

# Development and Evaluation of Bayesian Software for Improving Therapeutic Drug Monitoring of Gentamicin in Neonates

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- NPSA alert



Alert

## Patient Safety Alert

NPSA/2010/PSA001  
09 February 2010

**NHS**  
National Patient  
Safety Agency

National Reporting  
and Learning Service

# Safer use of intravenous gentamicin for neonates

Patient safety incidents have been reported involving administration of gentamicin at the incorrect time, prescribing errors and **issues relating to blood level monitoring.**

## Action for the NHS

NHS organisations, clinical directors and those responsible for the provision of neonatal services should ensure that by **9 February 2011**:

1. a local neonatal gentamicin protocol is available that clarifies the initial dose and frequency of administration, blood level monitoring requirements, and arrangements

## UK neonatal units:

- No single dosing & monitoring regimen

*J Antimicrob Chemother* 2011; **66**: 2647–2650

doi:10.1093/jac/dkr351 Advance Access publication 22 August 2011

## Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units

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Forty-three units across the ENN responded to the gentamicin questionnaire, revealing 24 different combinations of dose, timing of dose and timing of monitoring. Figure 1 demonstrates

# now and then

Now:

- ▶ Pre-dose trough levels
- ▶ Separate blood sample
- ▶ To give or not to give?
- ▶ Huge variation in published PK models (1,2,3 comp, covariates...)

Then (Aims):

- ▶ Use Prior information from neonatal population
- ▶ Combine TDM with routine blood samples
- ▶ Less invasive

# Overview:

- ▶ Introduction
- ▶ Methods
- ▶ Results
- ▶ Conclusions

# Methods

- ▶ Identify published PK data
- ▶ Develop popPK model
- ▶ Mechanistic covariates
- ▶ Prospectively collect:
  - ▶ Routine sample
  - ▶ Trough sample
- ▶ Evaluate model predictions on prospective data

# Results - Data

Model-building data: 2 studies only!

- ▶ N=174, samples=1163
- ▶ GA=23.3-42.1 weeks, PNA=0-65 days

Prospective data:

- ▶ St George's, Liverpool, Oxford, Portsmouth, Coventry
- ▶ June 2012 - November 2013
- ▶ N=163, samples=483
- ▶ GA=23.9-42.3 weeks, PNA=0-77 days

Nielsen El., et al, Clin Pharmacokinet 2009; 48: 253-63.

Thomson AH, et al., Dev Pharmacol Therapeut 1988; 11: 173-9.

## Final model

- 3-compartment model
- Residual error model: proportional + additive
- Inter-individual and inter-occasion variability: exponential model
- PNA and serum creatinine standardized for PMA: significant

$$CL = \theta_{CL} \cdot \left(\frac{WT}{70}\right)^{0.632} \cdot \frac{PMA^{3.33}}{55.4^{3.33} + PMA^{3.33}} \cdot \left(\frac{MSCr}{TSCr}\right)^{\theta_{SCr}} \cdot \frac{PNA}{\theta_{P50} + PNA} \cdot e^{(\eta_{CL} + \kappa_{CL})}$$

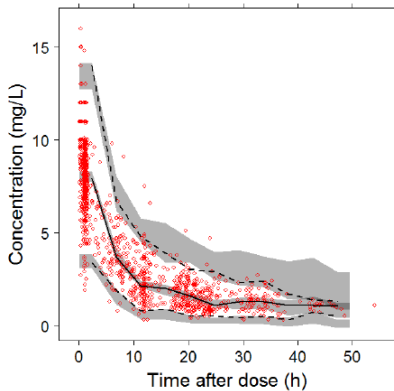
$$V = \theta_V \cdot \left(\frac{WT}{70}\right) \cdot e^{\eta_V} \quad Q = \theta_Q \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot e^{\eta_Q}$$

$$TSCr = -2.8488 \cdot PMA \text{ [weeks]} + 166.48$$

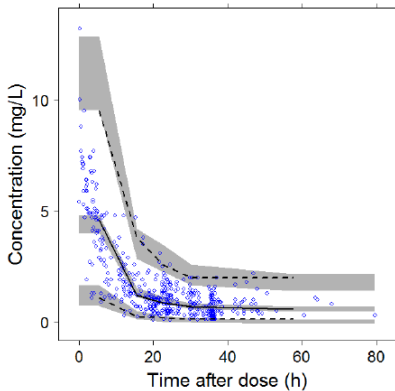


# Visual predictive check

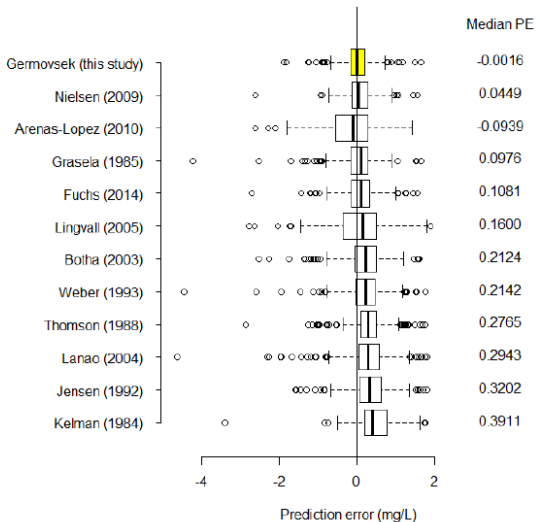
Internal VPC



External VPC

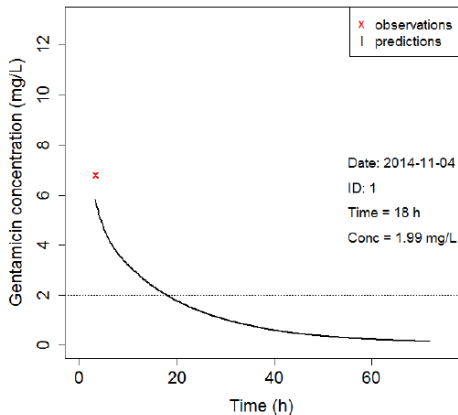


## Comparison with other published models



## An example of the neoGent output

SubjectID	Time(h)	PredConc(mg/L)
1	18	1.99

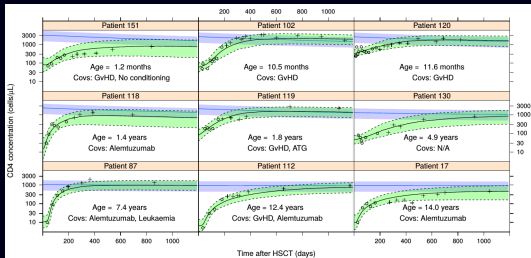


# Conclusion

- ▶ Can combine TDM and routine samples
- ▶ Don't need a lot of subjects, just good data

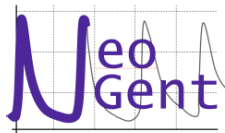
Future work:

- ▶ User-friendly/no interface
- ▶ Apply to other models:



## Acknowledgements

Patients, who  
participated in the  
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Dr Alison Thomson



London  
Pharmacometrics  
Interest  
Group

