Pharmacokinetic comparison of two neonatal gentamicin regimens: a quasi-experimental study

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Background & Aim

Sepsis is broadly defined as an infection of a sterile site (i.e. blood, cerebrospinal fluid, urine). Early onset infection is defined as an infection arising within the first 72 hours of life, and late onset infection beyond 72 hours of life [1].

Early and late onset infection have different likely causative organisms. Gentamicin, an aminoglycoside, is often used with a penicillin to provide adequate antimicrobial cover until gram negative sepsis is excluded [2]. There remains significant variation among gentamicin dosing regimens [3,4].

This study aimed to describe the effect of a dose and frequency change on the pharmacokinetic profile of gentamicin for the treatment of neonatal sepsis, in the medical and surgical neonatal intensive care unit and special care nursery at a tertiary paediatric hospital.

Method

At Monash Health, all neonates prescribed gentamicin follow the local protocol, and this was updated to reflect the intervention (change in gentamicin dosing regimen) in July 2016 (Figure 1).

This study compared the results of three pharmacokinetic parameters (area under the concentration-time curve (AUC), peak and trough concentration) calculated using a published neonatal gentamicin Bayesian model [5].

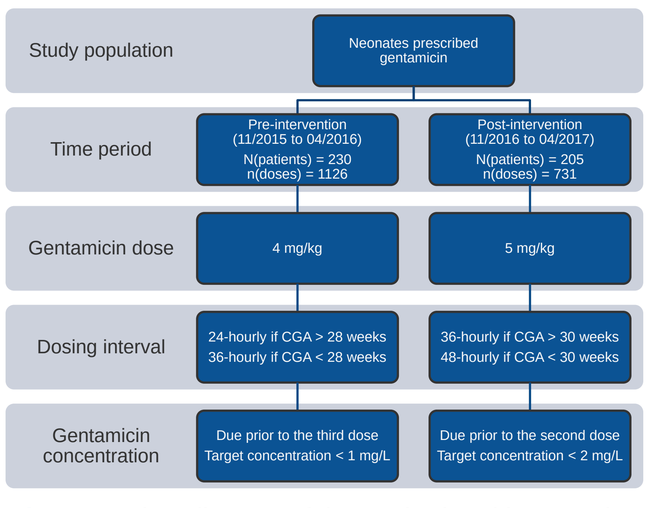

Figure 1: Flow diagram of the method and intervention.
CGA = corrected gestational age

Results

There was no significant difference between the AUC (p = 0.13) and peak concentration between the two cohorts (p = 0.27) (Figure 2 & 3).

Trough concentrations had a significantly narrower range, and lower median value in the post-intervention cohort (p < 0.01) (Figure 4). When analysed per-protocol, 64.2% of the pre-intervention cohort achieved a trough concentration of 1mg/L or less, and 99% of the post-intervention cohort achieved 2mg/L or less. If 2mg/L were the threshold for the pre-intervention cohort, this would have been achieved by 92%.

There was a significantly lower odds that a gentamicin trough would be > 2mg/L and thus require adjustment in the post-intervention cohort (OR = 8.45 (2.71-26.79), NNT = 2.52 (2.06-4.87), p < 0.01).

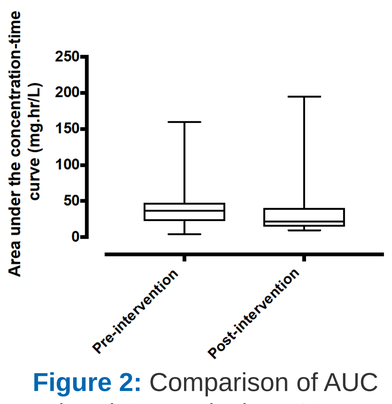

Figure 2: Comparison of AUC
n (pre-intervention) = 107;
n (post-intervention) = 88);
p = 0.13

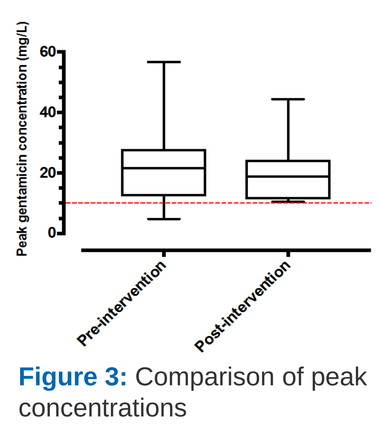

Figure 3: Comparison of peak concentrations
n (pre-intervention) = 107;
n (post-intervention) = 88);
p = 0.27

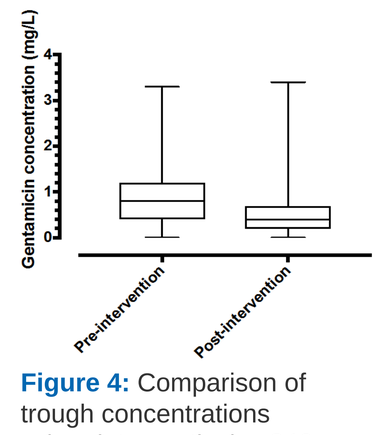

Figure 4: Comparison of trough concentrations
n (pre-intervention) = 346;
n (post-intervention) = 339;
p < 0.01

Discussion

Area Under the Curve (AUC)

The similar AUC was unexpected. It may be due to:

- differences between the local and model population
- procedures for measuring serum gentamicin and creatinine
- administration technique

Peak

Achieving adequate peak concentrations (target > 10mg/L) is beneficial for effective use of aminoglycosides for treating gram negative sepsis [5]. The target peak was achieved in 96.2% in the pre-intervention cohort and 100% in the post-intervention cohort. This result has important, positive patient outcomes.

Trough

The post-intervention cohort had more complete gentamicin clearance at the time a subsequent dose was due. Lower trough concentrations reduce the risk of acquired toxicities (i.e. ototoxicity or nephrotoxicity). Additionally, fewer patients in the post-intervention cohort required dosing interval adjustment and subsequent concentration monitoring or prescription adjustment.

Reduced dosing interval adjustment is a positive, patient important outcome, reducing the risk of acquired toxicities, prescription error and the number of painful procedures.

Conclusion

The increased gentamicin dose with extended dosing interval did not result in a significant change to the calculated medication exposure, but improved trough concentration.

The post-intervention regimen was superior to the pre-intervention regimen as it demonstrated improved clearance, and reduced incidence of requiring dose adjustment and the subsequent invasive blood testing and toxicity screening for the neonate.

References

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