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REVIEW

Vancomycin nephrotoxicity: myths and facts

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ABSTRACT

Vancomycin is a key antibiotic in the management of severe Gram-positive infections. Recent emergence of methicillin-resistant staphylococcal strains with reduced susceptibility to vancomycin has prompted internists to administer high-dose treatment to achieve trough levels of 15 to 20 mg/l. Such high doses might be causative in nephrotoxicity. The risk further increases in patients who are critically ill and are on vasopressor support and/or concomitant nephrotoxic agents, with baseline deranged renal function, undergoing prolonged duration of therapy and are obese. However, data are insufficient to recommend the superiority of continuous infusion regimens as compared with intermittent dosing. This review discusses the literature pertaining to vancomycin nephrotoxicity.

KEYWORDS

Dose, nephrotoxicity, trough levels, vancomycin

INTRODUCTION

Vancomycin is a cornerstone antibiotic for the management of severe Gram-positive infections. Introduced into clinical practice in 1956, it is a bactericidal glycopeptide with a molecular weight of 1446 Da.[1] It inhibits the cell wall synthesis of Gram-positive bacteria by the formation of stable complex murein pentapeptides, thus causing inhibition of further peptidoglycan formation.[2] The killing action of vancomycin is slow and is negatively affected by biofilm formation, stationary growth phase, large bacterial inoculates, and anaerobic growth conditions.[1] Early batches of vancomycin contained significant impurities, leading to a variable toxicity and the nickname *Mississippi mud*. Subsequently, production of this antibiotic was revised so that preparations are absolutely free of these impurities.[3]

The relationship between serum concentrations and treatment success or failure in serious *Staphylococcus aureus* infections has recently been established. The pharmacokinetic-pharmacodynamic (PK-PD) parameter best predicting activity of vancomycin against staphylococcal species is the 24-hour area under the concentrations curve over the minimal inhibitory concentration (AUC/MIC).[4] On the basis of *in vitro*, animal and limited human data, an AUC/MIC value of 400 has been established as the PK-PD target.[1] However, these values are hardly obtainable in *S. aureus* strains with a MIC of 2 μg/dl.[1] Also, the calculation of AUC/MIC is not practically feasible. Trough levels have a good correlation with total drug exposure given by the AUC/MIC and are therefore recommended as the most precise and workable monitoring method in daily clinical practice. These trough levels should be obtained just before the fourth dose at steady state conditions.[1,5]

MECHANISM OF VANCOMYCIN NEPHROTOXICITY

Elimination of vancomycin is almost exclusively renal. Vancomycin is renally eliminated mainly via glomerular filtration, and to some extent via active tubular secretion.[6] Animal studies have suggested proximal renal tubular cell necrosis by vancomycin accumulation as mechanism of nephrotoxicity.[7] Vancomycin-induced renal damage requires energy-dependent transport from the blood to the tubular cells across the basolateral membrane.[8] In the tubular cells, vancomycin presents a pronounced lysosomal tropism.[8] Animal studies suggested oxidative stress might underlie the pathogenesis of vancomycin-induced toxicity.[9,10] Gene expression analyses in mice have suggested involvement of oxidative stress and mitochondrial damage in vancomycin-induced kidney injury. More importantly, a potential contribution of complement pathway and inflammation in the vancomycin-induced renal toxicity has been

postulated. In addition to necrosis, signs of tissue repair were also detected in vancomycin-treated animals.[7] Severe vancomycin renal toxicity may present histologically as tubulointerstitial nephritis, sometimes with granulomas.[11] Apparently, in rats, curcumin ameliorated vancomycin-induced decrease in the activities of antioxidant enzymes and glutathione peroxidase and could be able to antagonise vancomycin nephrotoxicity.[12] A protective and antioxidant effect of vitamin E, vitamin C, N-acetylcysteine, caffeic acid phenyl ester, and erythropoietin on vancomycin-induced nephrotoxicity in rats has also been reported.[13,14] Whether antioxidant therapy is protective against vancomycin-induced nephrotoxicity in humans remains to be established.

Approximately 5 to 8.5% of vancomycin clearance is extrarenal, possibly by hepatic conjugation, leading to vancomycin crystalline degeneration products. The clearance decreases with creatinine clearance in a linear fashion, resulting in markedly increased half-life of 100 to 200 hours in anuric patients.[15]

STAPHYLOCOCCI SUSCEPTIBILITY AND VANCOMYCIN TROUGH LEVELS

In 2006, the Clinical and Laboratory Standard Institute established breakpoints for vancomycin for *S. aureus*. A MIC ≤2 μg/ml is defined as susceptible, a MIC of 4 to 8 μg/ml is intermediary susceptible and a MIC ≥ 16 μg/ml as resistant (vancomycin-resistant *S. aureus* or VRSA).[2] VRSA have acquired *vanA* gene from vancomycin-resistant enterococci, leading to altered murein pentapeptide target with strongly decreased binding affinity for vancomycin and thus a high level vancomycin resistance with MIC >512 μg/ml.[2] Within the group of susceptible *S. aureus,* the proportion of staphylococci with a MIC for vancomycin between 1 to 2 μg/ml is steadily increasing, indicating a further shift of MIC to the right. Staphylococci with a MIC between 1 to 2 μg/ml pose a higher risk for treatment failure than more susceptible species.[2]

VANCOMYCIN NEPHROTOXICITY-LITERATURE REVIEW (*TABLE 1*)

A computerised literature search of PubMed for all relevant data was done using the terminology "vancomycin nephrotoxicity". High dose was defined as either a daily dose of ≥4g or >30 mg/kg or regimens that achieved serum vancomycin trough concentrations of 15 to 20 mg/l. Nephrotoxicity was defined as ≥50% increase in serum creatinine (SCR) from baseline value or a 50% decrease in creatinine clearance (CCL) from baseline. The majority of studies were retrospective in design.

Table 1. *Studies evaluating nephrotoxicity of vancomycin*

Reference	N	Dose	Nephrotoxicity
Hermsen et al. [16]	55	Trough ≥15 vs <15	HD 31% SD 10%
Hidayat et al. [17]	95	Dose to achieve trough concentration of 4-5 times MIC of MRSA strain	HD 12% SD 0%
Jeffres et al. [18]	94	30 mg/kg/d to target trough of 15-20 μg/ml	42.6%
Lodise et al. [19]	291	≥4 g/d vs <4g/d	HD 34.6% SD 9.7%
Lodise et al. [5]	166	Trough ≥15 vs <15	25.9% vs 10.1%
Mora et al. [25]	163	Trough ≥15 vs <15	HD 8% SD 3%
Ingram et al. [27]	167	CI vs IA	15.6%
Hutschala et al. [28]	149	CI vs IA	29.5% overall 27.7% in CI 36.7% in IA
Vuagnat et al. [29]	44	CI vs IA	8.7% in CI* 42.9% in IA*

N = number of patients; HD = high dose; SD = standard dose; CI = continuous infusion; IA = intermittent administration; * = adverse drug effects.

This definition of vancomycin-induced nephrotoxicity has been accepted by the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists consensus statement with the rider that multiple (at least two or three consecutive) high serum concentrations should be documented after several days of therapy in the absence of an alternative explanation.[1]

INCIDENCE OF NEPHROTOXICITY

The incidence of vancomycin-induced nephrotoxicity is variable ranging from <1% to >40% in various studies. The variability is due to the baseline population studied, different dosing regimes, and under-reporting of nephrotoxicity. Many of the studies did not target adverse events as their endpoints.

TROUGH LEVELS AND NEPHROTOXICITY

Lodise *et al.* identified vancomycin trough level as the pharmacodynamic parameter that best describes the relationship between exposure and toxicity. In retrospective analysis of 166 patients (27 high dose, 139 standard dose), AUC and trough levels obtained within 96 hours of therapy were modelled as continuous, dichotomous and categorical variables to describe the relationship

between drug exposure and toxicity. A multivariate logistic regression yielded an adjusted odds ratio of 1.13 for an increased likelihood of nephrotoxicity with each one-unit rise in the initial vancomycin trough value (95% confidence interval (CI) 1.05 to 1.21; p=0.001).[5]

Ten studies have identified elevated vancomycin trough level (>15mg/l) as a significant predictor of nephrotoxicity, with an overall incidence of 27% for trough exposure of 15 to 20 mg/l; all studies included patients with other known causes of acute kidney injury (AKI), comprising concomitant receipt of nephrotoxins.[5,16-24] For patients who achieved a trough level of >20 mg/l, the reported incidence rates were 21%,[22] 33%[5,21] and 65%.[18] However, it was not clear whether the trough level of >20 mg/l was measured after the onset of nephrotoxicity in the above studies. Thus, the elevated levels may represent the effect rather the cause of nephrotoxicity. Moreover, the temporal relationship between elevated trough concentrations and development of nephrotoxicity is unclear in most studies, leaving a gray zone regarding a cause-effect relationship. Additionally, whether trough levels represent a steady-state value is also uncertain from most studies. In a small study, where trough levels were measured prior to the onset of nephrotoxicity, all eight patients without concomitant risk factors who attained trough levels of >20 mg/l had nephrotoxicity.[20]

Observational data analysing vancomycin doses and nephrotoxicity are compromised by the presence of a selection bias.[18,19] Patients with a greater severity of illness and an increased baseline risk of nephrotoxicity are more likely to receive aggressive vancomycin dosing regimes. Selection biases make the previous studies inadequate to accurately identify the rate of nephrotoxicity with higher vancomycin dosing. This is in agreement with the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists consensus statement acknowledging that there are limited data to suggest a direct causal relationship between nephrotoxicity and a specific vancomycin concentration.[1]

ONSET, DEGREE AND RESOLUTION OF NEPHROTOXICITY

The onset of nephrotoxicity ranges from four to eight days from the start of therapy.[5,19,20,22] It is of considerable importance to understand the fact that SCR is insensitive to detect mild changes in renal functions and the exact relationship between vancomycin exposure and onset of nephrotoxicity cannot be precisely determined based on changes in SCR values. Perhaps, urinary and/or serum biomarkers of AKI might help in future to solve this question.

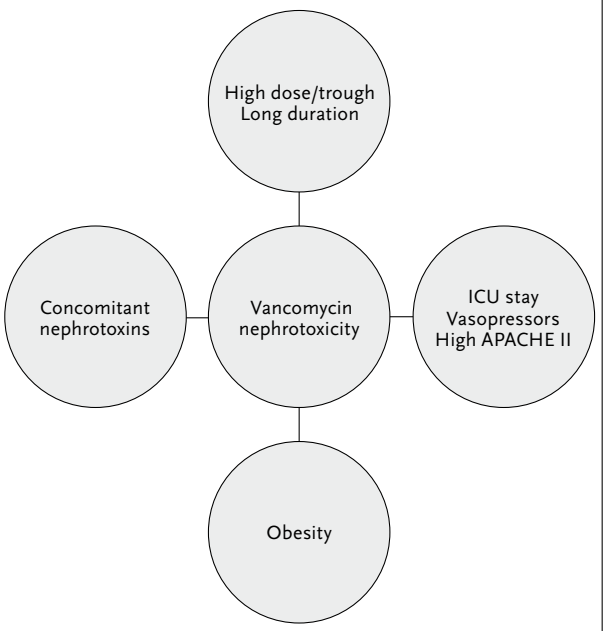
The resolution of nephrotoxicity was seen in 71% (50% while on vancomycin therapy and 21% within 72 hours of discontinuation) in one study.[22] In another study, 72.5% of patients had a return of SCR to their baseline value at the time of discharge and none of their study patients required renal replacement therapy as a consequence of nephrotoxicity.[18] Nephrotoxicity resolved in 81% (17/21) of cases evaluated in a retrospective study.[24]

RISK FACTORS FOR VANCOMYCIN NEPHROTOXICITY (*FIGURE 1*)

In retrospective data from various studies, in total 307 patients were evaluated. Nephrotoxicity occurred in 6.6% of patients on high-dose therapy compared with 2% in patients on standard-dose therapy in absence of concomitant risk factors for nephrotoxicity.[17,23,25] In one study where primary analysis was on patients without concomitant nephrotoxicity risk, minimal increases in SCR values from baseline were seen for the high-dose group (88.4 to 97.2 μmol/l), whilst SCR values remained unchanged in the standard-dose group.[25]

In studies from intensive care units (ICU), various concomitant risk factors confound the analysis when comparing vancomycin exposure and nephrotoxicity. However, a high Acute Physiology and Chronic Health Evaluation II score,[18,21] ICU residence[5,19,26] and receipt

Figure 1. *Risk factors for vancomycin-induced nephrotoxicity*



ICU= intensive care unit, APACHE= Acute Physiology and Chronic Health Evaluation.

of vasopressor agents[18,22] appear to be significant risk factors for the development of nephrotoxicity. Lodise *et al*. observed that ICU patients have a higher baseline risk for development of nephrotoxicity than non-ICU patients at a lower trough concentration threshold: >20% probability of nephrotoxicity at a trough >10 mg/l in ICU patients versus trough >20 mg/l in non-ICU patients.[5] Obesity was seen to be a significant predictor for occurrence and time of development of nephrotoxicity.[5,19] The authors postulated that dosing from total (including fat) mass will increase the dose if dosing is weight based and, therefore, increase the vancomycin AUC, thus shortening the time to event. Also, the volume of distribution in the central compartment (V) did not increase proportionally with weight and that V accounted for the higher trough values observed among obese patients in their study.[5]

Sepsis[16,23] and duration of therapy[17,22-24] were other factors more likely to be associated with development of nephrotoxicity. Prabaker *et al*. observed that the rate of nephrotoxicity increased from 12 to 22% beyond ten days of therapy.[22] Jeffres *et al*. observed an odds ratio of 2.55 for nephrotoxicity after ≥14 days of treatment.[18] In another study, Hidayat *et al*. found that the risk appeared to increase incrementally as the treatment was prolonged in patients who achieved high trough levels (15 to 20 mg/l): 6% for ≤7 days, 21% for 8 to 14 days and 30% for >14 days.[17] A recent two-phase retrospective analysis identified vancomycin serum trough concentrations ≥14 mg/l, duration of vancomycin therapy ≥7 days, and baseline SCR levels ≥1.7 mg/dl as independent predictors of nephrotoxicity.[24]

The use of concomitant nephrotoxins appears to be a significant risk factor for development of nephrotoxicity.[16,17,22,23] However, most studies did not specify the number of concomitant nephrotoxins and none reported the duration of concomitant nephrotoxin exposure during vancomycin therapy. In a recent retrospective analysis in a paediatric population, nephrotoxicity occurred in 14% of the population especially in those with targeted troughs of ≥15 mg/l, in the intensive care unit, and receiving furosemide.[26] Furosemide is not a direct nephrotoxin, but its use may cause dehydration, in which the addition of vancomycin may further increase the risk of developing nephrotoxicity. Another study showed that a loop diuretic was present in 63% of adult patients who had nephrotoxicity during vancomycin therapy as compared with 44% with no renal toxicity (p=0.083).[18]

CONTINUOUS VERSUS INTERMITTENT THERAPY

Data on beneficial effects of continuous infusion regimens are variable. Ingram *et al*. reported that in adult outpatients with normal renal functions, vancomycin by continuous infusion was associated with slower onset of nephrotoxicity.[27] However, the ultimate prevalence of nephrotoxicity was identical and associated with cumulative vancomycin exposure. Furthermore, in a retrospective cohort study, Hutschala *et al*. showed a tendency for less nephrotoxicity with continuous infusion compared with intermittent infusion of vancomycin in critically ill patients after cardiac surgery.[28] But, there was no significant difference in the requirement of continuous veno-venous haemofiltration amongst the groups and the intermittent administration group tended to have higher baseline SCR values. In a prospective study, Vuagnat *et al*. showed that continuous vancomycin infusion was logistically more convenient, achieved target concentrations faster, resulted in less variability in serum vancomycin concentrations, required less therapeutic drug monitoring and caused less adverse effects, but the clinical superiority was not established.[29] The consensus guidelines recommend that continuous infusion regimens are unlikely to substantially improve patient outcomes, compared with intermittent dosing.[1] Data on comparative vancomycin toxicity for continuous versus intermittent administration are conflicting and no recommendations can be made.[1]

OTHER TOXICITIES

Historically, the most common vancomycin toxicity was the red man syndrome.[3] It is an acute hypersensitivity reaction, consisting of flushing and pruritus, occasionally accompanied by hypotension. The onset may occur within a few minutes and usually resolves over several hours, after completion of the infusion. Patients usually tolerate subsequent doses if the dilution and the period of infusion are increased.

Another adverse effect is ototoxicity, the overall incidence of which appears to be low. Despite clinical case reports of a relationship between vancomycin serum concentrations and ototoxicity, there are no animal models that have demonstrated this relationship. The majority of experts feel that this drug is not ototoxic.[30-32]

Other side effects include neutropenia, fever, phlebitis, thrombocytopenia, lacrimation, linear IgA bullous dermatosis, necrotising cutaneous vasculitis, toxic epidermal necrolysis and Stevens-Johnson syndrome.[33]

CONCLUSIONS

Vancomycin nephrotoxicity is an important clinical adverse outcome to one of the commonly used antibiotics in modern-age medicine practice. It is unclear from the studies whether this is a result of targeting higher drug levels or a result of use in patients who have significant

AKI, especially in the ICU setting. There is lack of evidence and a myth that this is solely due to one of the above factors and it may very well be a combination of both. Clinicians are targeting trough levels of 15 to 20 mg/l. There is difficulty in discerning whether vancomycin levels are a cause of nephrotoxicity or are raised secondarily to nephrotoxicity. Physicians have to be aware of this entity while managing patients who are treated with this antibiotic and one needs to remember one of the important pillars of our decision making '*to do no harm*' while managing these sick individuals.

Timely detection of this clinical adverse outcome and discontinuation or replacement with other antibiotics has shown to prevent long-term kidney damage. That acute vancomycin nephrotoxicity leads to chronic kidney damage is a myth, unfounded, as per current literature. One must also be aware of concomitant nephrotoxins which contribute to this phenomenon and these should be avoided. Until molecular/biomarkers of AKI become available, cautious use of vancomycin is justified. Nevertheless, the patient should not be deprived of the benefits of this magic bullet, at least, in the critically ill stages.

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