# Monitoring of Serum Vancomycin Concentrations in Pediatric Patients with Normal Renal Function

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**Abstract-** Vancomycin is a a glycopeptide antibiotic with bacetiocidal effects on gram positive bacteria by interfering with cell wall synthesis. The necessity for monitoring of serum vancomycin concentrations (SVCs) has been recently noticed at many institutions because of concerns for its nephrotoxicity. We aimed to describe the SVCs monitoring in pediatric patients, in an effort to determine subtherapeutic or toxic levels. The medical records were reviewed for all patients older than 60 days of age admitted to the general or subspecialty services who received intravenous vancomycin at Children's Medical Hospital in Tehran, Iran between July 2003 and December 2005. Because pharmacokinetic parameters for children with cancer may be different, this group was evaluated separately. During the study, 167 infants and children without cancer and 42 patients with cancer; aged between 3 months to 17.5 years were treated with vancomycin for various infections. In children without cancer, peak SVCs were in an adequate therapeutic range for 93% of patients (8-55 μg/ml). For children with cancer, peak SVCs was lower than 10 μg/ml (10%), and trough values were lower than 5 μg/ml (21%). In conclusion, according to the results of this research, due to different pharmacokinetics of vancomycin in cancerous patients, the monitoring of vancomycin plasma concentrations is necessary for the best therapeutic antibacterial activities with a fewer occurrence of serious adverse effects.

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## Introduction

The necessity for routine monitoring of serum vancomycin concentrations (SVCs) has recently come under intense review at many institutions, because initial concerns for nephrotoxicity have been largely alleviated. Many experts currently do not recommend measurement of SVCs in patients with normal renal function who are treated with the usual dosages of vancomycin (1-5), whereas others continue to firmly support routine monitoring (6).

Early studies documented dosage and serum concentrations adequate for management of various infections in children, and adjustments were not required to assure cure in subsequent efficacy trials (7). The recommendation to monitor this antibiotic was introduced after anecdotal reports of nephrotoxicity usually in elderly adults who were also being treated with other potentially nephrotoxic agents such as aminoglycosides. It has never been established what concentration of vancomycin may actually be nephrotoxic under any circumstances.

Measuring vancomycin levels in serum might be helpful to prevent toxicity and to assure an adequate therapeutic drug concentration. However, many clinicians preferred to know whether the regimen they prescribed achieved an expected serum concentration, especially if dosage adjustments were necessitated by renal failure. Some investigators compared individualized dosing based on the actual serum concentration with dosing based on data from nomograms and found the individualized method to be superior. Others recommended monitoring of serum levels in certain situations-for example, when patients receive vancomycin/aminoglycoside combinations, when anephric patients undergoing hemodialysis receive

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infrequent doses of vancomycin, and when patients receive higher than usual doses of vancomycin. With no clear consensus, many clinicians chose to dose according to nomogram data, whereas others measured serum concentrations in every case (4, 8).

The purpose of this study was to review our experience about monitoring SVCs at a large Children's Hospital, in an effort to determine what concentrations might be in a potentially subtherapeutic or toxic range.

## Patients and Methods

The medical records at Children's Medical Hospital in Tehran, Iran were reviewed for all patients older than 60 days of age admitted to the general or subspecialty services, who received intravenous vancomycin between July 2003 and December 2005. Because earlier reports had suggested that pharmacokinetic determinations for children with cancer might be different from those of other patients (9), this group was evaluated separately. We excluded neonates and infants younger than 60 days of age. The diagnosis, dosage of drug, initial serum creatinine, initial measurement of SVCs and any dosage adjustment as a response to this determination were recorded. The concomitant administration of other potentially nephrotoxic drugs was also noted. Patients with an elevated creatinine or other evidence of renal dysfunction were excluded. Patients requiring longer infusion times because of adverse drug reactions ("red man" or "red neck" syndrome) were also excluded.

Vancomycin was administrated intravenously by a syringe pump infusion over 45 to 60 min at 7.5 to 10 mg/kg of body weight. Serum samples were obtained by venipuncture, 60 min after finishing the infusion. SVCs were determined by fluorescence polarization immunoassay (AxSYM; Abbott Laboratories).

General guideline recommendations at our institution during this time period, similar to those previously published (7, 9-11), were as follows: children with normal renal function receive 40 to 50 mg/kg/day of intravenous vancomycin divided every 6 h, that a serum creatinine be obtained within 24 h of the first dose, that vancomycin peak and trough serum concentrations be measured after the third dose (or the next daytime dose thereafter) and that dosage adjustments be made by the responsible physician if peak serum concentrations were not between 20 and 40 μg/ml.

For data analysis, peak SVCs between 15 and 40 μg/ml and trough values of 5 to 15 μg/ml were considered acceptable, based on our literature review (7, 10, 12).

**Table 1.** Peak and trough SVCs after an intravenous vancomycin dose of 40-50 mg/kg in children with normal renal function

| SVCs (μg/ml) | Patients without Cancer (%) |
|---|---|
| **Peak** | |
| *Very low* | |
| <10 | 3/167 (2)* |
| 10-15 | 9/167 (5) |
| *Therapeutic* | |
| 15-40 | 147/167 (88) |
| 40-50 | 6/167 (4) |
| *Very high* | |
| >50 | 2/167 (1) |
| *Trough* | |
| <5 | 18/169 (11) |
| 5-15 | 148/167 (89) |
| >15 | 1/167 (1) |

* Numbers in parentheses, percent

## Results

During the study, 167 infants and children without cancer and 42 patients with cancer; aged 3 months to 17.5 years were treated with vancomycin for various presumed or documented infections. Seventeen additional patients were excluded from our analysis, 12 with renal impairment and 5 requiring longer infusion times. Monitoring data for peak and trough SVCs are summarized in Tables 1, 2. In children without cancer, peak SVCs were in an adequate therapeutic range for 93% of patients, with the highest value being 55 μg/ml and the lowest 8 μg/ml.

**Table 2.** Peak and trough SVCs after an intravenous vancomycin dose of 40-50 mg/kg in children with normal renal function

| SVCs (μg/ml) | Patients with Cancer (%) |
|---|---|
| **Peak** | |
| *Very low* | |
| <10 | 4/42 (10)* |
| 10-15 | 17/42 (40) |
| *Therapeutic* | |
| 15-40 | 20/42 (48) |
| 40-50 | 0/42 (0) |
| *Very high* | |
| >50 | 1/42 (2) |
| *Trough* | |
| <5 | 9/42 (21) |
| 5-15 | 31/42 (74) |
| >15 | 2/42 (5) |

* Numbers in parentheses, percent

In children with cancer, a higher percentage had peak SVCs below 10 μg/ml (10%), and trough values <5 μg/ml (21%). These patients required an increased dosage of 48 to 65mg/kg/day to achieve peak concentrations of >20 μg/ml.

In this series, there were no treatment failures in the group with routine infections or in six patients with cancer and bacteremia, five caused by Staphylococcus epidermidis and one by Staphylococcus aureus.

## Discussion

When vancomycin was first approved by the Food and Drug Administration (FDA) in 1958, nephrotoxicity and ototoxicity were included as potential adverse effects. This caution was based on a report of renal dysfunction in two patients in whom vancomycin serum concentrations had reached 80 to 100 μg/ml (4, 13). It was also suggested that toxicity might have resulted from impurities in the original vancomycin product which was dark brown and muddy. Subsequently, production of this antibiotic was revised so that preparations are now absolutely free of such impurities.

Controlled investigations in animals, undertaken 20 years after the drug was released (11, 14), failed to demonstrate either nephrotoxicity or ototoxicity attributable to vancomycin when administered without other nephrotoxic agents such as aminoglycosides. Moreover, post marketing reporting and surveys have rarely identified nephrotoxicity in patients with normal renal function who were not receiving concomitant nephrotoxic agents (1). Although more than 150 cases of nephrotoxicity and 50 cases of hearing loss associated with vancomycin use have been reported, the majority had additional confounding risk factors either from their underlying disease or from concomitant drug use. Of those without confounding variables where serum drug concentrations were measured, most had peak and trough concentrations within the recommended range. Still this is a very small number of reports considering the current extensive use of vancomycin. In spite of highly questionable causality, a recent review concluded that although literature is conflicting concerning synergistic nephrotoxicity for the combination of evaluations of the serum creatinine level should be performed on the basis of a patient's risk for renal insufficiency secondary to disease states or co treatment with nephrotoxic drugs (1).

Original dosage recommendations for pediatric patients published in 1959 were guided by experience in adult patients and based on just 23 children, aged 1 month to 18 years who received dosage regimens between 40 and 180 mg/kg/day (15).

However, additional data many years later supported the initial dosage recommendation of 40 mg/kg/day in infants and children with normal renal function, to achieve optimal peak SVCs; in that study SVCs >12μg/ml or 8-fold greater than the MIC of the pathogen being treated generally correlated with clinical cure (10, 16), although subsequent recommendations usually suggested a higher range of 20 to 40 μg/ml as ideal peak concentrations (13). The largest clinical trial including neonates and children used fixed doses of vancomycin from 30 to 60 mg/kg/day and found peak and trough concentrations ranging from 18 to 57 μg/ml and 3 to 19 μg/ml respectively (7).

Clinical outcome for these staphylococcal infections was excellent. Unfortunately, there has never been any clear correlation between peak SVCs and clinical cure rates either in pediatric or adult efficacy trials. This lack of data makes it difficult to offer firm recommendations either for appropriate serum concentrations or dosage regimens.

The minimal inhibitory concentration (MIC) of vancomycin for most susceptible organisms is <5 μg/ml and in almost all clinical trials, trough as well as peak levels have exceeded this value. There is no enhancement of bacterial killing with higher serum concentrations, suggesting that current standards for minimum serum concentrations may be high. More importantly, the levels where toxicity might occur are least 2-fold higher than those achieved with currently recommended dosages. With such a wide safety margin, it would appear prudent to dose this antibiotic in the higher range, i.e. 40 mg/kg/day and for children with cancer at an even higher dose of 60 mg/kg/day because they more likely to have peak concentrations.

The present report confirms that concentrations of vancomycin are quite predictable in the majority of infants and young children with normal renal function. An exception appears to be children with cancer who for reasons incompletely understood exhibit increased metabolism and elimination of the drug, with resulting reduced serum concentrations (3, 9, 16). Our current data support this observation.

Based on our experience and review of the literature, we launched the following guidelines at our institution for monitoring SVCs in pediatric patients:

Serum creatinine measurement is recommended within 24 h of beginning to verify that renal function is normal and repeated at least two times weekly during therapy. An increase in serum creatinine of 0.5 mg/dl or

more from baseline during therapy suggests a change in function and potential need to monitor SVCs.

Peak and trough vancomycin serum concentration measurements are not generally necessary for children receiving doses of 40 to 50 mg/kg/day or less who have normal renal function, are not receiving other potentially nephrotoxic medications and do not have cancer. Responsible physicians may, however, choose to individualize this approach based on other factors such as degree of illness, poor clinical response or persistent positive cultures.

In this study, we conclude that monitoring of vancomycin serum concentrations should be considered for patients with cancer. We also propose other studies on neonates, those receiving concurrent nephrotoxic drugs such as aminoglycosides, and patients with abnormal renal function.

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