A Pharmacokinetic Study of Ranitidine in a Paediatric Population

P Westwood[1, 2], P Collier[1], S Yakkundi[1]

[1]School of Pharmacy, Queen's University Belfast, Northern Ireland; [2]Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Queen's University Belfast

PAGE BERLIN 2010

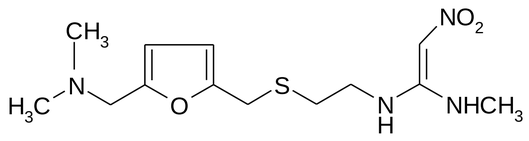
INTRODUCTION TO RANITIDINE

The most widely used H_2RA in the treatment of gastric-related symptoms in the hospital environment, as a prophylaxis for stress ulcer syndrome or gastric aspiration, to negate the effects of GOR or persistent vomiting, and to counteract the damage to the stomach lining by steroids.

Potent and long-acting. First launched by Glaxo in the United States in October 1981. Represented the second member of the class of H_2RAs approved for clinical use. Revolutionised the treatment of peptic ulceration. Good safety profile and lack of significant drug interactions. Rapidly became accepted as the first-line H_2RA in both the general medical and critical care settings. But still does not have a marketing authorization for the paediatric population.

An ongoing programme by the Childrens Medical Research Group in the School of Pharmacy at Queen's University, Belfast is currently researching several drugs used off-label and unlicensed in the treatment of children by employing population pharmacokinetic (PopPK) analysis Including ranitidine, midazolam, potassium canrenoate, spironolactone, omeprazole, codeine and diclofenac.

Prior PK investigations have used both non-compartmental and compartmental pharmacokinetic analyses (PK). Different compartmental models have been used, ascertaining several influential covariates e.g. gender, type of surgery, concomitant drugs. Several have concerned the PopPK analyses of paediatric data using different pharmacokinetic techniques[1, 2, 3]. However, clinical results and the conclusions drawn from these trials have sometimes been contradictory.



AIMS AND OBJECTIVES

Investigate the PK profile of both i.v (infusion and intermittent bolus doses) and oral ranitidine in paediatric patients and to determine the influence of age, gender, weight, several concomitant drugs and disease states.

METHODS

Patients and data collection

Study approved by the Office for Research Ethics Committees of Northern Ireland (ORECNI). Informed consent was obtained from each child's parent or legal guardian before enrolment. 91 children who attended The Royal Belfast Hospital for Sick Children (RBHSC) between the 24th of August 1998 and the 13th of November 2006 were included in the study. Drug was either oral or bolus intravenous dose, or a combination of the two. All 91 patients receiving treatment in the PICU at the RBHSC. Drug administered to alleviate possible stress ulcer syndrome, the effects of GOR (or GORD) and the erosive effects of steroids.

Drug analysis

Samples were analysed using a novel method developed and validated within the Children's Medicines Research Group at Queen's University, Belfast. Measurements below the limit of quantification (BLQ) were replaced by LOQ/2 (12.5ng/ml), subjects where all measurements were BLQ were omitted.

Data analysis

A population PK model was fitted to the data using the FOCE method with INTERACTION in NONMEM VI[4].

One- and two-compartment PK models with an absorption rate constant were fitted to the data, and a double peak absorption model was also tested.

The interindividual variability in the PK parameters was modelled exponentially:

$$\theta_{jk} = \hat{\theta}_k \bullet e^{\eta jk}$$

The residual variability was modelled using both a proportional and an additive error:

$$C_{jt} = \hat{C}_{jt} + \hat{C}_{jt} \bullet \varepsilon_{jt}^{prop} + \varepsilon_{jt}^{additive}$$

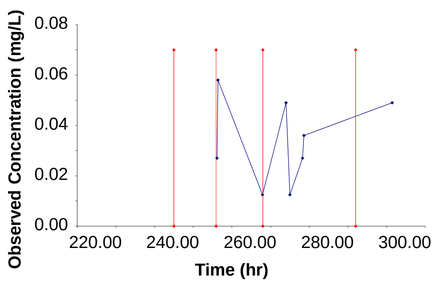
The following were then added into the dataset for identification of significant covariates: WT (weight of subject), AGE (age of subject at time of sampling), presence of specific condition (yes=1, no=0); concomitant drug therapy (presence of specific concomitant drug, yes=1, no=0); and gender (male=1, female=0). To be considered in the model there had to be 10% or more of the population in the categorical group under investigation. The log likelihood test (as the objective function value, OFV) was used as the principle model selection criterion.

The backward stepwise elimination technique was used for the model development, which combines the forward selection and backward elimination techniques using a stay criterion of 5% (ΔOFV≥+3.841, df=1) and an entry criterion of 1% (ΔOFV≤-6.635, df=1).

Model validation

The Bootstrapping re-sampling procedure (1000 runs) was performed to assess the model's stability and to calculate the 95% confidence intervals. Jack-Knife procedure also performed to assess the influence of any individual on the final model. Principal Component Analysis (PCA) also performed to investigate any possible subgroups within the patient population which was not identified from the model development, and VPCs were also generated.

Example of individual concentration profile (oral)



A double peak absorption model was not successful. On closer inspection of the oral dataset, only one subject had more than three sequential samples which did not include dosing in between (ID #98) (above, with time of dose administered represented by a red line).

RESULTS

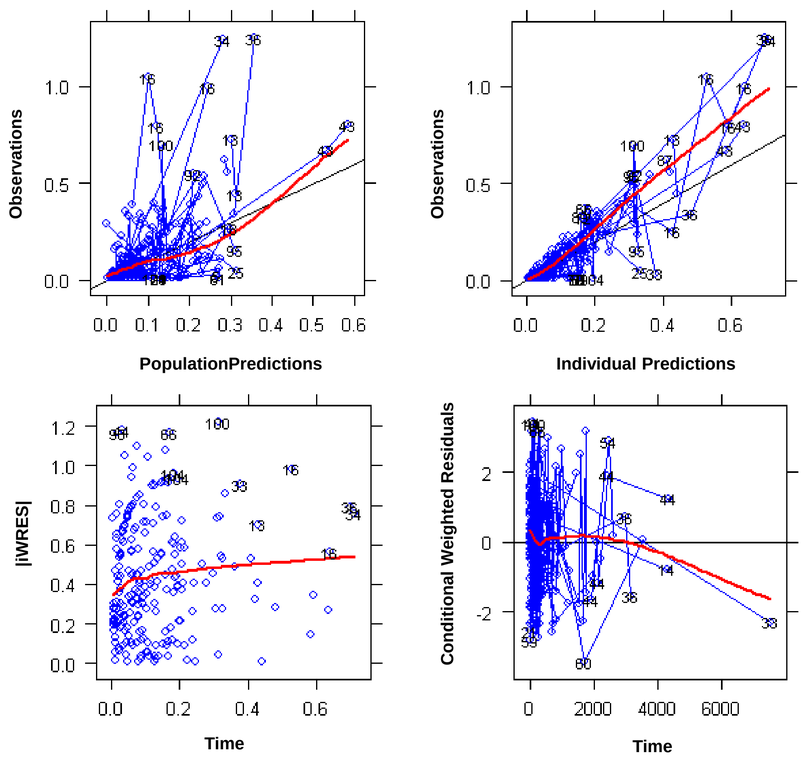
Patient demographics

13 subjects had concentrations which were all BLQ (21 samples) therefore the remaining subjects after this omission numbered 78 (248 samples), drawn opportunistically with a median number of two samples per patient (range 1 – 13).

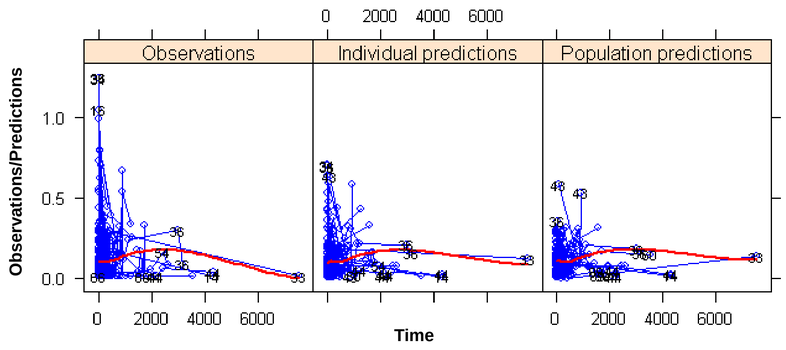
Total number of subjects	78 (91 before removal of subjects with BLQs only)		
Total number of samples	248 (269 before removal of subjects with BLQs only)		
Route of administration	**i.v.**	**Oral**	**Both**
Number of subjects	16	12	50
Mean dose	1.18 ±0.43 mg/kg	2.15 ± 1.32 mg/kg	2.10 ± 0.80 mg/kg
Mean of treatment	15.48 ± 34.49 days	24.09 ± 42.15 days	41.62 ± 85.04 days
Mean age	4.57 ± 4.48 years (range 15 days – 15.51 years)		
Mean weight	16.27 ± 12.24 kg, (range 1.3 – 47 kg)		
Gender	**Male**	**Female**	
	37	41	
No. of concomitant drug therapies	247		

Final model

The one-compartmental model was found to be the best to describe the ranitidine data. Implementation of a two- or three- compartment model, or a double peak absorption model did not improve the fit. A proportional model was found to be the best to describe the residual error, with two etas in the model on the CL and V parameters. Parameter estimates were similar to previous studies - 32.1 L/hr and 285L for CL and V, respectively - both allometrically modelled for a 70kg adult (power model with a power coefficient of 0.75). Final estimates for k_a and F was 1.31hr^{-1} and 27.5%, respectively. Gender covariate found to have a significant effect on both CL and V, but model validation with bootstrapping found the model to be unstable, therefore the effect of gender was removed from both parameters. Weight covariate most significant in the model and heart-related problems or illness was shown to significantly reduce the clearance by a factor of 0.463.



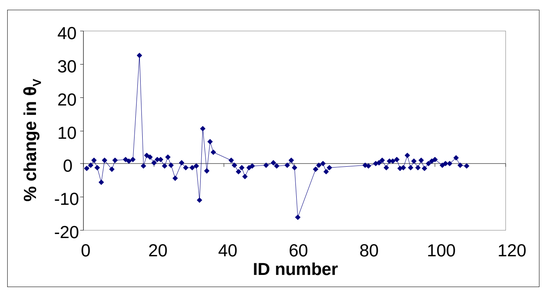
The goodness of fit plots (above) and the individual and population prediction plots (below) showed good agreement between the model predictions and the observed data.



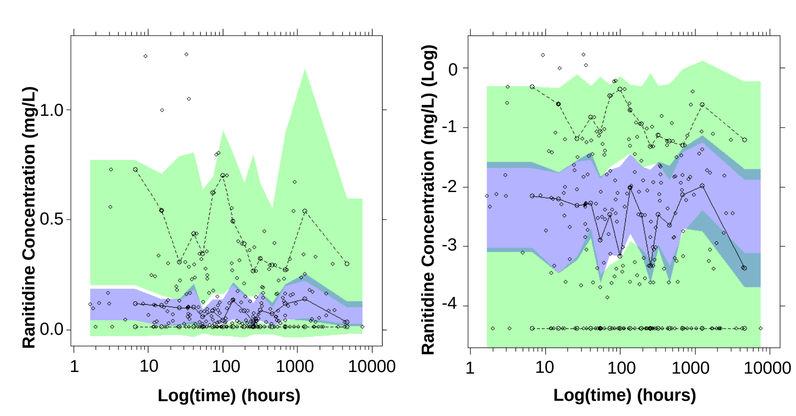
Model evaluation

1000 bootstrapping datasets were generated, and the final model was then run through each dataset. Of the 1000 runs, 866 minimised successfully, with 31 failing to minimise, which gave no indication of model instability.

Jack-Knifing was performed using NONMEM, WfN and Census. The model for each jack-knifed (JKK) dataset successfully minimised. All parameter estimates from JKK were within ±20% of the final estimates for the full dataset except for subject #16 with 378L for θ_V (132% of original, shown below as an example) and 0.34 for θ_{F1} (122% of original), and subject # 60 with 1.01hr^{-1} for θ_{KA} (77.0% of original). On further investigation of the individuals this was not deemed as significant.



This was not a designed trial with a structured dosing and sampling regimen. Instead, the study was performed during therapeutic drug monitoring (TDM) with the samples being taken opportunistically. Therefore, it was difficult to obtain a satisfactory VPC even with log times (below left), but by then taking log concentrations (below right) it was shown that the final model exhibited no evidence of misspecification.



Principal Component Analysis (PCA)

Principal Component Analysis (PCA) was performed on the final model for the full dataset. This involved using the final parameter estimates from the individual Jack-Knifed datasets, ascertaining which subjects had the most influential effect, and also determining if there were any correlations between individuals or parameters which was not discovered by the final model. The use of PCA in this manner means that a lack of a positive result is desirable. The analysis was performed using SPSS® (V. 15.0).

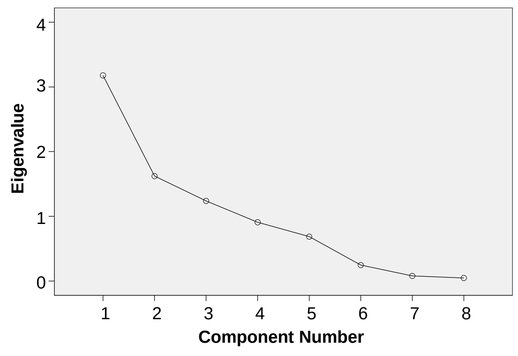
Component	Initial Eigenvalues		
	Total	Variance (%)	Cumulative (%)
1	3.178	39.728	39.728
2	1.622	20.271	59.999
3	1.237	15.466	75.464
4	.907	11.342	86.807
5	.686	8.573	95.380
6	.246	3.070	98.450
7	.078	.973	99.423
8	.046	.577	100.000

The eigenvalues for each component in the analysis (left) are the amount of variance in the original parameter estimates accounted for by each component. The second column gives the magnitude of the component eigenvalues. Eigenvalues greater than 1 were requested in the analysis, therefore the first three components were extracted. The third column gives the variance accounted for by each component, and the last column gives the cumulative variance. The three components explained over 75% of the variance in the parameter estimates with a loss of less than 25%.

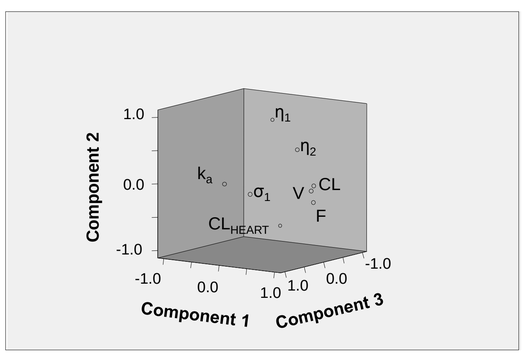
Parameter	Component		
	1	2	3
θ_{CL}	.956	.025	.034
θ_V	.962	-.042	.107
θ_{KA}	-.155	.042	.750
θ_{F1}	.917	-.237	-.012
$\theta_{(HEART,CL)}$	.107	-.710	-.311
ω_1	-.079	.853	-.378
ω_2	.596	.518	-.058
σ	.278	-.074	.706

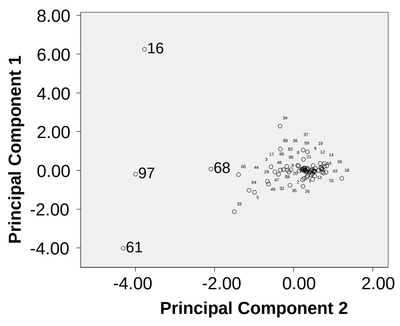
The component scores (left) for the three components for each parameter are from the unrotated component matrix. The first component corresponded most strongly to the parameters θ_{CL}, θ_V and θ_{F1}. The second corresponded to ω_1 and to a lesser extent ω_2. The third component corresponded to the two parameters where the solution accounted for the least variance; θ_{KA} and σ.

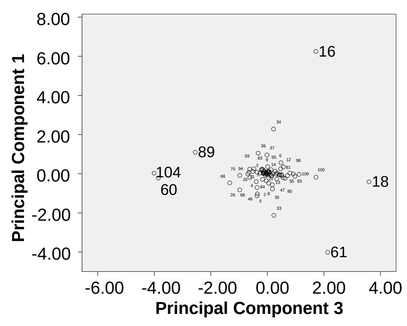
The components on the steep slope of the scree plot (right) are generally the ones that should be chosen for the final selection. As shown, there were indeed three components on the initial part of the steep slope, however there was a further drop between components five and six. This could be seen in the variance associated with these components where there was a drop from 8.57% to 3.07%, but as the eigenvalues were significantly less than one these components were deemed not a part of the final solution.

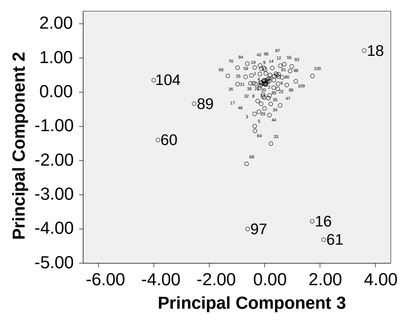


The component loadings plot (right) is a visual representation of the three rotated components and did not reveal any significant correlation between any of the parameters which was not explained by the model.









The scatterplots for the principal components (above and to the left) did not reveal any groupings which would indicate any significant correlation between individuals. A review of the demographics of the outlying subjects failed to reveal any significant trends

Therefore, the results of the PCA did not ascertain any underlying trends not identified by the earlier analysis, thus giving no evidence for concerns to the validity of the final model.

CONCLUSION

After weight was taken into account, heart-related problems or illness was the most significant covariate in the model. Cardiac failure is known to alter the pharmacokinetics of many drugs due to the subsequent physiological changes in the body[5]. Postoperative renal dysfunction is one of the most severe complications of cardiac surgery. Also a decrease in hepatic blood flow occurs which is proportionate to the decrease in cardiac output[6] and an inverse relationship between cardiac index and hepatic blood flow[7]. Therefore, both hepatic and renal blood flow decrease in proportion to the decrease in the cardiac output[8], which would account for the decreased clearance of ranitidine associated with a heart condition seen in this study.

References

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