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Vancomycin dosing in neonates and sub-therapeutic levels

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Vancomycin is a glycopeptide antibiotic prescribed for Gram-positive infections including MRSA (methicillin-resistant *S. aureus)*, Coagulase negative Staphylococci (CoNS) and ampicillin-resistant Enterococci. It is commonly used in infants with severe sepsis or septic shock, and is vital in the treatment of late-onset sepsis - that is sepsis occurring >72 hours after birth - which carries a mortality rate of 15% in very low birth weight infants (<1.5kg)[1]. Vancomycin is bactericidal and exhibits time-dependant killing. The best prediction of outcome is the ratio of the 24-hour area under the concentration-time curve to the Minimum Inhibitory Concentration of the organism (AUC_{24}/MIC). To ensure adequate dosing, measurement of serum steady-state trough level i.e. therapeutic drug monitoring (TDM) is required. Monitoring of this trough vancomycin level is important because the effectiveness of the drug relies on serum levels above the MIC for the duration of therapy. Vancomycin pharmacokinetics is complex in neonates because of increased volume of distribution and reduced clearance, particularly if renally-impaired or if on other nephrotoxic agents[2,3].

In our neonatal intensive care unit, dosing guidelines conform to the BNF-C[4] which suggests a standard dose of 15mg/kg, with the dosing frequency dependant on the post-menstrual age (PMA) - <29 weeks 24-hourly, 29-35 weeks 12-hourly, >35 weeks 8-hourly. A vancomycin trough level is taken at the time of the fourth dose, and a level of 10-15mg/L is recommended except in deep-seated infections where the target is 15-20mg/L. Dose modifications, if required, are to shorten or lengthen the dosing interval while maintaining the same dose.

We retrospectively reviewed neonates who had vancomycin trough levels taken from January 2018 to July 2022. A total of 77 samples were obtained from 38 neonates. 79% (n=30) were dosed correctly, and 82% (n=31) had trough levels collected at the correct time. Overall, 58% (n=22) of neonates had sub-therapeutic levels (<10mg/L), 29% (n=11) had therapeutic levels (10-20mg/L) and 13% (n=5) had supra-therapeutic levels (>20mg/L) at the time of the first TDM check [Table 1]. In the <29 week PMA group, i.e. those prescribed 24-hourly dosing, 86% (n=12) had sub-therapeutic levels at the time of the fourth dose, despite accurate dosing as per BNF-C. Eight (of these twelve) neonates required dose interval shortening to 12-hourly as per the dosing algorithm and the majority (n=7) of neonates then became therapeutic [Table 2]. In the 29-35 week PMA neonates, i.e. those prescribed 12-hourly dosing, 48% (n=10) had sub-therapeutic levels. Five (of these ten) neonates required dose interval shortening to 8-hourly, and the majority (n=4) became therapeutic. Two of the five neonates with supra-therapeutic TDM levels may be explained by renal impairment (Creatinine >81µmol/L).

These results prompted a review of national and international guidelines pertaining to neonatal vancomycin dosing. An overwhelming inconsistency between guidelines was observed. Three large neonatal units in Ireland use a different guideline that base dosing intervals on neonatal weight, days of life and gestational age, have a more complex TDM regime, and dose modifications involving dose changes as opposed to interval changes. This dosing monograph recommends 15mg/kg 18-hourly to neonates <1.2kg, and notably, all our audited neonates <29 weeks PMA weighed <1.2kg. An American Neonatal guideline[5] uses a dosing algorithm based on serum creatinine concentration, and notably, 12 out of 14 of our <29 week PMA neonates were under-dosed based on this algorithm.

Optimisation of vancomycin therapy is crucial. Under-dosing can contribute to ineffective therapy and vancomycin resistance, and over-dosing is associated with toxicity including ototoxicity and nephrotoxicity. Based on the results of our audit, and the review of approved guidelines, we proposed a change for the dosing frequency of neonates with PMA <29 weeks from 24-hourly to 18-hourly. This change is supported by other Irish guidelines and the Red Book Algorithm which both reflect that this neonatal group had been under-dosed as per the BNF-C guideline, and additionally most of our audited neonates achieved therapeutic levels at the 12-hourly dosing interval.

To conclude, vancomycin is the drug of choice for neonatal sepsis and infections caused by MRSA and CoNS. We believe that this review is the first of its kind in Ireland and that it highlights the challenge that is vancomycin dosing, in particular achieving therapeutic drug levels because of pharmacokinetic variability in neonates. We hope that this practice change will achieve better levels for neonates and thus result in shorter vancomycin courses.

Post-menstrual age (PMA)	<29 weeks (n=14)	29-35 weeks (n=21)	>35 weeks (n=3)
Vancomycin dose	15mg/kg 24-hourly	15mg/kg 12-hourly	15mg/kg 8-hourly
Therapeutic (10-20mg/L)	1	8	2
Sub-therapeutic (<10mg/L)	12	10	0
Supra-therapeutic (>20mg/L)	1	3	1
Weight range (Average) (kg)	0.56 – 1.12 (0.75)	0.7 – 3.21 (1.42)	2.35 – 3.12 (2.77)

Table 1: Summary of initial TDM levels in neonates (n=38) taken before the fourth dose

Post-menstrual age (PMA)	<29 weeks (n=12)	29-35 weeks (n=10)	>35 weeks (n=0)
Vancomycin dose change	15mg/kg 12-hourly	15mg/kg 8-hourly	
Therapeutic (10-20mg/L)	7	4	0
Sub-therapeutic (<10mg/L)	1	1	0
Supra-therapeutic (>20mg/L)	0	0	0
No further TDM	4	5	0

Table 2: Neonates with an initial sub-therapeutic level (n=22) and follow-up TDM levels when a dose interval adjustment was made

Declarations of Conflict of Interest:

None declared.

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