Glycopeptide pharmacokinetics in current paediatric cardiac surgery practice*§

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Objective: To examine the evolution of serum concentrations of prophylactic glycopeptides administered during state-of-the-art cardio-pulmonary bypass (CPB) and vigorous haemodiafiltration in paediatric patients undergoing cardiac surgery. Methods: We enrolled infants and children <3 years of age who, based on the preoperative microbiological screening, age and surgical complexity, were at high risk of methicillin-resistant Staphylococcus aureus (MRSA) infection. Antimicrobial prophylaxis with glycopeptides was administered to 22 patients, randomly assigned to vancomycin (VAN; n = 11) versus teicoplanin (TEC; n = 11). Fixed doses of each drug (15 mg/kg for VAN and 8 mg/kg for TEC) were administered immediately before the operation, at the time of priming of the extracorporeal circuit, upon admission to the intensive care unit and for 48 h thereafter, q. 8 h for VAN, and once daily for TEC. Vigorous haemodiafiltration was applied during and briefly after CPB. Results: The second dose of drug added to the prime prevented a fall in serum drug concentrations at the onset of CPB in both groups. A 77% decrease in VAN, versus 53% in TEC concentrations, was observed after the conclusion of CPB. Serum concentrations of TEC > 10 \( \mu \text{g/ml} \) were observed throughout the treatment period in 91% of patients, while 55% of patients assigned to VAN had serum concentrations consistently >5 \( \mu \text{g/ml} \) (p = 0.08). Therapeutic serum concentrations were maintained throughout the intraoperative period, particularly with TEC, administered before the first surgical incision, followed by a supplemental bolus in the priming fluid of CPB. Postoperative surgical wound infections occurred in neither group. Conclusions: The prophylactic use of glycopeptides in paediatric patients at high risk of MRSA infection undergoing cardiac surgery was safe and effective. TEC might be the drug of choice, since stable, therapeutic serum concentrations were easily maintained throughout the treatment period.

Keywords: Paediatric cardiac surgery; Cardiopulmonary bypass; Antimicrobial prophylaxis; Teicoplanin; Vancomycin

1. Introduction

Lowering the rates of perioperative infections and associated morbidity has been a priority in the management of paediatric patients after cardiac surgery. The perioperative prophylactic administration of antimicrobial agents has been effective in preventing infections, particularly at the surgical site. Staphylococcus aureus is a predominant pathogen among patients undergoing cardiac surgery. In settings where methicillin-resistant Staphylococcus aureus (MRSA) is endemic, glycopeptides might be recommended for surgical antimicrobial prophylaxis [1].

The intraoperative concentrations of antimicrobials have a prominent influence on rates of postoperative infection. Antibiotics should be administered within 1 h preceding the first surgical incision, and continued in doses sufficient to maintain effective serum concentrations over the subsequent 24 h postoperatively [2,3]. The pharmacokinetics of the two synthetic glycopeptides available for surgical prophylaxis, vancomycin (VAN) and teicoplanin (TEC) have not been thoroughly studied in the setting of paediatric cardiac surgery. To the best of our knowledge, a study of six patients treated with VAN is the only report of the clinical application of glycopeptides in paediatric patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) [4].

The purpose of this study was to examine the evolution of blood concentrations of VAN and TEC administered...
prophylactically, during state-of-the-art CPB and vigorous haemodiafiltration, in paediatric patients at high risk of postoperative MRSA infections undergoing cardiac surgery.

2. Materials and methods

The Institutional Committee for Clinical Investigation of Kyoto Prefectural University, School of Medicine, approved this study. All parents or responsible persons granted their written consent to include the patients in the study. Between November 2002 and March 2005, we enrolled 24 patients <3 years old who were admitted for cardiac surgery to the paediatric intensive care unit (PICU) of our University Hospital. They were randomly assigned 1:1 to one or the other prophylactic glycopeptide. The physicians were aware of the random assignment. We excluded from this analysis the patients who died intraoperatively or required postoperative extracorporeal cardiopulmonary support.

2.1. Indications for prophylactic glycopeptides

The 24 patients identified as candidates for surgical prophylaxis with glycopeptides fulfilled the following criteria: (1) carriage of MRSA in the nasal cavity, preoperatively confirmed by sampling the anterior nares [5], or (2) a history of MRSA infection in (a) a neonate or <3-month-old infant hospitalised since birth, or (b) a patient presenting with a major cardiac disorder, according to the cardiac complexity classification for paediatric cardiac surgery [6].

2.2. Drug administration

Patients were randomly assigned to receive either VAN (Shionogi & Co., Ltd., Osaka, Japan) or TEC (Astellas Pharma Inc., Tokyo, Japan). Based on the information provided by the pharmaceutical companies and certificated by the Japanese Ministry of Health, Welfare, and Labour, VAN (molecular weight = 1485) and TEC (molecular weight = 1564–1893) were administered in fixed doses of 15 and 8 mg/kg, respectively. A first dose of antimicrobial was administered after the induction of general anaesthesia, within 1 h before the first surgical incision, and a second, identical dose was added to the priming solution of CPB, based on an estimated volume of mean serum creatinine concentration in both study groups.

Blood was collected (1) immediately before the initiation of CPB, (2) after the initiation of CPB, (3) at the end of CPB, (4) upon admission to the PICU, (5) 24 h after the admission to the PICU (day-1 trough level) and (6) 48 h after the admission to the PICU (day-2 trough level).

Based on previous observations [7,8], we set the therapeutic serum concentration of TEC above 10 μg/ml, and that of VAN at above 5–10 μg/ml. In an analysis performed at our institution, the lowest concentrations of VAN or TEC at which 90% of MRSA isolates were inhibited is 2 μg/ml.

The serum creatinine concentration was measured daily before and after the operation. In addition, adverse effects attributable to the administration of the drugs, including red man syndrome or other allergic reactions, were recorded.

2.3. Cardiopulmonary bypass and haemodiafiltration

The CPB system consisted of non-pulsatile roller pumps (HAS, Senko Medical Industry Co., Tokyo, Japan) and a SAFE MICRO membrane oxygenator (Senko Medical Industry Co., Tokyo, Japan). The amount of priming solution needed for the extracorporeal circuit ranged between 240 and 500 ml, according to the patients’ size and oxygenator used. The amount of priming solution contained 10% mannitol, 5 ml/kg; 8.5% sodium bicarbonate, 3 ml/kg; acetylated Ringer’s solution and packed red cells, as needed. CPB was performed under conditions of moderate haemodilution and a haematocrit near 30%, hypothermia to 30°C for simple procedures and 25–28°C for complicated procedures, and whole body heparinisation with 375 U/kg. The pump flow was controlled to maintain a >70% systemic venous oxygen saturation, with the minimum flow kept at 2.7 l/min/m² for neonates, 2.4 l/min/m² for infants and 2.2 l/min/m² for children.

Continuous haemodiafiltration, performed with a circuit included within the extracorporeal circulation, was started immediately after circulatory stabilisation, and maintained throughout CPB. The haemodiafiltration circuit consisted of a dialysis membrane of polymethyl methacrylate (HEMOFEEL CH-0.6N, Toray, Japan) and dialysate (Sublood BS, Fuso-
The blood flowed from the venous circuit at a rate of 100 ml/min and returned into the venous reservoir. The dialysate flow and fluid removal rate were set at 2000–2500 ml/h and approximately 500 ml/h, respectively, to maintain a sufficient venous reservoir volume and a haematocrit near 30%. After discontinuation of CPB, haemodiafiltration was continued for 10–15 min, using the CPB circuit as a blood access, at a fluid removal rate of approximately 20 ml/kg/10 min.

2.4. Statistical analyses

The data are expressed as means ± SD for continuous variables and n (%) for categorical valuables. Student’s t-test, repeated measures analysis of variance or Fisher’s exact test was used to examine the statistical significance of between-groups differences. A p-value <0.05 (two-tailed) was considered significant.

3. Results

3.1. Patient characteristics

During the study period, a total of 286 patients were admitted to our PICU after having undergone cardiac surgery under CPB. Of those, 24 patients were enrolled based on the aforementioned criteria. Positive nasal carriage of MRSA was detected in 18 patients, and 6 patients had previous MRSA infections of the surgical site. There were 3 neonates, 12 infants and 9 children. After randomisation, one VAN-treated patient was excluded from the analysis because of early death, and another VAN-treated patient was excluded because of postoperative application of extracorporeal cardiopulmonary support. Thus, data from 11 patients in each group were analysable.

Except for the younger mean age of the VAN-treated patients (p = 0.02), the demographic characteristics of the study groups were similar (Table 1). Likewise, no difference was observed between the two study groups in the mean duration of operation, mean duration of CPB and estimated percent of plasma volume diluted by the extracorporeal circuit (Table 1). No postoperative infection of the surgical site was observed in either group.

3.2. Changes in serum glycopeptide concentrations

The mean serum concentrations of VAN immediately before and after the onset of CPB were 28.1 ± 19.3 and 54.1 ± 13.6 μg/ml, and mean concentrations of TEC 43.8 ± 15.4 and 54.5 ± 8.5 μg/ml, respectively, confirming that the second dose of antimicrobial effectively maintained therapeutic concentrations, despite the relatively abundant volume of priming solution needed in paediatric patients. The serum concentration of VAN before the onset of CPB was specifically low in three neonates (13.1, 13.8 and 14.5 μg/ml, respectively).

At the end of CPB, the mean serum concentration of VAN fell to 12.7 ± 7.9 μg/ml, a 77% decrease from the initial measurement, while the mean TEC concentration fell less markedly to 24.7 ± 9.6 μg/ml, a 53% decrease (p = 0.04 vs VAN). The mean serum concentrations of TEC remained significantly higher than those of VAN throughout the treatment period (p < 0.001 by repeated measures ANOVA; Fig. 1). Intraoperatively, all patients in the TEC group maintained serum concentrations above 10 μg/ml, versus eight patients treated with VAN (73%, p = 0.06; Fisher’s exact test). Furthermore, serum concentrations of TEC were kept in the therapeutic range for up to 48 h postoperatively in 10 patients (91%), versus only 6 patients (55%) treated with VAN kept in the therapeutic range of above 5 μg/ml, though the difference was of borderline statistical significance (p = 0.08). In addition, a single patient treated with VAN (9%) maintained serum concentrations in the therapeutic range after resetting the minimum therapeutic serum concentration of VAN above 10 μg/ml (p < 0.001).

3.3. Adverse effects and costs

No patient had a rise in serum creatinine consistent with drug-induced nephrotoxicity. The mean serum creatinine concentration, measured preoperatively and on days 3 and 7 after surgery, remained similar and within normal limits in both study groups (Table 1). In two neonates assigned to VAN, however, a postoperative increase in serum creatinine concentration above 1.0 mg/dl was observed, associated with trough drug concentrations of 24.5 and 36.5 μg/ml, respectively, on day 2. No drug-induced allergy was observed.

The costs of antimicrobials were almost identical between the two groups: 37,179 yen (approximately $315) in the VAN group versus 38,745 yen (approximately $326) in the TEC group.

4. Discussion

4.1. Serum concentrations of glycopeptides

This study examined the perioperative serum concentrations of VAN and TEC administered prophylactically in
paediatric patients undergoing cardiac surgery. The administration of glycopeptide, starting immediately before the surgical incision followed by an additional identical dose in the CPB priming solution, prevented a pronounced decrease in serum concentration of drug after the induction of CPB. The administration of five perioperative 8.0 mg/kg doses of TEC, reliably maintained therapeutic serum concentrations during and after the operation.

In view of the recent increase in the prevalence of MRSA, the prophylactic use of glycopeptides is expected to lower the morbidity associated with postoperative infections among high-risk patients undergoing cardiac surgery [3]. In adults, the preoperative administration of 15 mg/kg (or of 1 g) of VAN in a single dose appears sufficient to achieve therapeutic perioperative blood concentrations [9—14]. Studies of TEC suggest that a single 6-mg/kg dose administered preoperatively produces therapeutic perioperative blood concentrations [15], although higher doses of 12-mg/kg or single 600-mg doses have been recommended recently [16—20]. In our own study, 15 mg/kg of VAN or 8 mg/kg of TEC produced sufficiently high blood concentrations before the initiation of CPB. A larger first dose of VAN, however, might be appropriate to maintain the blood concentrations at target levels, specifically in neonates, considering their greater distribution volume.

Care must be taken to prevent the reported up to 41% decrease in VAN [9—11,13,14] and up to 46% decrease in TEC [15,16,18] concentrations due to the haemodilution by the CPB priming solution, a phenomenon which is accentuated in paediatric patients. A single study, however, has described the use of glycopeptides in paediatric cardiac surgery. Hatzopoulos et al. reported a 45% decrease in serum concentrations of VAN after the onset of CPB in children between the ages of 0.8 and 4.8 years [4]. In our own study, after calculations of the plasma volumes, we anticipated nearly 50% decreases in serum concentrations of drug at the onset of CPB, which we successfully prevented by adding a second identical dose of antimicrobial to the priming solution.

A near 80% decrease in the mean VAN serum concentration was observed during CPB, in contrast to just over 50% for TEC. Consequently, the TEC concentrations remained consistently above 10 μg/ml during CPB, whereas the VAN concentrations regularly fell below 5 μg/ml. This difference in measured drug concentrations might be explained by the 4—8-h elimination half-life of VAN versus 83—168-h elimination half-life of TEC, and in the 10—55% protein-binding capacity of VAN versus 90% protein-binding capacity of TEC [21]. Although we did not measure the clearance of the drugs, it is likely that a considerable amount of free VAN was lost during vigorous haemodilatation. Recent paediatric cardiac surgery practice studies recommend the vigorous use of haemodilatation during as well as after CPB. Besides helping to compensate for a reduced renal function and fluid removal, meticulous haemodilatation might remove noxious humoural mediators with molecular weights between 2 and 20 kD, including cytokines [22, 23]. This might explain the faster removal of VAN than TEC during CPB with haemodilatation in our study. It appears that TEC allows the maintenance of stable serum concentrations during the use of state-of-the-art paediatric CPB.

4.2. Limitations of this study

We measured the serum concentration of glycopeptide as the total of protein-bound and unbound drug. Selective measurements of the unbound form of drug combined with the total amount might be more relevant, since the drug efficacy is probably attributable to the unbound form. Given that the lower detection limit of both glycopeptides in assays currently available in our laboratory is 2 μg/ml, the unbound form of the drug cannot be selectively measured with precision.

We did not measure the tissue concentrations of the drugs. In a previous study, following the administration of 12 mg/kg of TEC, only 12 and 18% of the drug concentration measured in serum was recovered in pericardial fluid and fat, respectively [20], a ratio similar to that between free and protein-bound TEC in plasma [21]. In another study, however, the proportion of drug recovered from heart and mediastinal tissues after the administration of 6 or 12 mg/kg of TEC was approximately 40% of that measured in serum [19]. The different tissues studied might explain these discordant results. The serum concentrations of TEC and VAN needed to achieve therapeutic concentrations of drugs in tissues warrant further investigations, considering the specific pharmacokinetics and pharmacodynamics of each pharmaceutical.

Finally, this study was apparently underpowered to assess the impact of the two glycopeptides on infectious outcome. Given the 3—8% incidence of postoperative infection observed in several other studies [5,6,24], more patients would have been needed to detect differences in infectious complications between patients assigned to one antimicrobial versus the other. The numbers of patients were limited as we selectively applied glycopeptides to our patients, as the systematic prescription of glycopeptides is not fully supported by sufficient evidence. The frequent decreases in VAN concentrations below 5 μg/ml observed in this study suggest that it might negatively influence the postoperative infectious outcome. This needs to be addressed in a large multicentre study.

5. Conclusions

The use of glycopeptides, administered immediately before the first surgical incision, followed by a second dose added to the CPB circuit prime, was associated with stable serum concentrations throughout the intraoperative period of paediatric cardiac surgery, despite vigorous haemodilatation. Specifically, an 8 mg/kg/dose of TEC maintained serum concentrations above 10 μg/ml throughout the treatment period. Additional desirable characteristics of TEC [25], including infrequent dosing and low toxicity, suggest that its use in paediatric cardiovascular surgery might be suitable. When using VAN in paediatric patients, we recommend the close monitoring of its serum concentrations intra- and postoperatively, and the administration of higher or more frequent doses should be considered. Finally, in view of the high cost of glycopeptides, the efficacy of preoperative/intraoperative dosing, while omitting its administration postoperatively, should also be examined.
References


