ORIGINAL RESEARCH ARTICLE

ASSESSMENT OF THERAPEUTIC PRESCRIBING AND MONITORING OF VANCOMYCIN IN PRETERM AND FULL-TERM NEONATES AT A TERTIARY CARE HOSPITAL IN KARACHI

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ABSTRACT

Objective: To assess the appropriateness of therapeutic prescribing and monitoring of vancomycin in preterm and full-term neonates.

Methodology: A retrospective, descriptive study was planned. Data were obtained from the NICU record of patients from Ziauddin hospital, North Nazimabad. Patient data set comprising neonates admitted from January 2019 to December 2020 were included. Vancomycin utilization and clinical monitoring parameters were assessed for both neonatal status, gestational age, age groups and time intervals.

Results: A total of 180 patients met study requirements out of which 90 were preterm and 90 were full-term neonates. An average dose of 15.28 ± 3.12 mg and 11.78 ± 6.89 mg were given to preterm and full-term neonates respectively. Serum trough levels were reviewed. All 90 preterm infants complied with the desired target trough concentrations (10-15 mcg/ml), while 11 out of 90 full- term neonates showed trough vancomycin concentration beyond standard range (>15mcg/ml).

Conclusion: The current study emphasizes the importance for monitoring of vancomycin, more closely in neonatal subgroups. This strategy may well likely contribute to curtailing bacterial resistance, over exposure and consequential nephrotoxicity.

Keywords: Vancomycin; Therapeutic Monitoring; Prescribing; Neonates

INTRODUCTION

Drug prescribing in neonates is a great challenge for healthcare professionals in many settings. This is primarily due to lesser information available on evidence-based pharmacokinetics and pharmacodynamics of the given drugs in the specialized population which may translate to either lesser efficacy or higher toxicity profiles. (Al-Turkait et al., 2020) This informational gap sometimes translates into bigger challenges in understanding of the available evidence, leading to disparities in practice on one hand and the continuation of incorrect practices on the other. (Al-Turkait et al., 2020).

Among bacterial infectious conditions, neonatal bacterial sepsis along with meningitis and endocarditis (Schlapbach et al., 2010) are main causes of mortality and morbidity in infants. (Makhoul et al., 2005) Vancomycin, a glycopeptide antibiotic, is widely used for managing late-onset sepsis due to methicillin-resistant Staphylococcus aureus and coagulase-negative staphylococci in neonatal intensive care units (NICUs) (Jacqz-Aigrain et al., 2013); however, the clinical use of vancomycin still faces hindrances due to it being narrow therapeutic index with high pharmacokinetic variability among various population subgroups, especially infants (de Hoog et al., 2004).

The dosing of vancomycin can be done based on gestational age and postnatal age, body weight, and serum creatinine (Rybak, 2006a). Numerous vancomycin dosing strategies are employed for

neonates, but targeted therapeutic concentration may not be attained many a times. This is mainly due to the disparities in pharmacokinetic properties like volume of distribution [VD] and clearance [CL] among the neonatal group, and variances in dosing schedules available in reference literatures. Protein binding should also be focused on when determining ideal dosing in newborns. Neonates have larger fraction of unbound drug than children and adults (Smits et al., 2018). Monitoring of vancomycin concentration during therapy is significant to evade bacterial resistance and drug toxicity, chiefly vancomycin-induced nephrotoxicity (VIN). (Craig, 2003, Rybak, 2006a) In 2011, the Infectious Diseases Society of America (IDSA) published the first set of guidelines, suggesting an initial vancomycin loading dose of 25-30 mg/kg followed by a maintenance dose of 15-20 mg/kg based on actual body weight and patient's estimated creatinine clearance (CrCl). (Li et al., 1992, Rybak, 2006a) Minimum trough concentration of vancomycin must be sustained above 10 mcg/mL to achieve desired therapeutic outcomes (Rybak, 2006b). Insufficient dosing and monitoring of vancomycin may cause sub-therapeutic bactericidal activity, treatment failure, toxicity, and the rise of resistance. Familiarity of vancomycin dosing restrictions and target trough levels is perilous for effective handling of infection. (Schilling et al., 2011).

Nephrotoxicity in neonates has been reported incidentally, especially when vancomycin is given in combination with an aminoglycoside. It has been shown that no relation exists between peak serum concentrations >40 mg/L and nephrotoxicity in neonates, although a relation to very high concentrations over >60 mg/L has been suggested. Recent articles have discussed the necessity of therapeutic drug monitoring of vancomycin. Therefore, it seems to be more clinically relevant to look at serum trough concentrations as the main determinant of effective therapy. (de Hoog et al., 2004, de Hoog et al., 2000, Giuliano et al., 2010, Goetz and Sayers, 1993, Hing et al., 2004, Jacqz-Aigrain et al., 2013, Makhoul et al., 2005).

In this study we have investigated the appropriateness of vancomycin therapeutics among preterm and full-term neonates by evaluating their target plasma vancomycin concentration profiles during routine clinical investigations.

METHODOLOGY

Study design

This study utilized clinical data that was routinely collected and was available in a classified format. Since it was a retrospective data collection procedure, no consent form was required from the participants. An ethical review was undertaken and got approval from the institutional review board (IRB) at the Ziauddin Hospital.

At initial stage of the study, the hospital's medical records were searched in a retrospective manner between January 2019 and December 2020. Patients were chosen carefully who were administered with intravenous vancomycin for alleged or known Gram-positive bacterial infections and with their serum vancomycin concentrations measured and recorded. Demographic data and routine clinical therapeutic data were also collected for the selected patients.

Inclusion and exclusion criteria

The inclusion criteria were set as 1) age of <60 days at the time of admission to the hospital; 2) suspected or confirmed bacterial infection that required intravenous infusion of vancomycin; and, 3) documentation of at least one serum vancomycin concentration that had been taken during the therapeutic procedure. The exclusion criteria were set as 1) neonates receiving renal replacement therapy; 2) treatment with vancomycin for < 24 h; or, 3) absence of demographic data.

The neonates were classified as preterm who were born before 37 weeks of pregnancy while full term neonates were classified as infants born after 37 weeks and before 42 weeks of gestation (Quinn et al., 2016).

Serum vancomycin concentrations were determined by the hospital's in-house 'Clinical Pharmacokinetic Services'. Following data was retrieved from the records of all preterm infants included in the study gestational age (GA), postnatal age (PNA), body weight (BW), height (HT), serum creatinine (SrCr). Moreover, data of vancomycin dose, administration time, blood sampling time and the assessed concentrations of vancomycin were also collected.

Statistical analysis

Data was analyzed using the Statistical Package of Social Sciences (SPSS), version 21.0 software (IBM Corp., Armonk, NY, USA). For descriptive analysis, weight, gestational and post-natal age, dose, frequency and observed trough concentration was taken. Mean, minimum and maximum values, median and standard deviation was also calculated. *Chi-square* test was employed to analyze significance between neonatal status and dose compliance and neonatal status and trough achieved.

RESULTS & DISCUSSION

The study group consists of 180 neonates of which 90 were preterm and the other 90 were full term. Only those newborns were included who were being treated with vancomycin. Out of 90 preterm neonates, 27 were diagnosed with bacterial meningitis, 52 were confirmed for neonatal sepsis and 6 had endocarditis. Out of 90 full term neonates 22 were diagnosed with bacterial meningitis and 57 were confirmed for neonatal sepsis.

For dose compliance with reference to neonatal status, it was found that all 90 preterm and full-term neonates were given the doses according to the established guidelines for neonatal dosing of vancomycin. Preterm neonates on average were infused with 15.28 ± 3.12 mg/kg/dose and full-term infants were, on average given the dose of 11.78 ± 6.89 mg/kg/dose (see Table-1).

Table-1 Descriptive statistics of various informational parameters for dosing of vancomycin and resultant plasma-drug concentration values

Parameter (unit)	Term Status	Mean ± SD (Range); Median
Gestational age (wk)	Preterm	27.4 ± 7.7
	Full-term	40.3 ± 7.0
Post-natal age (d)	Preterm	13.21 ± 4.2
	Full-term	8.53 ± 3.3
Weight (kg)	Preterm	2.79 ± 1.91
	Full-term	4.67 ± 1.43
Height (cm)	Preterm	36.9 ± 3.4
	Full-term	54.14 ± 4.2
SrCr (mg/dL)	Preterm	0.93 ± 0.28
	Full-term	1.12 ± 0.26
Dose (mg/kg)	Preterm	15.28 ± 3.12
	Full-term	11.78 ± 6.89
Observed Cp (mcg/mL)	Preterm	12.36 ± 1.71
	Full-term	13.40 ± 1.83

The average serum creatinine of preterm neonates is 1.4 mg/dL with 24 – 27 weeks of gestational age, 0.8 mg/dL from 28 – 29 weeks of gestation and 0.5 – 0.7 mg/dL in full term neonates. (Jee and Ra, 1985) Our data shows a serum creatinine, 0.93 ± 0.33 in preterm infants and 1.12 ± 0.34 full-term neonates. Values of serum creatinine in full term infants show an increased value. This may be indicative of the progressive nephrotoxicity due to vancomycin. Previous studies, however, have not established a direct link between recommended doses of vancomycin and toxicity. (Benner et al., 2009, Bhatt-Mehta et al., 1999, Goetz and Sayers, 1993) As NICU patients are frequently very ill and may suffer from multiple disorders, they may not always have to be suitable candidate to receive vancomycin therapy. Same inclinations have been stated in other vancomycin drug usage valuations. (Jacqz-Aigrain et al., 2013, Rayner et al., 1998).

Our data lies well between the desired plasma trough concentrations with preterm having an average trough level of 12.36 ± 1.41 mcg/ml and full-term with trough levels of 13.40 ± 1.83 mcg/ml. However, the desired plasma concentration couldn't be achieved in 11 full-term neonates with chi-square test significance of $p < 0.001$ (see Figure-1 and Table-2).

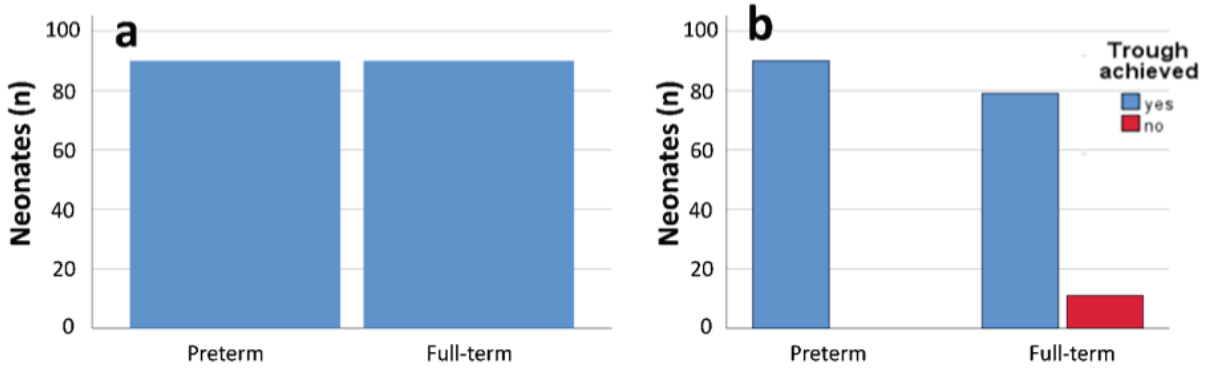

Figure-1. Bar graph of (a) dosing compliance with respect to neonatal status [preterm, full-term], (b) appropriateness of desired steady state plasma-drug [vancomycin] concentration achieved in clinical routine investigations.

Table-2. Appropriateness of desired steady state plasma – drug [vancomycin] concentration achieved in clinical routine investigations

Neonatal status		Trough target achieved*		
		yes	no	Total
	Preterm	90	0	90
	Full term	79	11	90
Total		169	11	180

*Chi square test value = 11.716, df = 1 (p < 0.001) **

One reason may be the failure of physicians to abide by the new guidelines, which states that irrespective of the severity of the infection, the target serum trough concentration should be maintained between 10-15 mcg/ml. (Pagana et al., 2019, Pharmacists). Regrettably, available guidelines are erratic in the projecting value of vancomycin peak and trough values. (Makhoul et al., 2005)
It is pertinent to mention here that some inadequacies in prescribing and monitoring of vancomycin were observed. The prescription of vancomycin is not in accordance with the alleged or confirmed diagnosis and sampling time may have been erroneous. (Hing et al., 2004).

Despite the argument, vancomycin serum monitoring is done without fail in the hospital setting for this study. The justification is grounded primarily on the element that practice abides by the guidelines given by MMIDSP and ASHP which advocates regular monitoring of serum vancomycin levels (Hashmi et al., 2015) (Swartling et al., 2012). The available preliminary dosing schedules or nomograms are built on population pharmacokinetics. It has been stated that individuation of dosing schedules using measured vancomycin concentrations provides more precise dosing in neonatal and pediatric populations. (Rodvold et al., 1997) Miles et al. have informed that the monitoring of vancomycin levels seems to be vital for averting underdosing in pediatric populations. (Miles et al., 1997, Hing et al., 2004)

Advances are required to make vancomycin monitoring more cost-effective. If monitoring of vancomycin concentrations is considered essential, then it should be done correctly to justify the time and money used on it.

In short, intravenous vancomycin remains to be a vital antibiotic for the management of serious infections caused by Gram-positive bacteria. At higher doses desired to overcome growing resistance, we have scarce clinical data associating vancomycin serum concentrations to its efficacy and safety in neonatal patients. Thus, it seems rational to keenly monitor its serum concentrations in this population. Employing clear principles can reduce needless vancomycin serum concentration monitoring and costs without poorly affecting health outcomes. (Lee and Phelps, 2004).

The current study underscores the need for monitoring of vancomycin more closely specially in the neonatal subgroups. Discrepancy in trough levels of full-term neonates was seen. The contributing factors needs to be evaluated in detailed investigation through population pharmacokinetic study. To improve drug utilization and facilitate effective therapeutic drug monitoring, efficient systems like recording of dosing and sampling time must be done. This strategy may well likely contribute to curtailing bacterial resistance, over exposure and consequential nephrotoxicity.

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