Qeios

Peer Review

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

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This study addresses an important topic in neonatology by evaluating whether estimated gentamicin dosage regimens for neonates achieve effective and safe serum concentrations. The presented results contribute to clarifying the pharmacokinetic behavior of gentamicin in this population. However, I perceive that the topic has not been adequately developed and requires a comprehensive revision. Below, I present the points of major concern.

Abstract

1. Line 1-2. "Gentamicin is the empirical therapy of choice for sepsis in newborns, with dosing of 4mg/kg every 24 – 36 hours, [...]". Gentamicin is usually an empirical therapeutic choice; however, it can also be a culture-guided selection.

2. Line 7-8. “Trough and peak levels were measured on the third dose, where the therapeutic ranges were <1.0 mg/L and >5.0 mg/L, respectively.” The therapeutic range for peak and trough concentrations is not well-defined. What are the ranges for both concentrations (lower limit - upper limit)?

3. Lines 8-9. “Elevated serum creatinine was defined as a serum creatinine level (SCr) >71 μmol/L.” What is the reference for defining elevated SCr? Would not any increase from the baseline value represent elevated SCr?

Introduction

4. Paragraph 2, lines 9-11. "Gentamicin is a narrow therapeutic drug that requires therapeutic drug monitoring (TDM) during the treatment period in order to ensure the efficacy of the drug while avoiding

 doi.org/10.32388/V02SOC

toxicity due to the use of Gentamicin." Avoid repetition of the terms. Please remove the passage: "due to the use of Gentamicin".

5. Paragraph 4, lines 21-22. “Gentamicin will be prescribed as the empirical treatment at a dose of 4 mg/kg, either 24 or 36 hours depending on the postmenstrual age [...].” This information is presented in the preceding paragraph. Please provide a summary. What type of guideline does Hospital Sultan Ismail Petra follow?

6. Paragraph 4, lines 24-25. “The therapeutic ranges for trough and peak levels were <1.0 μg/mL and >5.0 μg/mL, respectively.” See point 2.

7. Paragraph 5. The relevance of the study was not adequately presented. What causes dosage regimens to be suitable for one group of individuals and not another? Are there other studies that evaluate the quality of gentamicin regimens in neonates? What is the importance of determining factors associated with achieving therapeutic concentrations (peak and trough)?

Methodology

8. Please describe the TDM protocol. Were the sample collections performed 1 hour post-administration for peak concentrations and 30 minutes for trough concentrations?

9. Paragraph 2. Would certain malformations not be considered exclusion criteria? What about neonates with renal malformations?

10. Paragraph 2. I see that your most important toxicity variable is serum creatinine. Is the exclusion of patients without serum urea truly important?

11. Paragraph 3. What are the demographic variables included in the study? Why was the use of other medications not considered in the analysis? I believe that other known nephrotoxic medications could enrich the analysis with information about potential interactions.

Results

12. Paragraph 1. Did the 227 samples included in the study represent 227 patients? Did one patient have two sample measurements (peak and trough) or only one sample measurement?

13. Paragraph 4. "[..] hence we can conclude that a dose of 4mg/kg is effective in achieving its desired effect." This sentence belongs to the Discussion section.

14. Table 4 could be added without detriment to Table 3.

15. Tables 7 and 8 could be combined into a single table.

16. Table 9 is unnecessary. It could be described in the Results section.

17. Paragraph 6. "Nevertheless, dose and body weight played no significant role in having a toxic trough level or sub-therapeutic peak level, as shown in Tables 6 and 7." Are you referring to Table 5?

18. Paragraph 7. “The p-value is greater than 0.05, indicating that there is no statistically significant difference in mean serum urea levels between the non-toxic and toxic groups for gentamicin trough and peak concentration.” It is recommended to describe only the variables with statistically significant differences or associations.

19. Paragraph 7. "These results suggest that serum creatinine levels might be a more sensitive indicator of toxicity and effectiveness of gentamicin concentrations compared to serum urea levels in this context.” This excerpt belongs to the Discussion section.

Discussion

20. The first three paragraphs of the discussion section concern the presentation of the results, which has already been presented in the appropriate section.

21. Please do not reference the tables in the discussion. The tables should be mentioned only in the Results section.

22. Paragraph 6. “Both diagnoses showed high efficacy rates (>70%) with the current treatment regimen of 4mg/kg: congenital pneumonia at 76.61% (n=131) and presumed sepsis at 78.38% (n=29).” Please clarify that the efficacy rate refers to peak concentrations within the therapeutic range.

23. Paragraph 9. “Instead, the use of a 3rd generation cephalosporin, such as Cefotaxime, will be added as an alternative due to its lower nephrotoxicity effect while still offering spectrum coverage against gram-negative bacteria. However, caution is highly necessary to prevent the overuse of third-generation cephalosporins to mitigate the emergence of resistant gram-negative bacteria.” In this paragraph, you address the cutoff point for serum creatinine and state that you avoid the use of gentamicin with elevated SCr values. However, you then discuss the use of third-generation cephalosporins. What is the main argument of this paragraph?

24. Paragraph 10. "Could toxic trough levels of gentamicin not be related to limitations of the dosage regimen?

25. Paragraph 11. In what way would knowing the baseline SCr personalize the gentamicin dose? Is there a nomogram that considers SCr for defining the appropriate therapeutic regimen?

26. Paragraph 12. “In patients with SCr ≥71μmol/L, the dosing interval of gentamicin may be prolonged by 12 hours to prevent toxic trough levels.” What is the reference?

Conclusion

27. “In summary, elevated SCr levels in neonates indicate reduced kidney function, which can lead to prolonged half-life, altered clearance, and delayed attainment of steady-state concentrations of gentamicin, necessitating adjustments in dosing and careful monitoring to ensure effective and safe therapy.” This excerpt does not represent the object of study. Please exclude it.

Declarations

Potential competing interests: No potential competing interests to declare.