Population Pharmacokinetics of Teicoplanin in Patients Treated Within an Outpatient and Home Parenteral Antibiotic Therapy (OHPAT) Programme

E Lamont[1], AH Thomson[2,3], M Dawber[3], L Semple[4], E Bell[4], RA Seaton[4]

[1]Pharmacy Department, Gartnavel General Hospital, [2]Pharmacy Department, Western Infirmary, [3]CAMS Division, University of Glasgow, [4]Brownlee Centre, Gartnavel General Hospital, Glasgow.

INTRODUCTION

- A new service has been introduced that allows patients to be given antibiotic treatment with intravenous teicoplanin in an outpatient setting.
- As teicoplanin has a long elimination half-life, it can be administered three times a week.
- Current doses are determined empirically as there are no published guidelines

AIMS

- To describe the PopPK of teicoplanin in outpatients who are receiving thrice weekly IV therapy
- To identify clinical factors that influence the pharmacokinetics of teicoplanin in this population
- To develop dosage guidelines for future use

METHODS

Dosage regimen and blood sampling

- Loading doses of 15 - 25 mg/kg/day were given for three days followed by 15-25 mg/kg on Mondays, Wednesdays and Fridays
- Troughs were withdrawn Monday mornings (72 hours after the last dose).
- Teicoplanin doses were adjusted to maintain troughs of 20 – 30 mg/L (deep seated infections) or 10 - 20 mg/L (bacteraemia or soft tissue infections)
- Concentrations were measured by fluorescence polarisation immunoassay

Data analysis

- NONMEM V with FOCE interaction (1). 1 and 2-compartment models were tested, interindividual variability (IIV) was assumed to be log-additive; additive, proportional, combined residual error models compared.
- *Covariates* : age; weight (TBW); ideal body weight (IBW); height; serum creatinine concentration; creatinine clearance using the Cockcroft-Gault equation (2) with TBW (CCl) or IBW (CrCl) and the Salazar-Corcoran equation CCLB (4). Scatterplots were examined using Xpose version 3.0 (4).
- *Model comparison*: change in OFV (3.84 significant) scatterplots and IIV and residual variability.

Development of dosage guidelines

- Typical trough profiles were simulated for patients weighing 40, 50, 60, 70, 80, 90, 100,120 kg with creatinine CL of 20, 25, 30, 35, 40, 50, 60, 70, 80, 100,120, 140 ml/min
- Dosage regimens that achieved troughs of 20-30 mg/L were identified and used to construct dosage guidelines

RESULTS

Table 1. Clinical characteristics of the patients (n = 93).

Clinical characteristic	Median (range)/Number
Male / Female	55/39
Age (years)	63 (15-94)
Weight (kg)	73 (43-146)
> 20 % above IBW	46
Height (m)	1.68 (1.37-1.93)
Creatinine (µmol/l)	95 (58-308)
CrCl ml/min	53 (16-136)
CCl ml/min	64 (16.8-195)
CCLB ml/min	22.6 (5.33-77)

Model development – Basic model

- 1-cpt model with proportional residual error
- Clearance = 0.537 L/hr (IIV 42%)
- Volume = 99.5 L (IIV 51%)
- Residual variability = 12%

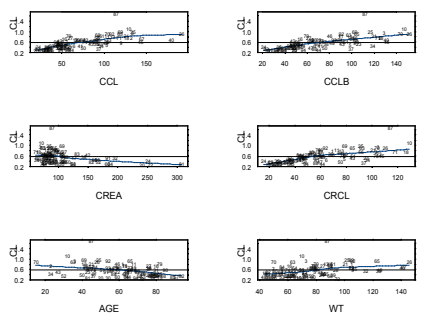

Figure 1. Scatterplots of teicoplanin clearance vs clinical characteristics.

Table 2. Summary of influence of individual clinical factors on clearance.

Covariate	OFV	OFV change
Basic	2036	-
Creatinine	2018	18
Total body weight	2029	7
Ideal body weight	2018	18
Sex	2017	19
Age	2016	20
CRCL	1984	52
CCL	1970	66
CCLB	1976	60

Final model

CL (L/h)	=	$0.533 \times (1 + 0.01 \times (CrCl_{CGT} - 65)$	IIV 22%
Volume (L)	=	$95 \times (1 + 0.00597 \times (weight-72))$	IIV 38%
Residual error	=	CV 13%	

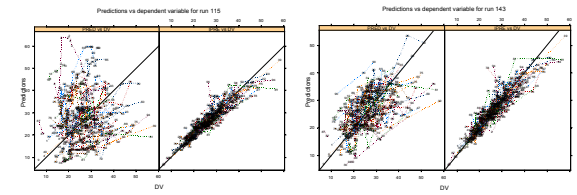

Figure 2. Plot of PRED vs DV and Plot of IPRED vs DV for basic model (L) and final model (R)

Table 3. Dosage guidelines to maintain troughs of 20-30 mg/L.

Loading doses: 800-1800 mg daily for 3 days

Maintenance doses:

CrCl (ml/min)	40kg	50kg	60kg	70kg	80kg	90kg	100kg	120kg
20	400	400	400	400	400	400	400	400
25	600	600	600	600	600	600	400	400
30	600	600	600	600	600	600	600	600
35	600	600	600	600	600	600	600	600
40	600	800	800	600	800	600	600	600
50	800	800	800	800	800	800	800	800
60	800	800	800	800	1000	800	800	800
80	1200	1000	1200	1200	1200	1200	1200	1000
100	1200	1200	1200	1200	1200	1200	1200	1200
140	1800	1800	1800	1800	1800	1800	1800	1800

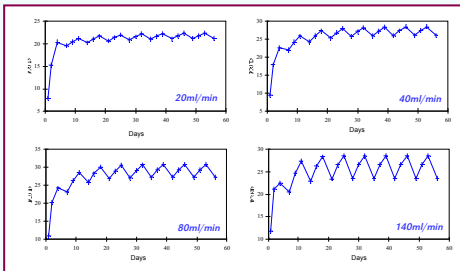

Figure 3. Simulated trough profiles for a range of CCL estimates and a weight of 70kg.

SUMMARY

- Routine TDM data were collected from patients receiving a new approach to intravenous antibiotic therapy with teicoplanin.
- A population model was developed that related teicoplanin clearance to creatinine clearance (based on total body weight) and volume of distribution to total body weight.
- Dosage guidelines were developed based on weight and estimated creatinine clearance.

CONCLUSIONS

- Teicoplanin dosage regimens for patients receiving thrice-weekly therapy should be based on estimated creatinine clearance and weight, not just weight.
- Further work is underway to evaluate the model and to develop the dosage guidelines in a separate group of patients receiving the same treatment approach. The guidelines will then be introduced into clinical practice.

REFERENCES

1. Beal SL, Sheiner LB (1992) NONMEM (User's Guide), parts 1-VII. Technical Report, University of California, San Francisco
2. Cockcroft DW and Galt H. Nephron 1976; 16: 31-41.
3. Salazar D and Corcoran G. Am J Med 1988; 84:1053-1060.
4. Jonsson EN, Karlsson MO (1999) Xpose – an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comp Meth Prog Biomed 58: 51

Produced by Medical Illustration, Gartnavel General Hospital G032452.