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A Short Communication on Pharmacokinetic Parameters of Vancomycin used in Severe Infections in Children

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Short Communication

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ABSTRACT

Infectious diseases are one of the main diseases in children, and Gram-Positive Bacteria (GPB) infection is an important part of them. For the treatment of GPB, vancomycin is our "last line of defense". By monitoring and calculating the pharmacokinetic parameters of vancomycin and formulating individualized vancomycin administration regimen, it plays a very important role in improving the outcome of GPB infection in children. The current article reviews the application of vancomycin pharmacokinetic parameters in severe infections in children.

INTRODUCTION

Vancomycin is one of the primary agents for the treatment of severe infections caused by GPB, particularly against drug-resistant Gram-positive bacteria, including Methicillin-Resistant Staphylococcus Aureus (MRSA). Given the safety factors of this class of special use antibiotics and the changing levels of liver and kidney function as children grow and develop, Therapeutic Drug Monitoring (TDM) is very important for us, and combine the monitoring results and its original pharmacokinetic parameters to develop an individualized vancomycin anti-infection program for patients, so as to ensure the safety and effectiveness of clinical treatment [1].

The samples used for vancomycin TDM are serum or plasma. It is recommended to take samples to monitor valley concentration 30 minutes before the fourth dose of medication, and 0.5-1 hours after the end of medication to monitor peak concentration [2]. For patients with continuous medication, TDM can be performed weekly according to the needs of the condition, while for children with hemodynamic instability, high-dose medication, and renal dysfunction, TDM should be performed more times [3,4].

VANCOMYCIN TDM IN PEDIATRIC PATIENTS

The biggest difference between children and adults is that children are in the stage of continuous growth and development, which will result in the pharmacokinetic parameters of vancomycin in children are different from those of adults, and there are even large differences in children of different ages [5]. This will lead to the possibility of large individual differences in the treatment of vancomycin in children with severe infections. Therefore, the need for therapeutic drug monitoring of vancomycin is higher in children than in adults, especially in neonates, obesity, burns, concomitant use of renal damage drugs (such as aminoglycosides, amphotericin B, etc.), admission to PICUs, or concomitant Continuous Renal Replacement Therapy(CRRT) treatment. We should consider routine monitoring of vancomycin for these exceptional children [6].

THE VALLEY CONCENTRATION OF VANCOMYCIN

Steady-state valley concentration is a classical pharmacokinetic parameter to evaluate the efficacy and safety of all drugs, especially for antibiotics such as vancomycin. Previous studies have shown that for adult patients, the valley concentration of vancomycin can be maintained at 10~15 mg/L or 10~20 mg/L according to the severity of infection. For neonates or children, maintaining vancomycin valley concentration at 5-15 mg /L is likely to produce better efficacy and minimize adverse drug events [7]. However, the pharmacokinetics (PK) and pharmacodynamics (PD) characteristics of vancomycin in children may be different from those of adults. Therefore, no matter how TDM is performed in children or what the outcome of TDM is, each should be analyzed separately. This is also one of the reasons why some children with vancomycin are still effective in clinical treatment when the steady-state valley concentration of vancomycin is less than 10 mg/L[8]. If the dosage is blindly increased at this time, it will bring additional risk of renal toxicity [9]. Therefore, the new version of TDM guideline of Vancomycin Pharmacist published by American Society of Health-System Pharmacist (ASHP) in 2020 no longer recommended monitoring vancomycin valley concentration, but recommended monitoring the area under the curve(AUC0~24 h) level of vancomycin more [10].

MONITORING AUC0~24 H OF VANCOMYCIN

Different from monitoring valley concentration, monitoring vancomycin AUC0~24 h will more accurately and objectively show the degree of drug absorption and utilization, which is an important parameter for evaluating drug bioavailability and bioequivalence? Currently, the AUC0~24 h of vancomycin can be mainly calculated by Bayesian estimation method or primary pharmacokinetic formula. Based on the high proportion of minimum inhibitory

concentration (MIC) ≤ 1 mg/L of vancomycin against MRSA and other pathogens, a number of studies have suggested that the target range of vancomycin AUC0~24 h should be set at 400~650 mg•h•L^{-1} (the results of systematic evaluation show that AUC0~24 h/MIC>400 correlated with the efficacy of vancomycin treatment,AUC0~24 h>650 mg•h•L^{-1} is associated with a higher risk of renal toxicity), but more solid evidence is needed to confirm these recommendations in neonatal or pediatric patients[10]. We have previously discussed that it may be an appropriate threshold for predicting vancomycin-related nephrotoxicity that AUC0~24 h>537.18 mg•h•L^{-1} [11]. For patients with abnormal renal function, the monitoring of vancomycin AUC0~24 h is not fully applicable, and a comprehensive analysis should be made based on the valley concentration level [12].

REPEAT TDM

If the dose of the patient is adjusted according to valley concentration or AUC0~24 h after the initial TDM, it is recommended to repeat the TDM at 4~5 doses after the dose adjustment, because the blood concentration of vancomycin in the new regimen has reached a new stable state at this time. In addition, patients admitted to PICU, receiving vasoactive agents, or receiving renal replacement therapy often have hemodynamic instability, which may lead to large individual differences in vancomycin PK characteristics, and these patients should repeat TDM. For severe infections, more intensive TDM can ensure that the PK/PD target is consistently reached during treatment [13].

VANCOMYCIN INDIVIDUALIZED ADMINISTRATION REGIMEN BASED ON PK/PD

No matter monitoring vancomycin valley concentration or AUC0~24 h, after the implementation of TDM, using Bayesian estimation method, two-point method or one-point method to individually design subsequent vancomycin administration scheme is currently considered the most appropriate vancomycin administration adjustment method[14]. In addition to dose adjustment after TDM, the combination of population pharmacokinetic model and Bayesian estimation method can also be used to assist the initial measurement design. Continuous optimization of PK based vancomycin individualized administration regimen can improve the standard rate of blood drug concentration, indicating the risk of renal toxicity in patients to a certain extent, but its correlation with clinical efficacy needs to be confirmed by further studies [15].

RESULTS OF APPLICATION OF VANCOMYCIN PHARMACOKINETIC PARAMETERS IN CHILDREN

By monitoring the pharmacokinetic parameters of vancomycin, more and more studies recommend loading dose of the first dose for patients with substandard blood concentration in addition to increasing the dose and extending the infusion time. Compared with the no-load dose group, this method can significantly increase the standard rate of vancomycin concentration without increasing the risk of renal toxicity (adult single dose 25-30 mg/kg, children single dose 30 mg/kg) [16]. In addition, for children, the initial dose of 60 mg•kg^{-1}•d^{-1} is not enough to guarantee the standard blood concentration level. Especially for children aged 1-6 years, the risk of low blood concentration may be higher, and the dosage of more than 60 mg•kg^{-1}•d^{-1} may be considered when necessary. Consideration of the risk of renal toxicity at high doses of vancomycin should be accompanied by consideration of the need to switch to other antimicrobial agents [17].

DISCUSSION

For children with severe infection, valley concentration and AUC0~24 h are the main pharmacokinetic parameters currently monitored during vancomycin treatment, and whether these two indicators reach the standard or not will predict the effectiveness and safety of treatment to a certain extent [18]. It is feasible to monitor valley concentration by TDM, but its predictive significance may vary greatly among children. AUC0~24>537.18 mg•h•L-1 may be an

appropriate threshold for predicting vancomycin-related nephrotoxicity in children, but for children, whether 400~650 mg•h•L^{-1}, the target value of AUC0~24 h, is related to clinical efficacy needs to be further studied [11,19].

CONCLUSION

This article reviews the monitoring of vancomycin in the treatment of severe infection in children and the application of pharmacokinetic parameters. AUC0~24 h and valley concentration were associated with safety and efficacy in children treated with vancomycin, respectively. For children patients, hospitals with conditions can consider AUC0~24 h monitoring for children with normal renal function, which will ensure the drug safety of vancomycin to a greater extent. Hospitals that cannot carry out AUC0~24 h monitoring can monitor vancomycin valley concentration and guide further adjustment of drug use plan.

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