Children's Continuous Infusion of Vancomycin

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Vancomycin is a glycopeptide antibiotic used to treat a wide variety of systemic Gram-positive infections, including methicillin resistantStaphylococcus aureus(MRSA) and methicillin resistant coagulase-negativeStaphylococcus(MRCNS) in adult and pediatric populations. Vancomycin exhibits time-dependent bactericidal activity, meaning that the time in which the concentration of the drug in the body is above the minimum inhibitory concentration (MIC) affects antimicrobial efficacy.

Keywords: vancomycin ; continuous ; infusion ; pediatrics ; children

1. Introduction

In adults, the vancomycin area under the plasma concentration-time curve (AUC) to MIC ratio (AUC/MIC) > 400 has long been the best predictor of clinical and bacteriological efficacy for patients with severe infections caused by MRSA [1]. Recently, a revised consensus guideline developed by different scientific associations has been published, recommending a target of an AUC/MIC ratio of 400 to 600 (assuming a MIC of 1 mg/L) for empiric dosing in both adult and pediatric patients to maximize clinical efficacy and minimize nephrotoxicity [2]. However, there is a lack of evidence for this parameter in children due to the complexity of vancomycin clearance in the various pediatric age groups, and the differences in tissue site-of-infection drug exposure as a consequence of higher pharmacokinetic variability [2][3]. Due to the impracticalities of calculating the AUC, target trough concentrations of 15 to 20 mg/L are used as a surrogate marker in adults with normal renal function when MIC is ≤1 mg/mL [4][5]. For the pediatric population, there is more controversy in establishing a target trough concentration. The majority of studies suggest a trough concentration between 6–11 mg/L to achieve AUC/MIC > 400, however no consensus has been reached [6][7][8].

In adults, continuous infusion of vancomycin (CIV) has been evaluated as an alternative to intermittent infusion of vancomycin (IIV) with potential advantages including: earlier concentration target attainment, less variability in serum concentrations, ease of drug level monitoring, and lower risk of nephrotoxicity [2][9][10]. When compared to adults, achieving therapeutic serum vancomycin concentrations (SVCs) with IIV in children requires higher doses and shorter intervals given their increased renal clearance [7][11]. However, higher doses have also been associated with increased nephrotoxicity in pediatrics [3].

Consequently, the use of CIV in children is increasing through a number of heterogenous practices, despite limited efficacy and safety data in this population [11][12][13].

This systematic review aims to provide efficacy and safety evidence for CIV within the pediatric population

2. Clinical Efficacy

Three articles [14][15][16] included in this review evaluated the clinical efficacy of CIV vancomycin treatment. However, none of them were designed for this purpose.

The first one [14] analyzed clinical efficacy only for patients with a final diagnosis of infection treatable by vancomycin and who had received vancomycin for at least seven days. No statistically significant differences were found between patients treated with CIV with and without an early Bayesian dose adjustment regarding sustainable apyrexy, C-reactive protein reduction and bacteraemia duration. Fung et al. [15] evaluated three patients with cystic fibrosis and concluded that there had been a clinical improvement in all of them. Finally, Zylbersztajn et al. [16] reported six cases of patients treated with CIV. They observed clinical improvement in all six patients, with four of these also showing microbiological cure.

3. Safety

All articles, except one [17] evaluated nephrotoxicity. Two articles [14][18] defined nephrotoxicity as an increase in serum creatinine (SCr) ≥ 0.5 mg/dL or a 50% increase from the baseline SCr. One study [11] evaluated effects on renal function using the RIFLE (risk, injury, failure, loss of kidney function, and end stage kidney disease) classification [19]. Two studies [13][16] exclusively evaluated SCr levels and Fung et al. [15] evaluated variation in SCr levels (on admission and prior to discharge), blood urea nitrogen and urine output.

Cases of nephrotoxicity were observed only in two out of six studies [13][14], giving results of 11% and 12% respectively.

Only three studies evaluated immediate adverse events. McKamy et al. [18] evaluated phlebitis, peripheral line loss, and infusion reactions. The frequencies of these adverse reactions to CIV therapy were low and not specified. Berthaud et al. [14] evidenced four cases of red man syndrome and three deaths, however, none of the deaths were attributed to infection nor to iatrogenic events. Finally, Hurst et al. [11] did not note any patients who had any infusion reactions while on CIV therapy.

4. Discussion

This systematic review shows that there remains a lack of evidence for CIV use in pediatrics. Distinct to adults, vancomycin therapeutic drug monitoring adjustment presents a higher level of complexity in children, characterized by unique pharmacokinetic parameters due to important physiological changes because of their rapid development with an increased renal clearance [20].

Understandably, these unique characteristics may support CIV use in certain clinical conditions, since this seems to facilitate the achievement and maintenance of therapeutic SVCs avoiding high nephrotoxic doses as shown in this review. However, the limited data available in this vulnerable population has not allowed its routine use to be generalized in clinical practice and to suggest an optimal dosing regimen for pediatric CIV.

Most of the identified literature recommends CIV use in patients who were unable to achieve therapeutic SVCs or desired clinical outcome with IIV [11][15][18][16]. Yet, there is no prediction model to identify such patients in advance, which can lead to the loss of important days of therapy under suboptimal IIV regimens. The delay in optimizing therapeutic SCVs could result in treatment failure that may influence morbidity and mortality outcomes in those suffering severe infections. Furthermore, alternative antimicrobial therapy options could be wrongly selected if vancomycin treatment failure is suspected, when rather than spectrum or activity, attainment of SVTC is the main problem. This could develop a negative ecological impact and should be actively assessed by antimicrobial stewardship programs. For example, in the case series study of McKamy et al. [18], all patients except for one were converted from IIV to CIV therapy within four to seven days of the initiation of treatment with vancomycin after two consecutive suboptimal therapeutic SVCs. Also, in a retrospective observational study [11], therapeutic SVCs were not achieved even with doses higher than 80 mg/kg/day using IIV; however, when therapy was converted to CIV, 65% of patients achieved SVTC (78% in the goal SVC 10 to 15 mg/L group and 59% in the goal SVC 15 to 20 mg/L group). The initial dosing used for CIV therapy was 56% to 60% less than the final daily dosing of IIV therapy in both goal SVC groups (10–15 mg/L or 15–20 mg/L), but statistically significant higher initial CIV dosing was used in the younger age groups (p = 0.023 and 0.002 for the 10–15 and 15–20 mg/L goal SVC groups, respectively) [11]. This can be explained as age is a predictor of vancomycin clearance within the pediatric population, and younger patients have lower trough concentrations than older patients receiving the same dose [21]. Hoegy D et al. suggest that it is necessary to prescribe certain dosage regimens for each age group, being higher for young age groups [17].

Loading dose administration prior to CIV initiation can also improve the time to achieve SVTC. Two studies [13][14] used loading doses of 12 to 16 mg/kg to rapidly obtain desired steady-state SVTC; however, success in achieving the target ranges was dependent on the use of adequate initial CIV doses. Genuini et al. [13], observed that less than 50% of children achieved SVTC using the recommended dosing regimens, which authors described as an inappropriate result. Consequently, Genuini et al. [13], proposed the use of a pharmacokinetic model with a covariate-adjusted starting dose and Bayesian estimation to achieve the pharmacokinetic target in future studies. Subsequently, one year later, a randomized controlled trial [14] was conducted using a population-based PK (POPPK) model published by Le et al. in 2013 [22] that included age, bodyweight, and serum creatinine as covariates. This study achieved the vancomycin target in more than 50% of children (85% from the Bayesian group and 57% from the control group), showing that covariates could affect PK parameters that may be important to intersubject variability, and its use would be advisable to individualize CIV dose a priori.

The optimal approach for vancomycin therapeutic monitoring is not well established, but recent guidelines support AUC-based monitoring [2]. However, AUC-based monitoring is complicated with conventional IIV, so trough SVCs are used in clinical practice as a surrogate marker for the optimal vancomycin AUC/MIC > 400 if the MIC is ≤1 mg/L in patients with normal renal function. Trough SVCs in IIV cannot be extrapolated to CIV. Thus, for a target of AUC/MIC > 400–600, a SVCs of 10–15 mg/L is accepted in mild–moderate infections and 15–20 mg/L in severe infections or those with difficult access. However, in CIV a concentration of 20–25 mg/L is recommended for an expected AUC/MIC of 480–600 (assuming a MIC of 1 mg/L) [2].

Within the studies analyzed in this review, there was variability in defining the values for target attainment with CIV, with all studies reporting a wide range interval (10–40 mg/L). One study [14] used AUC/MIC > 400 as a primary pharmacological target for vancomycin, instead of an inaccurate approximation using SVCs that poorly correlate to exposure. Based on current available data, the proposal for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for one trough concentration or first-order PK equations with two concentrations [2]. Similarly, unlike intermittent administration, calculating AUC with CIV requires only one steady-state SVC, which can be scheduled along with other scheduled laboratory draws at any time [23].

In this review, most of the studies conducted therapeutic monitoring within 24 to 48 h of CIV therapy. This is recommended by clinical practice guidelines, with delays in therapeutic monitoring made depending on the severity of infection and clinical judgment [2]. Besides, a randomized controlled trial [14] has showed that early Bayesian dose adjustment at 6 h significantly and safely increased pharmacological target attainment in children at the 24 h of treatment with CIV, which could improve clinical and bacteriological outcomes for MRSA infections in this particular population [14].

Clinical and microbiologic efficacy were not evaluated in most studies. Just two small clinical case series without control group [15][16] showed a clinical improvement and negative blood cultures in the majority of patients. A randomized controlled trial [14] compared clinical outcomes between Bayesian and control groups, both with CIV, and there were no differences between groups. However, this clinical trial was not designed to evaluate this. In adults, there is no evidence to indicate that CIV is clinically superior to IIV. However, studies provide evidence supporting that the complexities of dosing and monitoring IIV can be attenuated by CIV therapy [24]. CIV is associated with lower variabilities in the serum concentration and favourable SVTC attainment, which translates into an improved vancomycin exposure, and is currently a better predictor of clinical efficacy [10].

Regarding CIV safety, nephrotoxicity was reported only in a small percentage of patients and was reversible in all cases [13][14]. Moreover, patients with vancomycin-attributable nephrotoxicity had vancomycin concentrations within the therapeutic range. This is in accordance with the hypothesis that elevated SVC is not the only predictive factor for vancomycin-induced renal injury, since it is known that intensive care unit admission, hypovolemia, concomitant administration of other nephrotoxic medications, such as aminoglycosides and diuretics, also contribute to the development of nephrotoxicity [3][13]. Although there is no evidence in children, several meta-analyses in adults have demonstrated that patients treated with CIV had a significantly lower incidence of nephrotoxicity compared with patients receiving IIV [9][25]. This can be explained as CIV minimizes vancomycin serum peak and maximizes trough concentrations, eliminating peak—trough variations of IIV and maintaining intermediate SVC once a steady-state is achieved. In these studies, CIV appeared to achieve a safer serum concentration profile when IIV and CIV dosing regimens were adjusted to achieve the same AUC [9][24][26]. The frequencies of immediate adverse reactions to CIV therapy, such as red man syndrome and phlebitis, were evaluated in three studies. One singular study [14] described the prevalence of red man syndrome as less than 5%, which suggests that it might be an alternative option for patients who experience infusion-related reactions with IIV dosing.

This systematic review of existing literature summarizes all the evidence published so far on CIV in children, analyzing important data and highlighting unresolved aspects that must be further studied to improve this valuable tool in pediatrics. The lack of neonatal data is a key limitation of this review; however, the neonatal population deserves its own analysis given high pharmacokinetics variability that is different from older children. Other limitations include high heterogeneity of the selected articles in terms of study design and quality that do not allow for pooled data analysis, and the lack of studies assessing clinical efficacy and adverse events other than nephrotoxicity.

References

1. Hwang, D.; Chiu, N.C.; Chang, L.; Peng, C.C.; Huang, D.T.; Huang, F.Y.; Chi, H. Vancomycin dosing and target attainment in children. J. Microbiol. Immunol. Infect. 2017, 50, 494–499.

2. Rybak, M.J.; Le, J.; Lodise, T.P.; Levine, D.P.; Bradley, J.S.; Liu, C.; Mueller, B.A.; Pai, M.P.; Wong-Beringer, A.; Rotschafer, J.C.; et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am. J. Health Pharm. 2020, 77, 835–864.
3. Fiorito, T.; Luther, M.K.; Dennehy, P.H.; LaPlante, K.; Matson, K.L. Nephrotoxicity with Vancomycin in the Pediatric Population: A Systematic Review and Meta-Analysis. Pediatr. Infect. Dis. J. 2018, 37, 654–661.
4. Liu, C.; Bayer, A.; Cosgrove, S.E.; Daum, R.S.; Fridkin, S.K.; Gorwitz, R.J.; Kaplan, S.L.; Karchmer, A.W.; Levine, D.P.; Murray, B.E.; et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children: Executive Summary. Clin. Infect. Dis. 2011, 52, 285–292.
5. Rybak, M.; Lomaestro, B.; Rotschafer, J.C.; Moellering, R.; Craig, W.; Billeter, M.; Dalovisio, J.R.; Levine, D.P. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am. J. Health Pharm. 2009, 66, 82–98.
6. Tkachuk, S.; Collins, K.; Ensom, M.H.H. The Relationship Between Vancomycin Trough Concentrations and AUC/MIC Ratios in Pediatric Patients: A Qualitative Systematic Review. Pediatr. Drugs 2018, 20, 153–164.
7. Kishk, O.A.; Lardieri, A.B.; Heil, E.L.; Morgan, J.A. Vancomycin AUC/MIC and Corresponding Troughs in a Pediatric Population. J. Pediatr. Pharmacol. Ther. 2017, 22, 41–47.
8. Frymoyer, A.; Guglielmo, B.J.; Hersh, A.L. Desired Vancomycin Trough Serum Concentration for Treating Invasive Methicillin-resistant Staphylococcal Infections. Pediatr. Infect. Dis. J. 2013, 32, 1077–1079.
9. Chu, Y.; Luo, Y.; Quan, X.; Jiang, M.; Zhou, B. Intermittent vs. continuous vancomycin infusion for gram-positive infections: A systematic review and meta-analysis. J. Infect. Public Health 2020, 13, 591–597.
10. Van Maarseveen, E.M.; Gipmans, S.G.H.; Van Zanten, A.R.H. Exposure Variability and Target Attainment of Vancomycin: A Systematic Review Comparing Intermittent and Continuous Infusion. Ther. Drug Monit. 2020, 42, 381–391.
11. Hurst, A.L.; Baumgartner, C.; MacBrayne, C.E.; Child, J. Experience with Continuous Infusion Vancomycin Dosing in a Large Pediatric Hospital. J. Pediatr. Infect. Dis. Soc. 2018, 8, 174–179.
12. Veluzat, S.; Pauquet, E.; Sarlangue, J. Practice survey on the use of vancomycin in pediatrics in the New Aquitaine region and guidelines of learned societies. Arch. Pédiatr. 2020, 27, 176–182.
13. Genuini, M.; Oualha, M.; Bouazza, N.; Moulin, F.; Treluyer, J.-M.; Lesage, F.; Renolleau, S.; Benaboud, S. Achievement of Therapeutic Vancomycin Exposure with Continuous Infusion in Critically Ill Children. Pediatr. Crit. Care Med. 2018, 19, e263–e269.
14. Berthaud, R.; Benaboud, S.; Hirt, D.; Genuini, M.; Oualha, M.; Castelle, M.; Briand, C.; Artru, S.; Norsa, L.; Boyer, O.; et al. Early Bayesian Dose Adjustment of Vancomycin Continuous Infusion in Children in a Randomized Controlled Trial. Antimicrob. Agents Chemother. 2019, 63.
15. Fung, L. Continuous Infusion Vancomycin for Treatment of Methicillin-Resistant Staphylococcus aureus in Cystic Fibrosis Patients. Ann. Pharmacother. 2012, 46, 1437.
16. Zylbersztajn, B.L.; Chicco, P.; Vega, L.; Centeno, M.; Filippini, S.; Ruvinsky, S. Continuous infusion of vancomycin in pediatric critical care. Arch. Argent. Pediatr. 2013, 111, e31-4.
17. Hoegy, D.; Goutelle, S.; Garnier, N.; Rénard, C.; Faure-Conter, C.; Bergeron, C.; Bertrand, Y.; Bleyzac, N. Continuous intravenous vancomycin in children with normal renal function hospitalized in hematology-oncology: Prospective validation of a dosing regimen optimizing steady-state concentration. Fundam. Clin. Pharmacol. 2018, 32, 323–329.
18. McKamy, S.; Chen, T.; Lee, M.; Ambrose, P.J. Evaluation of a pediatric continuous-infusion vancomycin therapy guideline. Am. J. Health-Syst. Pharm. 2012, 69, 2066–2071.
19. Lopes, J.A.; Jorge, S. The RIFLE and AKIN classifications for acute kidney injury: A critical and comprehensive review. Clin. Kidney J. 2013, 6, 8–14.
20. Murphy, J.E. Clinical Pharmacokinetics, 6th ed.; American Society of Health–System Pharmacists: Bethesda, MD, USA, 2016.
21. Madigan, T.; Sieve, R.M.; Graner, K.K.; Banerjee, R. The Effect of Age and Weight on Vancomycin Serum Trough Concentrations in Pediatric Patients. Pharmacother. J. Hum. Pharmacol. Drug Ther. 2013, 33, 1264–1272.

22. Le, J.; Bradley, J.S.; Murray, W.; Romanowski, G.L.; Tran, T.T.; Nguyen, N.; Cho, S.; Natale, S.; Bui, I.; Tran, T.M.; et al. Improved Vancomycin Dosing in Children Using Area Under the Curve Exposure. Pediatr. Infect. Dis. J. 2013, 32, e155–e163.
23. Girand, H.L. Continuous Infusion Vancomycin in Pediatric Patients: A Critical Review of the Evidence. J. Pediatr. Pharmacol. Ther. JPPT Off. J. PPAG 2020, 25, 198–214.
24. Waineo, M.F.; Kuhn, T.C.; Brown, D.L. The pharmacokinetic/pharmacodynamic rationale for administering vancomycin via continuous infusion. J. Clin. Pharm. Ther. 2015, 40, 259–265.
25. Hao, J.-J.; Chen, H.; Zhou, J.-X. Continuous versus intermittent infusion of vancomycin in adult patients: A systematic review and meta-analysis. Int. J. Antimicrob. Agents 2016, 47, 28–35.
26. Cataldo, M.A.; Tacconelli, E.; Grilli, E.; Pea, F.; Petrosillo, N. Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: Systematic review and meta-analysis. J. Antimicrob. Chemother. 2011, 67, 17–24.