# Parallel first order and mixed order elimination of pyrazinamide in South African patients with tuberculosis

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## BACKGROUND

We found that a zero-order input model with first order elimination of pyrazinamide [1] poorly described data in the absorption phase of a new cohort of South African patients with tuberculosis (TB). This may be due to model mis-specification for pyrazinamide absorption in [1] or a different dosage form with different absorption properties being used in the new cohort.

## OBJECTIVE

• To develop a pharmacokinetic model to describe the population pharmacokinetics of pyrazinamide in the new TB treated cohort.

## METHODS

• Seventy-nine patients were sampled 4-8 times during 2 steady state dosing intervals one month apart.

• All patients were receiving treatment with a fixed dose combination (Rifafour), each tablet containing rifampicin (150mg), isoniazid (75mg), ethambutol (275mg) and pyrazinamide (400mg) with directly observed administration.

• Liquid chromatography with tandem mass spectrometry was used for drug plasma concentration determination.

• Pharmacokinetic analysis used NONMEM VI FOCE with log-transformation of the data.

• Visual predictive checks (VPCs) were used for model evaluation.

• An external evaluation used an independent dataset compared by parameter estimates and VPC (Figure 1).

## RESULTS

• A combination of first order and mixed order elimination best described the elimination of pyrazinamide.

•The average steady state plasma concentration was 26mg/L, which results in 17% of pyrazinamide elimination being mixed order with the remainder being first order.

•A sequential, dual, first order process was used to describe drug absorption.

• A time-dependent residual error model was used to account for changes in the residual error with respect to time.

• Parameter estimates are shown in Table 1.

• Similar parameter estimates were obtained from the dataset used for external evaluation, except for a late $K_a$ of 2.2/h (cf 1.0/h), and females having 3% higher bioavailability compared to males (cf 26%).

• Figure 2 shows results of 2 simulations with patients at the lower end (38kg) and the upper end (54kg) of a typical pyrazinamide dosing weight band. One simulation is from our model and the other uses parameter estimates from an estimation using our model reduced to first order elimination only.

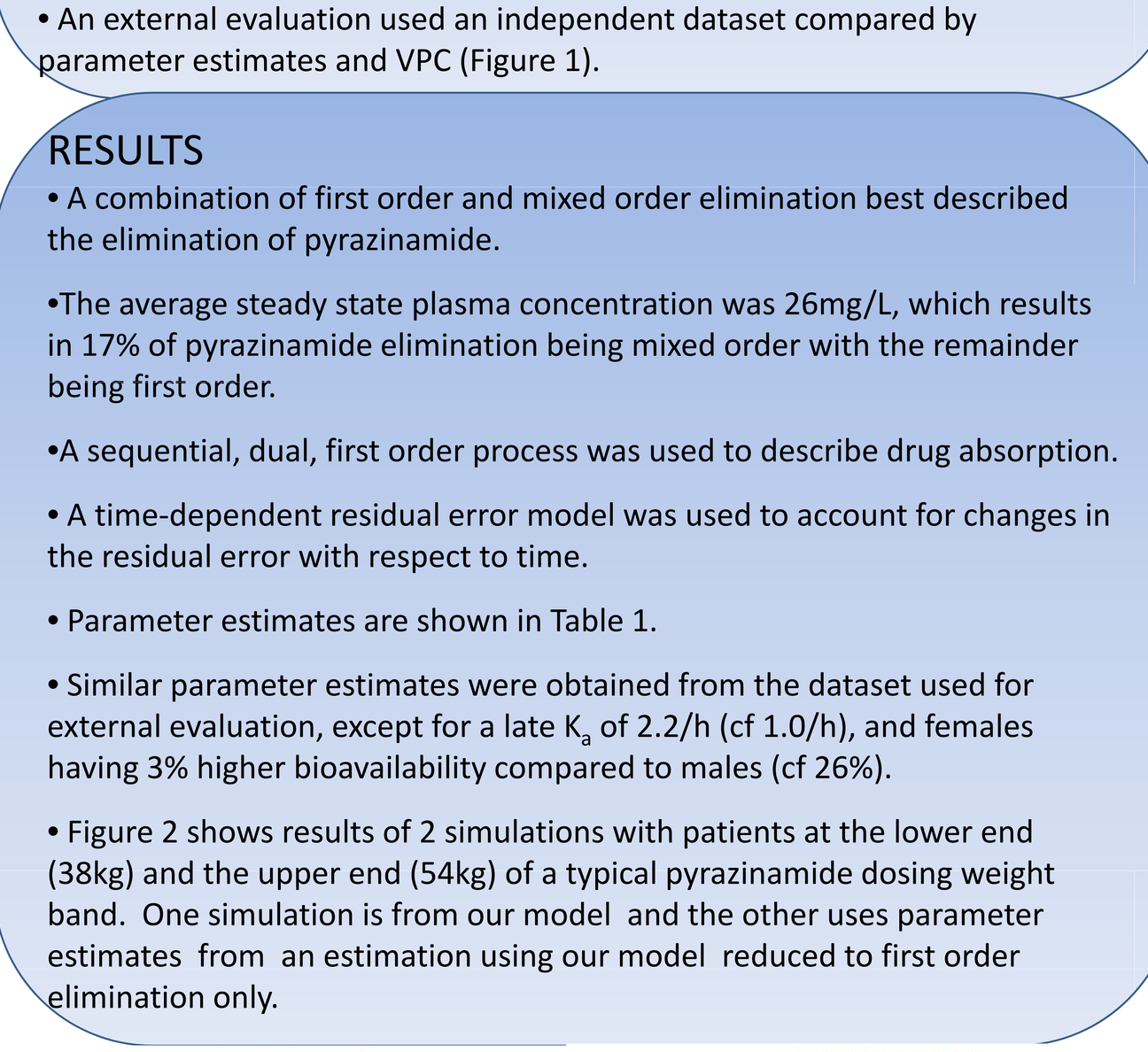


**Figure 1:** VPCs

## DISCUSSION and CONCLUSION

•Accurate PK of the existing antituberculosis drugs are needed to optimize doses in emerging regimens [2].

•To our knowledge, this is the first time that mixed order elimination has been noted for pyrazinamide.

•Pyrazinamide has been shown [3] to be eliminated unchanged renally (3%), and the rest as various metabolites through multiple metabolic pathways. Our model suggests that one or more of these pathways may be saturable.

•From Figure 2, the area-under-the-curve (AUC) is similar for the 54kg patients regardless of the description of the elimination process. However, the AUC is higher for the 38kg patient using the combined elimination model than for the same patient using first order elimination only. Therefore mixed order elimination may be important in small patients given standard doses.

•The clinical relevance of higher mg/kg doses within the currently recommended weight bands is unclear. However, any changes in dose recommendations should take into account the nonlinear elimination component.

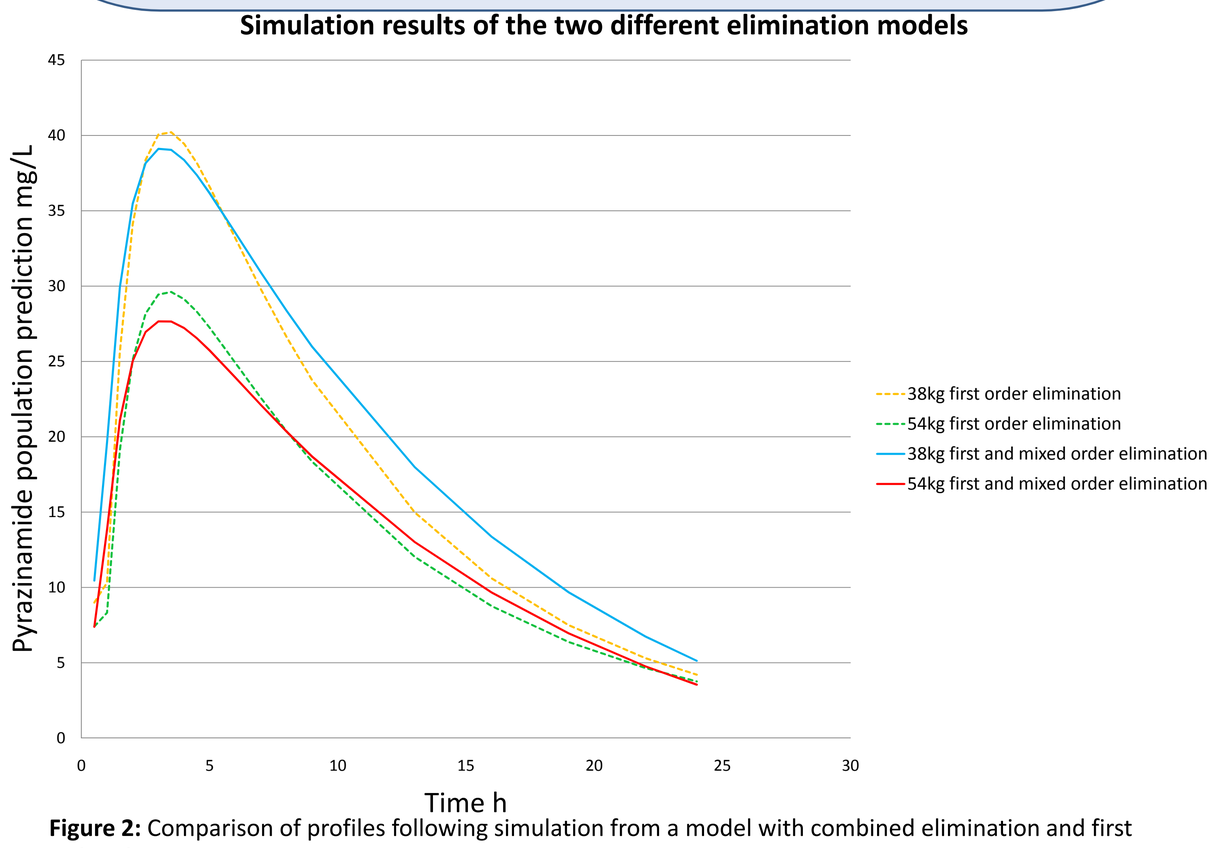


**Figure 2:** Comparison of profiles following simulation from a model with combined elimination and first order elimination

**Table 1:** Parameter estimates

| PARAMETER | ESTIMATE |
|---|---|
| First order oral clearance L/h/70kg | 2.6 |
| Vmax mg/h/70kg | 14.3 |
| $K_m$ mg/L | 0.5 |
| Early $K_a$ /h | 0.02 |
| Late $K_a$ /h | 1.0 |
| Change point for $K_a$ h | 0.7 |
| Volume L/70kg | 42 |
| Effect of female sex on relative oral bioavailability | +26% |
| Proportional error (up to 1.5h after dose) | 42% |
| Proportional error (from 1.5h after dose) | 14% |
| BSV for combined elimination | 17% |
| WSV for combined elimination | 16% |
| BSV for change point in $K_a$ | 45% |
| WSV for change point in $K_a$ | 48% |
| WSV for $K_a$ | 82% |
| BSV for bioavailability | 16% |

Vmax – Maximum elimination rate for mixed order process; Km – drug concentration that gives half maximal rate of velocity; Ka – first order absorption rate constant; BSV – Between subject variability; WSV – within subject variability

## References

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## Acknowledgements

• We are grateful to the Wellcome Trust and CIDRI (Fund 412164) for funding.
• We also thank the Medical Research Council of South Africa for funding.
• Dr Marianne Visser and the DELFT study team.
•Dr Paolo Denti for assistance with modeling.