walls of either the mortar, pestle or mixing cup were scraped off with a spatula, mixed with a small unmeasured amount of water and swallowed by the participant. A standard breakfast was given to all participants at least one hour after dosing. We recorded all concurrent medication, which could influence plasma drug concentrations via drug-drug interactions.

We sampled blood at the following time points on both pharmacokinetic sampling occasions: pre-dose and at 2, 4, 6, 8, and 10 hours post dose. After centrifugation, plasma was extracted using a pipette and stored temporarily on dry ice before being transported to the Division of Clinical Pharmacology at the University of Cape Town for storage at minus 80°C. Plasma drug concentrations were determined using liquid chromatography tandem-mass spectrometry assays. These assays were validated according to US Food and Drug Administration and European Medicines Agency guidelines.

We used Stata v15.0 (Stata Corp, College Station, Texas, USA) to perform the non-compartmental pharmacokinetic and statistical analysis. We determined the following pharmacokinetic parameters for each drug on both dosing occasions: area under the concentration-time curve at 0–10 hours (AUC$_{0–10}$) using the trapezoidal rule, area under the concentration-time curve extrapolated to infinity (AUC$_{\infty}$), half-life, peak concentration ($C_{\text{max}}$), and time to $C_{\text{max}}$. We regarded pre-dose drug concentrations below the lower level of quantification (BLQ) as zero if all the pre-dose concentrations for a particular drug were BLQ. If any pre-dose concentrations for a drug were quantifiable, we then regarded all pre-dose BLQ concentrations for that drug to be half the lower level of quantification (LLQ).

Similarly, since post-dose drug concentrations within the sampling interval are unlikely to be zero, we considered any post-dose BLQ results for any of the drugs to be half the LLQ. We used the Wilcoxon signed-rank test for paired data, to compare $C_{\text{max}}$ and AUC$_{0–10}$ at each occasion. The log-transformed $C_{\text{max}}$ and AUC$_{0–10}$ for the crushed and whole tablet exposure were then compared with t-tests. The geometric mean ratio (GMR) point estimates and 90% confidence intervals of the $C_{\text{max}}$ and AUC$_{0–10}$ for crushed versus whole tablets were calculated for pyrazinamide, moxifloxacin, ethambutol, isoniazid, and cycloserine.

Approval for this study was granted by the University of Cape Town Human Research Ethics Committee (106/2016). Written informed consent was taken from each participant in a language of their choice (English, Afrikaans or Xhosa). All informed consent was obtained prior to participant recruitment.
RESULTS

We recruited 25 participants, 20 of whom completed the study: four completed only the first pharmacokinetic sampling occasion and one participant was withdrawn before any pharmacokinetic sampling could be performed. Participant characteristics of the 20 participants who completed the study are shown in table 1. A descriptive comparison of the $C_{\text{max}}$ of each of the drugs in crushed and whole form compared with the expected range\textsuperscript{25} is shown in table 2. Table 3 demonstrates a comparison of the AUC\textsubscript{0–10} and $C_{\text{max}}$ of whole and crushed pyrazinamide, moxifloxacin, ethambutol, isoniazid and cycloserine. The AUC\textsubscript{0–10} of all drugs was reduced for crushed versus whole tablet formulations but the reduction was only significant for isoniazid. We did not evaluate ethionamide as too few participants (n=8) were receiving this drug at the time of pharmacokinetic sampling. The geometric mean ratios with 90% confidence intervals, for crushed versus whole tablets, are shown in Table 4. Table 5 compares additional pharmacokinetic parameters of whole and crushed forms for each of the drugs. The half-life and AUC\textsubscript{∞} of some drugs was incalculable in participants who had multiple drug concentration values reported as BLQ. Figure 1 shows the median time-concentration profiles of crushed and whole isoniazid to 10 hours post-dose. The median time-concentration profiles of crushed and whole cycloserine, pyrazinamide, moxifloxacin and ethambutol are shown in figure 2. The increased variability of isoniazid compared with the other drugs reflects the wider range of dosing, per isoniazid susceptibility, in participants with rifampicin-resistant TB.\textsuperscript{26}

DISCUSSION

We report significantly decreased exposure of isoniazid when the orally administered drugs in the MDR treatment regimen were crushed, and mixed with water. Dosing with crushed isoniazid could affect outcomes in MDR-TB, considering that low isoniazid exposure has been associated with a poor treatment response, including the development of drug resistance.\textsuperscript{14–16} The exposure of the crushed forms of the other drugs we assessed was also decreased compared to whole tablets at the same dose, but this did not reach statistical significance.

Little is known about the effect of crushing on drug exposure in the treatment of MDR-TB. Recently, a study in Cape Town observed low isoniazid exposures in children on MDR-therapy, most of whom were dosed with crushed isoniazid.\textsuperscript{27} Isoniazid is also a key drug in the treatment of drug-sensitive and drug-resistant TB and is the drug of choice in TB chemoprophylaxis,\textsuperscript{28,29} these findings therefore have important clinical implications, particularly in MDR-TB where the companion drugs are relatively less effective. The mechanism causing poor isoniazid exposure when MDR-TB drug formulations are crushed and mixed together in water, is currently unclear. Terizidone, which consists of two molecules of cycloserine,\textsuperscript{30} has been reported to interfere with the absorption of isoniazid, but this effect is poorly understood.\textsuperscript{31} A drug-drug interaction whereby cycloserine degrades isoniazid prior to absorption or inhibits isoniazid absorption could potentially be enhanced when the drugs are crushed and administered together in water. We observed the exposure of whole formulations of isoniazid at standard dose to be lower than reported in the literature (see table 2), with exposure of crushed isoniazid being significantly lower than the whole
formulation equivalent. Our finding of lower than expected exposures of whole formulations of isoniazid supports the notion of a possible drug-drug interaction, which is enhanced when the orally administered drugs are crushed together. We also considered that an interaction with an excipient used in the production of one of the other drugs in the regimen, may be a possible cause of isoniazid degradation when the tablets were crushed together. Another potential reason, which could explain the reduced exposure of crushed isoniazid, is that isoniazid is considered by some to be unstable when mixed with water, although to our knowledge there is no data to support this hypothesis. On the contrary, crushed isoniazid when included in a fixed drug combination has been shown to result in therapeutic concentrations in the treatment of adults with drug-sensitive TB. A powder formulation of isoniazid and crushed isoniazid tablets mixed with water have also been shown to achieve target concentrations in children.

In settings where the crushing of isoniazid is indicated, there are several possible approaches to ensure optimal dosing. Paediatric isoniazid formulations or constituting the dose with smaller isoniazid tablets (e.g.100mg) with proven bioequivalence that are more easily swallowed should be used instead of crushing isoniazid tablets in adults on treatment for MDR-TB. The extent to which the dose of isoniazid needs to be increased when crushed isoniazid is administered to patients is unclear and requires further study. We found a 42% reduction in AUC$_{0-10}$ of isoniazid when the tablets were crushed compared to whole formulations (geometric mean ratio 58%; 90% CI: 47% to 73%), indicating that the dose of isoniazid, if crushed together with the other drugs in the MDR-TB treatment regimen, will require a significant dose adjustment to achieve target concentrations. Although pyrazinamide, moxifloxacin, ethambutol, and cycloserine exposures were not significantly decreased by crushing, indicating that these drugs may be safely crushed when necessary, there was a trend toward lower exposure of crushed moxifloxacin compared with the whole formulation equivalent. It is possible that the effect on moxifloxacin exposure may have been enhanced with a larger sample size.

Our study has several additional limitations. First, when medication was crushed in our study, care was taken to ensure that as much of the crushed tablet remnants as possible were ingested by the participants by rinsing the mixing cup. We have observed nursing staff in busy treatment centers often do not have time to ensure that all crushed remnants are swallowed by the patients, which could result in a further reduction in drug exposure. It is possible that our study may have been more clinically relevant if we did not rinse the mortar, pestle and mixing cup after crushing the tablets on the second PK sampling day. Second, the crushed and whole tablet pharmacokinetic sampling occasions were not randomized. We therefore cannot exclude the possibility of a sequence effect on our bioavailability comparisons of crushed and whole tablet therapy. Third, the pre-dose sample on the second crushed pharmacokinetic sampling occasion reflects concentrations of whole tablets, which may have had some effect on the AUC, as there was insufficient time for complete washout of drugs with longer half-lives, particularly cycloserine.
CONCLUSIONS

We recommend that the crushing of isoniazid together with the other orally administered drugs in the MDR treatment regimen be avoided, and that paediatric isoniazid formulations be considered for use in adults instead if tablet crushing is indicated.

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REFERENCES

1. WHO. Global tuberculosis report [Internet]. 2017 [cited 2018 Jan 10]. p. 248 Available from: http://www.who.int/tb/publications/global_report/gtbr2017_annex4.pdf?ua=1
2. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2001;5(7):648–55. [PubMed: 11467371]
3. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One. 2012;7(7):e40781. [PubMed: 22792406]
4. Shin SS, Pasechnikov AD, Gelmanova IY, Peremtín GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis. 2007;11(12):1314–20. [PubMed: 18034952]
5. Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. “I cry every day”: experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Heal. 2013;18(9):1128–33.
6. Bélard S, Isaacs W, Black F, Bateman L, Madolo L, Munro J, et al. Treatment of childhood tuberculosis: caregivers’ practices and perceptions in Cape Town, South Africa. Paediatr Child Health. 2015;35(1):24–8. [PubMed: 25034798]
7. Royal pharmaceutical society. Pharmaceutical Issues when Crushing, Opening or Splitting Oral Dosage Forms [Internet]. 2011 [cited 2018 Aug 6]. Available from: https://www.rpharms.com/Portals/0/RPSdocumentlibrary/Openaccess/Support/toolkit/pharmaceuticalissuesdosageforms-%282%29.pdf
8. Weiner M, Savic RM, Kenzve WRM, Wing D, Peloquin CA, Engle M, et al. Rifapentine Pharmacokinetics and Tolerability in Children and Adults Treated Once Weekly With Rifapentine and Isoniazid for Latent Tuberculosis Infection. J Pediatric Infect Dis Soc. 2014;1–14. [PubMed: 26624904]
9. Best B, Capparelli E, Diep H, Rossi S, Farrell M, Williams E, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr. 2012;58(629):385–91.
10. Argenti D, Ireland D, Heald DL. A pharmacokinetic and pharmacodynamic comparison of desmopressin administered as whole, chewed and crushed tablets, and as an oral solution. J Urol. 2001;165(5):1446–51. [PubMed: 11342894]
11. Dodds Ashley ES, Zaas AK, Fang AF, Damle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. Antimicrob Agents Chemother. 2007;51(3):877–80. [PubMed: 17145785]

12. Rao KV, Kailasam S, Menon NR. Inactivation of isoniazid by condensation in a syrup preparation. Indian J Med Res. 1971;59(9):1343–53. [PubMed: 5161562]

13. Wu W, Chin T, Lach J. Interaction of isoniazid with magnesium oxide and lactose. J Pharm Sci. 1970;59(9):1234–42. [PubMed: 5469781]

14. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. J Infect Dis. 2013;208(9):1464–73. [PubMed: 23901086]

15. Chigutso E, Pasipanodya JG, Visser ME, Van Helden PD, Smith PJ, Sirgel FA, et al. Impact of nonlinear interactions of pharmacokinetics and mics on sputum bacillary kill rates as a marker of sterilizing effect in tuberculosis. Antimicrob Agents Chemother. 2015;59(1):38–45. [PubMed: 25313213]

16. Swaminathan S, Pasipanodya JG, Ramachandran G, Kumar AKH, Srivastava S, Deshpande D, et al. Drug Concentration Thresholds Predictive of Therapy Failure and Death in Children with Tuberculosis: Bread Crumb Trails in Random Forests. Clin Infect Dis. 2016;63(September):S63–74. [PubMed: 27742636]

17. WHO. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) [Internet]. 2018 [cited 2018 Aug 28]. Available from: http://www.who.int/tb/publications/2018/rapid_communications_MDR/en/

18. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10(9):621–9. [PubMed: 20797644]

19. South African department of health. Management of drug resistant tuberculosis [Internet]. 2013 p. 42–50. Available from: https://www.health-e.org.za/wp-content/uploads/2014/06/MDR-TB-Clinical-Guidelines-Updated-Jan-2013.pdf

20. Thee S, Garcia-Prats AJ, Draper HR, McIlleron HM, Wiesner L, Castel S, et al. Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. Clin Infect Dis. 2015;60(4):549–56. [PubMed: 25362206]

21. Bekker A, Schaa H, Draper HR, Laan L, Van Der, Murray S, Wiesner L, et al. Pharmacokinetics of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines. Antimicrob Agents Chemother. 2016;60(4):2171–9. [PubMed: 26810651]

22. Court R, Wiesner L, Stewart A, de Vries N, Harding J, Maartens G, et al. Steady state pharmacokinetics of cycloserine in patients on terizidone for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2018;22(1):30–3. [PubMed: 29297422]

23. European medicines agency. Guideline on bioanalytical method validation [Internet]. [cited 2018 Aug 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

24. FDA Center for Drug Evaluation and Research. Guidance for industry: bioanalytical method validation [Internet]. [cited 2017 Nov 30]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm368107.pdf.

25. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: An update. Drugs. 2014;74(8):839–54. [PubMed: 24846578]

26. Koegelenberg N, Nortje A, Lalla U, Enslin A, Irusen E, Rosenkranz B, et al. The pharmacokinetics of enteral antituberculosis drugs in patients requiring intensive care. South African Med J. 2013;103(6):394–8.

27. Winckler JL, Schaaf S, Draper HR, McIlleron H, Norman J, Van der Laan LE, et al. The pharmacokinetics of high dose isoniazid for the prevention or treatment of drug-resistant tuberculosis in HIV-infected and -uninfected children. In: 49th Union World Conference on Lung Health The Hague; 2018 Abstract EP04–128-26.

28. WHO. Guidelines for treatment of drug-susceptible tuberculosis and patient care [Internet]. 2017 [cited 2018 Jun 24]. 10–1. Available from http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/
29. WHO. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings [Internet]. 2015 [cited 2018 Jun 26]. Available from: http://apps.who.int/iris/bitstream/handle/10665/174052/9789241508872_eng.pdf?sequence=1

30. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: A meta-analysis. Vol. 17, International Journal of Tuberculosis and Lung Disease 2013 p. 1257–66.

31. TB Alliance. Cycloserine. Tuberculosis. 2008;88:100–1. [PubMed: 18486041]

32. Glass B, Haywood A. Stability considerations in liquid dosage forms extemporaneously. Can Soc Pharm Sci. 2006;9(3):398–426.

33. Schaaf HS, Parkin DP, Seifart HI, Werely CJ, Hesseling PB, Van Helden PD, et al. Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child. 2005;90(6):614–8. [PubMed: 15908628]

34. Kiser JJ, Zhu R, Argenio DZD, Cotton MF, Bobat R, Mcsherry GD, et al. Isoniazid pharmacokinetics, pharmacodynamics and dosing in South African infants. Clin Infect Dis. 2013;34(4):446–51.

35. NIH. AIDSinfo [Internet]. 2018 [cited 2018 Jul 26]. Available from: https://aidsinfo.nih.gov/drugs/123/isoniazid/10/professional
Figure 1:
Concentration-time profile of crushed versus whole isoniazid in 17 participants on treatment for multidrug-resistant tuberculosis
Upper and lower bound of whiskers: Upper and lower interquartile range
Median concentrations of crushed and whole tablets at each time point were offset for clarity
Figure 2:
Concentration-time profiles of crushed versus whole cycloserine, pyrazinamide, moxifloxacin and ethambutol in the treatment of patients* with multidrug-resistant tuberculosis
*n=20 unless otherwise indicated
Upper and lower bound of whiskers: Upper and lower interquartile range
Median concentrations of crushed and whole tablets at each time point are offset for clarity
Cycloserine and pyrazinamide concentrations are 10-fold the concentration displayed on the y-axis.
**Table 1:**
Participant characteristics* of 20 patients on therapy for multidrug-resistant tuberculosis in a sequential comparative pharmacokinetic analysis

|                          | Occasion 1       | Occasion 2       |
|--------------------------|------------------|------------------|
| Men/women                | 15/5             |                  |
| Multidrug-resistant tuberculosis/rifampicin mono-resistant tuberculosis |                  | 13/7             |
| Age (years)              | 31.5 (25.8 to 44.0) |                  |
| HIV-positive/negative    | 10/10            |                  |
| Weight (kg)              | 49 (44 to 54)    | 50 (44 to 55)    |
| BMI (kg/m²)              | 17.4 (16.0 to 19.3) | 17.1 (16.6 to 19.6) |
| Creatinine clearance (mL/min)‡ | 94.4 (81.1 to 105.5) | 92.1 (80.7 to 103.8) |
| Duration on treatment at time of pharmacokinetic sampling (days) | 40.5 (32 to 45) | 53 (44.5 to 60) |
| Dose (mg/kg)             |                  |                  |
| Pyrazinamide, n=20       | 29.8 (27.8 to 30.9) | 29.4 (27.3 to 31.1) |
| Isoniazid, n=17          | 11.8 (6.5 to 12.2) | 11.4 (6.4 to 12.1) |
| Moxifloxacin, n=20       | 8.2 (7.6 to 9.0)  | 8 (7.4 to 9.1)   |
| Ethambutol, n=19         | 16.7 (16 to 20)   | 17 (15.7 to 19.0) |
| Terizidone, n=20         | 15 (13.9 to 16.3) | 15 (13.8 to 16.0) |

* Unless otherwise indicated summarized as median (interquartile range)

‡ Cockcroft-Gault method
Table 2:
Comparison of peak concentrations of pyrazinamide, isoniazid, moxifloxacin, ethambutol and terizidone with expected ranges in patients on therapy for multidrug-resistant tuberculosis

| Drug            | Whole Cmax (mg/L) | Crushed Cmax (mg/L) | Expected Cmax (mg/L) |
|-----------------|-------------------|---------------------|----------------------|
| Pyrazinamide    | 42.7 (36.85 to 46.5) | 4.0 (38.25 to 46.95) | 20 to 60             |
| Isoniazid       |                   |                     |                      |
| Standard dose (5mg/kg), n=6 | 0.89 (0.56 to 1.22) | 0.55 (0.28 to 1.09) | 3 to 6               |
| High dose (10–15 mg/kg), n=11 | 4.83 (3.54 to 6.88) | 2.84 (2.08 to 4.22) |                      |
| Moxifloxacin, n=20 | 2.44 (2.06 to 2.68) | 2.27 (1.82 to 2.67) | 3 to 5               |
| Ethambutol, n=19 | 1.91 (1.58 to 2.27) | 1.82 (1.34 to 2.87) | 2 to 6               |
| Cycloserine, n=20 | 33 (26.6 to 36.6)  | 34.45 (29.45 to 38.95) | 20 to 35             |

Cmax: Peak concentration
Interquartile range in brackets
**Table 3:**
Comparison of median AUC\(_{0–10}\) and C\(_{\text{max}}\) between whole and crushed tablets in patients on treatment for multidrug-resistant tuberculosis

| Drug          | Whole AUC\(_{0–10}\)* | Crushed AUC\(_{0–10}\) | p  | Whole C\(_{\text{max}}\)† | Crushed C\(_{\text{max}}\) | p  |
|---------------|-------------------------|-------------------------|----|---------------------------|---------------------------|----|
| Isoniazid (n=17) | 13.8 (4.6 to 24.8)     | 7.3 (1.8 to 12.3)       | 0.02 | 3.5 (1.2 to 5.2)        | 2.1 (0.3 to 3.3)        | 0.02 |
| Pyrazinamide (n=20) | 316.1 (256.5 to 354.6) | 307.0 (281.8 to 341.4) | 0.35 | 42.7 (36.9 to 46.5)   | 41.0 (38.3 to 47.0)   | 0.13 |
| Moxifloxacin (n=20) | 15.2 (10.3 to 18.7)    | 14.2 (9.3 to 17.6)      | 0.22 | 2.4 (2.1 to 2.7)       | 2.3 (1.8 to 2.7)       | 0.06 |
| Ethambutol (n=19)  | 11.3 (9.5 to 12.8)     | 11.0 (8.4 to 15.2)      | 0.63 | 1.9 (1.6 to 2.3)       | 1.8 (1.3 to 2.9)       | 0.75 |
| Cycloserine (n=17) | 281.9 (227.7 to 308.7) | 281.2 (259.0 to 327.3) | 0.49 | 32.7 (26.4 to 34.8)   | 34.3 (29.9 to 39.2)   | 0.39 |

Interquartile range in brackets

* AUC\(_{0–10}\): Area under the concentration-time Curve from 0 to 10 hours
† C\(_{\text{max}}\): Peak concentration
Table 4:
Geometric mean ratio (90% confidence interval) of AUC_{0-10} and C_{max} for crushed versus whole tablets in the treatment of patients with multidrug-resistant tuberculosis

| Drug          | Isoniazid (n=17) | Moxifloxacin (n=20) | Pyrazinamide (n=20) | Ethambutol (n=19) | Cycloserine (n=20) |
|---------------|------------------|---------------------|---------------------|-------------------|-------------------|
| AUC_{0-10} *  | 58% (47% to 73%) | 89% (80% to 99%)    | 98% (93% to 103%)   | 100% (89% to 112%)| 101% (91% to 113%)|
| C_{max} †     | 54% (40% to 73%) | 90% (82% to 98%)    | 97% (93% to 101%)   | 101% (85% to 121%)| 102% (91% to 114%)|

* AUC_{0-10}: Area under the concentration-time Curve to 10 hours
† C_{max}: Peak concentration
Table 5:
Additional median pharmacokinetic measures in patients on second line drugs for multidrug-resistant tuberculosis

| Drug          | AUC∞ (µg·h/mL) | Half-life (hrs) | Tmax (hrs) |
|---------------|----------------|----------------|------------|
|               | Whole | Crushed | Whole | Crushed | Whole | Crushed |
| Isoniazid     |       |         |       |         |       |         |
|               | n=16  | n=13    | n=16  | n=13    | n=17  | n=17    |
|               | 16.5 (6.0 to 25.8) | 12.1 (7.5 to 13.3) | 2.4 (1.6 to 3.6) | 2.5 (1.9 to 3.3) | 2 (2 to 2) | 2 (2 to 2) |
| Pyrazinamide  |       |         |       |         |       |         |
|               | 619.3 (473.1 to 718.5) | 517.7 (437.8 to 727.5) | 9.0 (6.8 to 9.7) | 7.7 (6.7 to 10.3) | 2 (2 to 2) | 2 (2 to 2) |
| Moxifloxacin  |       |         |       |         |       |         |
|               | 21.8 (11.9 to 27.1) | 21.2 (11.2 to 26.1) | 4.9 (4.0 to 6.1) | 4.8 (3.1 to 6.4) | 2 (2 to 2) | 2 (2 to 2) |
| Ethambutol    |       |         |       |         |       |         |
|               | n=19  | n=19    | n=19  | n=19    | n=19  | n=19    |
|               | 13.9 (12.0 to 16.4) | 14.4 (10.9 to 19.1) | 4.0 (3.3 to 4.6) | 3.8 (3.4 to 5.3) | 2 (2 to 2) | 2 (2 to 2) |
| Cycloserine   |       |         |       |         |       |         |
|               | n=18  | n=18    | n=18  | n=18    |       |         |
|               | 803.8 (575.0 to 1127.2) | 841.8 (553.3 to 1802.9) | 12.1 (11.0 to 28.4) | 11.8 (8.1 to 40.2) |       |         |

* n=20 unless otherwise indicated; interquartile range in brackets
† AUC∞: Area under the concentration-curve extrapolated to infinity
‡ Tmax: Time to peak concentration