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Peer Review

Review of: "Monitoring of Gentamicin Serum Concentrations Among Newborns in the Neonatal Ward at Hospital Sultan Ismail Petra, Malaysia"

Stephen Hughes[1]

1. Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom

Dear Editor,

Thank you for the opportunity to review this manuscript. It is an area of interest, and the authors have presented a thorough and large dataset on the topic. However, the findings and their interrogation are not supported by the literature, thus taking away from the study.

With these significant limitations, I do not think this manuscript is suitable for publication

The Definition of "Toxic Trough Level" (≥1.0 mg/L):

- **Major Point:** The most significant issue is defining a trough level of ≥1.0 mg/L as "toxic." While a trough <1.0 mg/L is often a desirable *goal* for prolonged therapy or extended-interval dosing to minimise cumulative toxicity, most guidelines for neonatal dosing allow levels up to **<2.0 mg/L** to be acceptable, especially in the initial phase of treatment or for shorter courses. The authors cite a single reference for their target <1mg/L (*Mohamad N, Rusli RA, Chelliah OA, Azmi Y, Chian TS, Leong GC, et al. Clinical Pharmacokinetics Pharmacy Handbook. 2nd ed. Putrajaya: Pharmacy Practice & Development Division, Ministry of Health Malaysia; 2019.)* yet exclude other more established resources. Reference 7 (*Stach LM, Pallotto E, Sandritter TL. Development of criteria for gentamicin monitoring in a neonatal intensive care unit. American Journal of Health-System Pharmacy. 2012 Aug 1;69(15):1319-25.)* uses a trough level of <2mg/L, as does Reference 10 (*Mulhall A, de Louvois J, Hurley R. Incidence of Potentially Toxic Concentrations of Gentamicin in the neonate. Archives of Disease in Childhood. 1983 Nov 1;58(11):897–900.)*,

doi.org/10.32388/KoMU3M

even though the latter is a multi-daily dose from a study in the 1980s. National bodies like NICE (UK) and other larger neonatal studies target levels <2mg/L, certainly for the initial 72 hours of treatment due to the expected higher levels in this population. Key citations include:

- **Hoff DS, et al. (2002). Pharmacokinetic outcomes of a simplified, weight-based, extended-interval gentamicin dosing protocol for critically ill neonates.** [1] ***Pediatric Drugs*****, 4(1), 15-23.**
- **Pacifici GM. (2015). Clinical pharmacology of gentamicin in neonates: regimen, toxicology and pharmacokinetics.** ***Medical Express (São Paulo, online)*****, 2(5), e150501.**
- **National Institute for Health and Care Excellence (NICE). (2014, updated 2017). Neonatal infection: antibiotics for prevention and treatment (CG149).**
- **Tugay S, Bircan Z, Caglayan C, Arisoy AE, Gökalp AS. Acute effects of gentamicin on glomerular and tubular functions in preterm neonates. Pediatr Nephrol. 2006;21(10):1389-92**
- **Hayani KC, Hatzopoulos FK, Frank AL, Thummala MR, Hantsch MJ, Schatz BM, John EG, Vidyasagar D. Pharmacokinetics of once-daily dosing of gentamicin in neonates. J Pediatr. 1997;131(1 Pt 1):76-80.**

Thus, the manuscript's conclusions on 'toxicity' with gentamicin 4mg/kg in neonates do not reflect current practice in this population and may mislead your readership. If this is to be published, then the definition of 'toxic' needs a critical appraisal. It may be acceptable to define >1mg/L as supra-therapeutic, but the authors have not provided any evidence that this is toxicity. It would be of interest to see what percentage of patient trough levels are 1-2mg/L and >2mg/L for more relatable outcomes.

Lack of Clinical Toxicity Outcomes:

Major point: There is no direct link to toxicity with therapeutic levels in this study. The higher levels will be confounded by patients with reduced renal clearance, but there are no adverse outcomes (e.g., gentamicin-induced AKI or ototoxicity) reported with these 'toxic' levels.

Without clinical outcome data, it's impossible to determine the clinical significance of the reported 52% "toxic" troughs based on their definition. Were these babies actually experiencing nephrotoxicity or ototoxicity?

Sub-therapeutic findings:

Major point: Much like the trough levels, there is little evidence provided to support the target peak levels. A peak of >5mg/L is reasonable, but the authors state in their discussion that despite approximately 25% of patients having low peak levels, they are satisfied with the current dosing. It is unclear how 1 in 4 newborns being potentially underdosed in severe infection is appropriate. Should higher doses not be considered in some of these children? e.g., other international guidance advises higher doses (e.g., NICE - 5mg/kg). The authors do not critically assess this difference nor the high burden of under-dosing they present.

Methodology and Reporting:

Minor point(s):

- TDM Timing: While stated as measured on the third dose, the precise timing (e.g., trough immediately before the 3rd dose, peak 30-60 minutes after the end of infusion) is crucial and not explicitly detailed. Peak levels, in particular, are highly variable depending on the timing of sampling.
- The methods state inclusion and exclusion criteria, but then the authors introduce a previously undescribed exclusion in their discussion (high SCr >87) where gentamicin is contra-indicated. This is an important exclusion that is not included in the methods.
- Table 1 should include a breakdown of neonatal postmenstrual/gestational corrected age; it is defined as pre-term or term only. It would be useful to know what ranges of pre-term neonates are included (<28 weeks, 28-32 weeks, etc.).
- The methods detail the number of samples but don't explicitly state the number of neonates included. Do we assume patients were only included once?

Discussion:

Minor points:

The first paragraph is a repetition of results and not an appropriate opening paragraph for the discussion.

The discussion on definitions of toxicity and therapeutic levels is limited to older studies or a single-centre study from Malaysia, with no consideration for other more contemporary peer-reviewed publications on this topic (see above). Without this, it makes for difficult interpretation as a reader.

The authors' conclusion that 'This outcome suggested that the 4mg/kg dose is considered effective in the neonatal population at our hospital' is not supported based on their own definitions of >50% toxicity and

25% underdosed

Comparing results of a ONCE (Extended) daily dosed gentamicin to a multi-daily dose (Mulhall) is not advised when looking at levels and % toxicity. This should be explicitly documented as a difference, and again, more contemporary once-daily dosed trials should be compared. The cited Stach (ref 7) paper is overlooked in the discussion.

Abstract:

Minor point: The abstract references ‘premenstrual age’ - this should be postmenstrual or gestational.

Declarations

Potential competing interests: No potential competing interests to declare.