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Vancomycin Loading Doses: A Systematic Review

Jillian Reardon[1], Tim T. Y. Lau, PharmD[1,2], and Mary H. H. Ensom, PharmD[1,3]

Abstract

Objective: To systematically assess the literature to ascertain the pharmacokinetics, pharmacodynamics, and clinical efficacy and safety associated with administration of a vancomycin loading dose (LD). **Data Sources:** MEDLINE (1948-December 31, 2014), EMBASE (1980-December 31, 2014), Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts (1970-December 31, 2014), Google and Google Scholar, and International Clinical Trials Registry Platform were searched using the following terms: *vancomycin, glycopeptides, loading dose, dose-response relationship*. **Study Selection and Data Extraction:** Pharmacokinetic, pharmacodynamic, and clinical efficacy studies using vancomycin LDs to achieve trough concentrations of 15 to 20 mg/L were included. Nonhuman, non-English, oral vancomycin, and dialysis patient studies were excluded. Abstracts were included. Study quality was ranked using US Preventative Services Task Force 1996 classification system. Data on study design, baseline characteristics, exclusion criteria, dosing, study outcomes, and conclusions were extracted. **Data Synthesis:** A total of 8 studies (5 manuscripts [2 level I, 3 level II-3] and 3 abstracts) were cited. Of 6 adult studies, 4 concluded that administration of vancomycin LDs resulted in significantly more patients achieving troughs of 15 to 20 mg/L. Studies in children found that LDs did not lead to rapid attainment of vancomycin levels ≥15 mg/L. No studies assessed clinical or microbiological outcomes. Limitations included heterogeneity and inconsistent timing of concentration measurements. **Conclusions:** High-quality data to guide the use of vancomycin LDs are lacking. LDs may more rapidly attain vancomycin troughs of 15 to 20 mg/L in adults, but information in pediatrics, obesity, and renal impairment is limited. Further studies are required to determine benefit of LDs on clinical and microbiological outcomes.

Keywords

vancomycin, glycopeptide, loading dose

Introduction

Vancomycin, a glycopeptide antibiotic, is effective against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Recent increases in vancomycin use, secondary to increasing MRSA infection rates, have contributed to its observed failure against strains exhibiting increased minimum inhibitory concentrations (MICs) of >1.5 mg/L.[2,3] In light of increasing vancomycin MICs, guidelines now recommend more aggressive dosing to target troughs of 15 to 20 mg/L for serious infections. The rationale to support higher targets is derived from data demonstrating improved clinical and microbiological outcomes in MRSA pneumonia when the vancomycin area-under-the-concentration-time curve (AUC) to MIC ratio (AUC/MIC) is ≥400.[4] As AUC/MIC is not routinely available in clinical practice, trough concentrations are utilized on the premise that concentrations of 15 to 20 mg/L effectively achieve AUC/MICs ≥400 (assuming MIC of the pathogen is ≤1 mg/L).[2,5]

To rapidly attain therapeutic vancomycin concentrations and optimize AUC/MIC, loading doses (LDs) of 25 to 30 mg/kg in adults and 20 to 25 mg/kg in children are recommended for seriously ill patients.[2] Guidelines cite level III evidence (expert opinion, clinical experience, descriptive studies, or case reports) to support this practice.[2,5]

The purpose of this review was to systematically assess the literature to ascertain the pharmacokinetics, pharmacodynamics,

[1]The University of British Columbia, Vancouver, British Columbia, Canada
[2]Vancouver General Hospital, Vancouver, British Columbia, Canada
[3]Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada

Corresponding Author:
Mary H. H. Ensom, Children's and Women's Health Centre of British Columbia, Pharmacy Department (0B7), 4500 Oak Street, Vancouver, BC, V6H 3N1, Canada.
Email: ensom@mail.ubc.ca

and clinical efficacy and safety associated with vancomycin LDs.

Methods

Data Sources

Searches of MEDLINE (1948-December 31, 2014) and EMBASE (1980-December 31, 2014) databases, the Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts (1970-December 31, 2014), Google and Google Scholar, and the International Clinical Trials Registry Platform were conducted to identify articles describing vancomycin LDs. The following search terms were combined: *vancomycin* or *glycopeptides* and *loading dose* or *dose-response relationship*. No search limits were applied. Reference lists of included studies were manually reviewed to identify articles not found previously.

Study Selection

Pharmacokinetic, pharmacodynamic, and clinical studies using vancomycin LDs to achieve trough concentrations of 15 to 20 mg/L were included. There were no restrictions on patient age or trial quality. Studies with the following characteristics were excluded: nonhuman data, non-English publications, oral vancomycin use, or exclusive use in dialysis patients. Conference abstracts reporting final results were eligible for inclusion.

Data Extraction and Evaluation

The following data were extracted from each study: design, number of participants and baseline characteristics, inclusion and exclusion criteria, drug dosing regimens, study outcomes, and conclusions. Each study was ranked on the basis of quality of evidence according to the US Preventive Services Task Force 1996 rating system.[6] Level I studies are randomized controlled trials (RCTs). Level II-1 studies are controlled, with patients acting as their own controls or with a parallel control group included. Level II-2 studies are cohort or case-control designs. Level II-3 studies are multiple time series or exceptional descriptive articles. Level III studies are expert opinion, descriptive studies, and case reports.

Results

In all, 5 published studies met inclusion criteria (Table 1).[7-11] Additionally, 3 abstracts of unpublished trials were reviewed.[12-14] Despite efforts to focus on studies targeting vancomycin troughs of 15 to 20 mg/L, an abstract of a study in children targeting 10 to 20 mg/L was included in light of limited available studies.[14]

Adult Studies

Level I Evidence. Rosini et al[7] randomized 99 adults, presenting to the emergency department (ED) with an indication for vancomycin, to receive an initial dose of 30 mg/kg (LD) or 15 mg/kg (non-LD; Table 1). The first concentration, drawn prior to the second dose, was 15 to 20 mg/L in 34% compared with 3% of those in the LD and non-LD groups, respectively ($P < 0.01$). Although not powered to detect a difference, nephrotoxicity, average length of hospital stay, and mortality were not different between the 2 groups. The authors concluded that an initial vancomycin LD of 30 mg/kg led to rapid attainment of therapeutic concentrations and that LD use did not increase adverse events.

Level II-3 Evidence. Truong et al[9] conducted an observational study of 113 courses of vancomycin therapy in adult intensive care unit (ICU) patients at preadoption and postadoption of an institutional policy to administer 2-g LDs (Table 1). Data were collected over two 4-week periods (2 months and 1 year postintervention) to assess policy impact and durability. No participant in the preintervention group received LDs; 4/31 (13%) initial vancomycin troughs were 15 to 20 mg/L versus 7/21 (33%) in the first postintervention group ($P = 0.08$) and 14/61 (23%) in the second postintervention group ($P = 0.12$). Compliance rates with LD use were 52.4% and 63.9% in the first and second postintervention groups, respectively. Nephrotoxicity developed in 5/34 (14.7%) patients postintervention, with initial troughs ≥20 mg/L. The authors summarized that standardized vancomycin LD appeared to be effective in increasing early trough concentrations in ICU patients.

An observational trial by Golenia et al[10] evaluated a high-target trough vancomycin dosing nomogram in adult ICU patients (Table 1). LDs ranged from 22.5 to 25 mg/kg. In the postnomogram implementation group (n = 60), 78% (n = 47) of patients received LDs, producing a mean steady-state trough of 17.3 ± 7.3 mg/L compared with 20.6 ± 6.9 mg/L in those with no LDs (n = 13; $P = 0.15$). Nephrotoxicity occurrence was not different between groups. The authors determined that their nomogram led to reliable achievement of vancomycin concentrations ≥15 mg/L in ICU patients without increasing nephrotoxicity.

Denetclaw et al[11] evaluated divided vancomycin LDs in 69 adult ICU patients in a prospective, observational study (Table 1). An initial LD of approximately 15 mg/kg was administered, followed by a repeat dose at 6, 8, or 12 hours (determined based on renal function). After the initial LD, 52.2% of patients achieved a trough of 15 to 20 mg/L. Repeat trough concentrations in 12 to 24 hours (after both initial and repeat LDs had been administered) were in the range of 15 to 20 mg/L in 89.8% of patients. Two patients experienced acute kidney injury. The authors concluded that a divided LD allows for achievement of early therapeutic vancomycin concentrations for most critically ill patients.

Table 1. Summary of Published Studies Evaluating the Use of Intravenous Vancomycin Loading Doses.

Study (Publication Year)	Design	n	Patient Characteristics	Dosing Regimen	Efficacy Results	Safety Results	Comments
Level I evidence (properly designed RCT)							
Rosini et al[7] (2014)	Single-center RCT	99	• Inclusion: adult ED patients receiving vancomycin for suspected or documented infection • Exclusion: Weight > 120 kg; CrCl < 50 mL/min; nephrotoxic medications; sepsis with pneumonia; pregnancy; breastfeeding Baseline characteristics, LD vs no LD, vancomycin indication (%) • SSTI: 32 vs 28.6 Pneumonia: 28 vs 24.5 Bacteremia: 12 vs 6.1 Meningitis: 0 vs 6.1 Osteomyelitis: 0 vs 6.1 • Neutropenic fever: 4 vs 2 Empirical therapy: 24 vs 26.5 • Sepsis: 12 vs 12.1 • Mean age (years): 57.5 ± 14.5 vs 58.4 ± 15.6 • Mean weight (kg): 81.6 ± 19 vs 86.7 ± 20.3 • Mean CrCl (mL/min): 93.4 ± 28.1 vs 104.1 ± 55.8	• LD: 30 mg/kg (NTE 3600 mg) Mean dose: 2433 ± 546 mg • No LD: 15 mg/kg (NTE 1800 mg) Mean dose: 1308 ± 307 mg • MD: 15 mg/kg every 12 h ×3 doses (initiated 12 hours after first dose) • Administration: doses infused at rate NTE 1000 mg/h • Trough timing: Pre–dose 2, 3, and 4	LD vs no LD • n (%), Trough > 15 mg/L at 12 hours: NR (34) vs NR (3), $P < 0.01$	LD vs no LD • Nephrotoxicity, n (%): 2/50 (4) vs 3/49 (6.1), P = NS • Infusion reactions, n (%): 3/50 (6) vs 2/49 (4.1), P = NR • Hospital length of stay (days): 5.84 ± 4.8 vs 6.33 ± 5.6 (NS) • Mortality: n = 1 vs n = 0 (NS)	• Nephrotoxicity defined as increase in serum creatinine by 0.5 mg/dL or ≥50% increase from baseline during hospitalization • Nephrotoxicity occurred within 24 hours in 4 patients and at day 9 in one • No participant required dialysis or readmission for nephrotoxicity within the month following trial enrollment
Demirjian et al[8] (2013)	Single-center RCT	59	• Inclusion: children aged 2-18 years receiving vancomycin for suspected or documented infection • Exclusion: Weight > 67 kg; CrCl < 50 mL/min/1.73m^2 (by original Schwartz equation) Baseline characteristics, LD vs No LD • Mean age (years) = 8.63 ± 4.40 vs 8.76 ± 4.04 • Mean CrCl (mL/min/1.73m^2) = 206 ± 55 vs 196 ± 51 • Vancomycin indication (%) Sepsis: 2 vs 5 • Meningitis: 2 vs 2 • Bacteremia: 14 vs 12 • SSTI: 7 vs 12 • Osteomyelitis: 0 vs 5 • Septic arthritis: 2 vs 0 • FN: 12 vs 7 • Undisclosed: 61 vs 64	• LD: 30 mg/kg • No LD: 20 mg/kg (NTE 2000 mg) • MD: 20 mg/kg every 8 hours • Administration: doses infused over 2 hours • Trough timing: 8 hours post–first dose	LD vs no LD • Trough 15-20 mg/L 8 hours post–first dose, n (%): 2/19 (11) vs 0/27 (0), P = 0.17 • Trough > 20 mg/L 8 hours post–first dose, n (%): 2/30 (7) vs 2/29 (7), P value not reported • AU C0-24 h (μg/mL/h): 446.5 ± 195.5 vs 434.0 ± 153.2	LD vs no LD Nephrotoxicity, n (%): 4/30 (13) vs 1/29 (3.4), P = 0.14 Red-man syndrome, n (%): 14/30 (46.7) vs 7/29 (24), P = 0.06	• 11 of 30 patients allocated to LD did not have a first trough drawn • Nephrotoxicity defined as doubling of baseline serum creatinine within 7 days of initial dose • In individuals developing nephrotoxicity, creatinine normalized by day 12 in all but one who was receiving concomitant nephrotoxins

(continued)

Table 1. (continued)

Study (Publication Year)	Design	n	Patient Characteristics	Dosing Regimen	Efficacy Results	Safety Results	Comments
Level II-3 evidence (multiple time series with or without intervention or dramatic results in uncontrolled experiments)							
Truong et al[9] (2012)	Pre/post observational trial	113[a]	Inclusion: adult ICU patients Exclusion: neurosurgery patients Patient characteristics Pre vs postintervention phase 1 vs postintervention phase 2 • Mean age (years): 50 ± 17.5 vs 51 ± 18.1 vs 60 ± 15.3 • Mean weight (kg): 76 ± 14.6 vs 73 ± 18.8 vs 79 ± 17.0 • CrCl ≥ 60 mL/min (%): 67.7 vs 52.4 vs 45.9 • CrCl 30-59 mL/min (%): 29 vs 0 vs 23 • CrCl < 30 mL/min (%): 0 vs 4.8 vs 3.3 • CRRT (%): 3.2 vs 42.9 vs 27.9	• LD: 2 g IV • No-LD: "standard therapy" • MD: "as per prescriber" • Administration: LD infused over 4 h; not reported for no-LD group • Trough timing: initial within 48 h after first dose (details re. exact timing not provided)	Preintervention phase (n = 31) • Initial trough (mg/L), no LD: 9.8 ± 6.6 mg/L • Postintervention phase 1 (n=21) • Mean trough (mg/L), LD (52.4% compliance) vs no LD: 16.7 ± 7.1 mg/L vs 12.9 ± 5 mg/L • Postintervention phase 2 (n = 61) • Mean trough (mg/L), LD (63.9% compliance) vs no LD: 15.7 ± 6.6 mg/L vs 12.5 ± 6.1 mg/L • Trough ≥20 mg/L, LD vs no LD: first postintervention group, 3/11 vs 1/10; second postintervention group, 11/39 vs 2/22	Nephrotoxicity LD: n = 4 (when trough > 20 mg/L); no additional details provided	• First postintervention group older vs preintervention group • Both postintervention groups had more renal impairment vs preintervention group • Nephrotoxicity defined as increase in serum creatinine > 50% from baseline or decrease in urine output to <0.5 mL/kg/h • All cases of nephrotoxicity occurred within 48-96 hours of vancomycin initiation; data regarding resolution not presented • 3.2% of individuals were receiving CRRT in preintervention group compared with 42.9% and 27.9 % in first and second postintervention group, respectively
Golenia et al[10] (2013)	Pre/Post observational trial	117	• Inclusion: adult ICU patients (cardiac, medical, general surgery), ≥3 vancomycin doses • Exclusion: eGFR < 30 mL/min/1.73^2; on dialysis; weight ≥150 kg or <40 kg • Patient characteristics pre- vs postnomogram • Mean age (years): 61 ± 19.4 vs 60 ± 16.7 • Mean weight (kg): 75 ± 20.8 vs 77 ± 16.9 • Mean CrCl (mL/min): 79.9 ± 38.9 vs 86.2 ± 40.1	• LD, postnomogram implementation: 22.5-25 mg/kg (range 1000 to 2250 mg) • No LD, prenomogram implementation: standard therapy • Administration: not reported • Trough timing: initial prefourth dose	Pre vs post nomogram • Percentage trough ≥15 mg/L: 39 vs 72 (P = 0.0004) • Percentage trough 15-20 mg/L: 19 vs 42 (P = 0.0099) • Initial supratherapeutic trough mean concentration: 26 ± 5.3 mg/L vs 27 ± 6.3 mg/L (P = 0.2) Mean initial trough: postimplementation LD (78% compliance) vs no LD • 17.3 ± 7.3 mg/L vs 20.6 ± 6.9 mg/L (P = 0.1500)	Pre vs post nomogram • Nephrotoxicity, n (%): 10/57 (17.5) vs 11/60 (18.3%), P = 1.0	• Pharmacokinetic data from preimplementation group (n = 57) used to develop nomogram based on actual body weight and eGFR via MDRD equation • Treating physicians determined who should receive LDs • Nomogram recommended • Nephrotoxicity defined as an increase in serum creatinine by 0.5 mg/dL or ≥50% increase from baseline in ≥2 consecutive measurements from vancomycin initiation to 72 hours after last vancomycin dose • Nephrotoxicity occurred after mean 5.7 vs 5.3 days in the pre and post groups, respectively
Denetclaw et al[11] (2013)	Retrospective observational trial	69	• Inclusion: adult ICU patients receiving vancomycin according to the institutional divided dose protocol • Exclusion: paralysis, pregnancy, nonadherence to protocol (Note: dialysis patients were included but analyzed separately.) Patient characteristics, weight ≤150% IBW vs weight ≥150% IBW: • Mean age (years): 70.7 ± 16.7 vs 78 ± 14.4 • Mean weight (kg): 72.2 ± 16.5 vs 109 ± 29.2 • Mean CrCl (mL/min): 46.4 ± 22 vs 38.8 ± 12.6	Divided LD protocol • Initial dose: 15 mg/kg ×2 doses, interval as per the following: CrCl (mL/min), time to second dose (hours): ≥65, 6; 35-64, 8; <21-34, 12, Renal failure, 12 • MD: per protocol • Administration: not reported • Trough timing: before each dose	• Average trough pre–third dose (mg/L): 15.1 ± 3.4 • Trough ≥14.8 mg/L by second dose, n (%): 36/69 (52.2) • Trough ≥14.8 mg/L by third dose, n (%): 62/69 (89.8)	Acute renal dysfunction, n (%): 2/69 (2.9)	• Initial trough concentrations in patients with severe sepsis not significantly different vs no severe sepsis • Definition of acute renal dysfunction not provided • Patients with acute kidney injury and/or on dialysis were not included in primary analysis • Based on predicted Css after first level: 39.1% required no change in dose/frequency 10.1% required an increase in dose/frequency 50.7% required a decrease in dose/frequency

Abbreviations: CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; FN, febrile neutropenia; IBW, ideal body weight; ICU, intensive care unit; LD, loading dose; MD, maintenance dose; MDRD, Modification of Diet in Renal Disease; NR, not reported; NS, not statistically significant; NTE, not to exceed; RCT, randomized controlled trial; SSTI, skin and soft-tissue infection.

[a]n Is the total number of vancomycin treatment courses included in analysis.

Abstracts. Balasubramanian et al[12] reported an observational comparison of 118 adult ICU patients receiving a vancomycin LD of 25 mg/kg or initial dose of 15 to 20 mg/kg. A steady-state target trough of 15 to 20 mg/L was achieved in 33% of the LD group compared with 13% in the non-LD group ($P < 0.01$). The authors suggested that a vancomycin LD of 25 mg/kg led to a higher proportion of patients achieving troughs of 15 to 20 mg/L at steady state without increasing nephrotoxicity.

Seyer et al[13] described a noncontrolled trial comparing a vancomycin LD administered as a single 25-mg/kg dose or split dose of 15 mg/kg every 12 hours for 2 doses with a standard 15-mg/kg dosing (interval determined by creatinine clearance). Vancomycin trough concentrations were drawn before the first MD in the LD group and before the second MD in the non-LD group. Mean initial trough was 15.3 mg/L (7.6-22.2 mg/L) in the LD group and 12.8 mg/L (6.9-19.3 mg/L) in the non-LD group ($P = 0.3278$). Acute renal dysfunction occurred in 6% of the LD group compared with 7% in the non-LD group ($P = 1.0$). The authors concluded that a vancomycin LD may facilitate achievement of overall higher trough concentrations but may not increase speed of target attainment.

Pediatric Studies

Level I Evidence. Demirjian et al[8] randomized children to receive a first vancomycin dose of 30 mg/kg (LD group; n = 30) or 20 mg/kg (non-LD group; n = 29; Table 1). Initial concentrations were not measured in 11 patients in the LD group and 2 in the non-LD group. Eight hours post–first dose, 2/19 (11%) in the LD group and 0/27 in the non-LD group achieved a vancomycin trough of 15 to 20 mg/L ($P = 0.17$). Despite subtherapeutic concentrations, median estimated $AUC_{0\text{-}24h}$/MIC (based on a hypothetical MIC of 1 mg/L) remained >400 in both groups ($P = 0.79$). Nephrotoxicity occurred in 4/30 (13%) versus 1/29 (3%) patients in the LD and non-LD groups, respectively ($P = 0.14$). Redman syndrome occurred in 48% (LD group) versus 24% (non-LD group; $P = 0.06$). The authors concluded that administration of vancomycin LD in children did not lead to more rapid attainment of therapeutic vancomycin troughs.

Abstract. Bartlett et al[14] described 54 children receiving vancomycin with a target trough aimed at 10 to 20 mg/L. In all, 11 patients received LDs in the range of 18 to 27 mg/kg. Ages ranged in the LD group from 3.5 months to 25 years (average age = 4.6 years), whereas ages were not reported for non-LD patients. The median steady-state trough was 10.5 mg/L (6.7-13.9 mg/L) in the LD group compared with 9.8 mg/L (<5.0-22.6 mg/L) in the non-LD group. No patients receiving LDs developed nephrotoxicity. The authors suggested that vancomycin LDs resulted in higher initial troughs and that more aggressive and standardized dosing strategies may benefit children receiving vancomycin.

Discussion

Although current practice guidelines endorse vancomycin LDs for serious infections, limited direct clinical evidence is available to support or refute this recommendation.[2,5] Studies assessed in this systematic review were of varying methodological quality, with the majority of data derived from small, observational trials.

In adults, 1 RCT in ED patients and 3 observational studies in ICU patients found that the use of a vancomycin LD achieved target trough concentrations in 23% to 52% of cases.[8,10,12,13] Unexpectedly, one study demonstrated a non–statistically significant achievement of higher troughs when an LD was not used (as compared with the LD group).[11] Although studies were not powered to detect a difference, nephrotoxicity rates were not significantly higher in the LD groups.[8,10-14]

In children, 1 RCT observed that 11% of vancomycin concentrations were at 15 to 20 mg/L after the first dose. However, half of the patients in the LD group experienced red-man syndrome. Of note, the calculated half-life of vancomycin in this trial was approximately 4 hours in each group, which may be explained by increased clearance leading to lower initial vancomycin concentrations as compared with the adult data.[8]

Pharmacokinetic Parameters (Vancomycin Trough Concentrations)

Attainment of vancomycin troughs of 15 to 20 mg/L has been advocated to optimize clinical and microbiological cure. However, rigorously designed, prospective studies are lacking to support this recommendation.[2,5] A retrospective, matched cohort study of 200 adults found that targeting vancomycin trough concentrations of 15 to 20 mg/L was associated with improved clinical cure and shorter duration of therapy, with no impact on hospitalization length.[15]

The rationale for using an LD is based on the premise that vancomycin has a half-life of 5 to 11 hours in adults, which may be significantly prolonged in renal insufficiency. Because it may take up to several days for vancomycin to reach steady-state concentrations, an LD would allow for more rapid achievement of target concentrations of 15 to 20 mg/mL, which may be beneficial in the severely ill. Generally, the LD is proportional to Desired serum drug concentration × Volume of distribution (V_d). As vancomycin distributes into total body water, need for LDs may be particularly important to reach concentrations of 15 to 20 mg/L in the critically ill who often display larger V_d secondary to sepsis, edema, ascites, and aggressive fluid resuscitation.[16] A study of ICU patients found that vancomycin LDs of 15 mg/kg, compared with initial doses of 500 mg, achieved higher initial troughs and were associated with increased clinical cure without increasing toxicity.[17] This trial was conducted prior to the new guidelines and

consequently was not designed to achieve troughs of 15 to 20 mg/L.

In our systematic review, all included studies assessed the pharmacokinetic end point of achievement of vancomycin target trough concentrations. Ideally, to clearly assess whether a vancomycin LD is able to rapidly achieve troughs of 15 to 20 mg/L, concentrations should be drawn after the LD administration and immediately prior to the first MD.

LD With Initial Vancomycin Concentration Drawn Postdose

Four trials evaluated vancomycin concentrations drawn post-LD and pre–first MD with mixed results.[7,8,11,13] Two trials did not find benefit in achieving initial vancomycin troughs of 15 to 20 mg/L; 1 study in children used an LD of 25 mg/kg,[9] whereas the other in adults used a single 25-mg/kg or divided 30-mg/kg LD (abstract only).[14] In the 2 adult trials reporting benefit with LD administration when compared with patients not receiving an LD, one utilized a divided weight-based loading dose (LD; ie, 2 doses of 15 mg/kg), whereas the other used a single 30-mg/kg weight-based dose.[8,12] Variations in dosing strategies make it difficult to compare results between studies.

LD With Initial Vancomycin Concentration Drawn After Multiple Doses

Four studies assessed initial vancomycin troughs after patients had received various numbers of vancomycin MDs.[10,11,13,14] One abstract comparing a 25-mg/kg LD to a non-LD group followed by standard MD[13] suggested that LD administration may increase the proportion of patients achieving steady-state targets of 15 to 20 mg/L but did not provide useful information on how rapidly target concentrations could be obtained. In the 3 remaining trials,[10,11,13] determination of appropriate MDs was at the discretion of the treating clinician. One trial found that LDs led to a greater proportion of adult patients achieving troughs of 15 to 20 mg/L at steady state,[10] whereas another found that a weight-based LD did not increase the proportion of patients achieving first target trough compared with those dosed via a weight-based nomogram without an LD.[11] One study (abstract only) in children found that mean trough concentrations were higher in those receiving vancomycin LD compared with those not receiving an LD; however, average trough concentrations were still <15 mg/L.[14] The subjectivity of MDs in these studies limits the extrapolation of results to practice.

Divided Vancomycin LDs

Two trials in adults used a divided vancomycin LD strategy in which an initial dose of 15 mg/kg was administered.[11,13] Seyer et al[14] did not find benefit with this strategy; however, because they combined results from divided LD (15 mg/kg ×2 doses) with those receiving single LD (25 mg/kg), the effect of the higher single LD on the first vancomycin trough concentration may have been diluted. Conversely, Denetclaw et al[12] found that >50% of patients met target trough concentrations by the second dose despite administration of an initial dose of 15 mg/kg, with nearly 90% of patients achieving target troughs within 24 hours of vancomycin initiation.[12] Notably, the study by Denetclaw et al administered LDs 6, 8, or 12 hours apart, depending on patients' renal function, whereas Seyer et al dosed all patients at 12-hour intervals, which may explain the observed differences. Because the study by Seyer et al is available only in abstract form, it is not possible to determine all factors responsible for variances in results. Although defined in these 2 studies by the investigators, an initial dose of 15 mg/kg would not typically be considered an LD in most practice environments because this dose is generally used as the MD. Selection of a suboptimal initial dose may explain the lower proportions of patients achieving vancomycin target concentrations by the first MD.

The studies included in this review highlight significant variations in practice around the timing of when vancomycin concentrations are obtained. In critically ill patients, to evaluate the effectiveness of an LD in attaining targets, it is most ideal for concentrations to be drawn immediately prior to the first vancomycin MD. In contrast, a vancomycin LD is unlikely to be beneficial for mild to moderate infections where rapid attainment of target concentrations is not thought to be critical for treatment success.

Pharmacodynamic Parameters (AUC/MIC)

An AUC/MIC ≥400 is recommended to optimize clinical response with vancomycin.[8] Even though the AUC/MIC is considered the best pharmacokinetic-pharmacodynamic predictor of vancomycin activity, this parameter was not collected in any of the studies reviewed. In 1 pediatric trial, a hypothetical MIC of 1 mg/L was used to calculate predicted AUC/MIC ratios. In both LD and non-LD groups, overall estimated $AUC_{0\text{-}24}$ /MIC was >400 regardless of initial vancomycin trough concentrations.[8] This suggests that a total daily vancomycin dose of 60 mg/kg/d in children may be optimal for clinical and microbiological activity and that more rapid achievement of a higher trough with an LD, per current guidelines, may not be the most appropriate surrogate marker for vancomycin efficacy in this population. These results should be interpreted with caution because this study used a simulated MIC of 1 mg/L (and not the actual MICs of the pathogens) for all patients and thus may not be reflective of vancomycin efficacy in patients with higher MIC values.[8]

Despite limited information on its efficacy in severe infections or in critically ill adult patients, an LD of 25 to 30 mg/kg may be rationalized based on[9] vancomycin's slower action of kill and the need to optimize its activity by achieving rapid concentrations of 15 to 20 mg/L and subsequent AUC/MICs of > 400. In pediatric patients with severe infections, an LD of at least 30 mg/kg may be considered; however, its ability to achieve a target of 15 to 20 mg/L and subsequent AUC/MICs of > 400 are questionable. With increasing MICs >1.5 mg/L, an increasing vancomycin AUC would be required to preserve this ratio.

Additionally, the true effect of MIC on patient outcomes remains to be elucidated. Although systematic reviews have observed an association between increased vancomycin MICs and mortality in patients with *S aureus* infections,[18-20] a recent systematic review of patients with *S aureus* bacteremia found no increased mortality with vancomycin MICs >1.5 mg/L.[21]

Clinical Efficacy

No study was powered to evaluate clinical cure as an end point, which leaves a knowledge gap regarding utility of vancomycin LDs in improving patient outcomes. In patients with *S aureus* bacteremia, delayed initiation of appropriate antimicrobials independently predicted increased mortality and was associated with prolonged hospitalization.[21] This lends additional support to the use of LDs as a means to rapidly achieve adequate vancomycin serum concentrations early in therapy. Mohammedi et al[17] reported higher clinical cure rates in a prospective, nonrandomized, controlled trial of 40 adult medical ICU patients with Gram-positive sepsis receiving a vancomycin LD of 15 mg/kg versus an initial dose of 500 mg. Concentrations were drawn 1 hour post-LD and patients were maintained on continuous IV infusion adjusted to target a vancomycin concentration of 20 mg/L. Clinical cure rates were 93.33% (15-mg/kg LD group) and 55.56% (500-mg LD group); $P < 0.02$. The overall mortality rates were 50% (15 mg/kg LD) and 35% (500 mg LD); P = NS. The results of this trial can only be interpreted in the context of continuous vancomycin infusion administration. Furthermore, it was conducted prior to the new vancomycin dosing recommendations, and the LD used was equivalent to the standard MD of 15 mg/kg. Thus, it does not serve to clarify the role of LDs in treating infections caused by pathogens with higher resistance profiles.[17]

Safety

Use of vancomycin LDs appeared to confer minimal risk of nephrotoxicity in adult and pediatric patients, although the trials were not powered for this outcome. One study found increased risk of nephrotoxicity in patients who achieved vancomycin concentrations >20 mg/L post-LD.[9] Contrary to these findings, a larger retrospective cohort (published only in abstract form) of 1441 adult patients concluded that administration of an LD of ≥15 mg/kg was independently associated with increased risk of new-onset nephrotoxicity within 48 hours of vancomycin initiation. In this trial, 22.5% and 16.5% of patients developed nephrotoxicity in the LD and non-LD groups, respectively (P = 0.01).[23] Furthermore, a systematic review indicated that vancomycin troughs of 15 mg/L or higher were associated with an increased probability of nephrotoxicity relative to troughs <15 mg/L. This association persisted when analysis was restricted to first trough concentrations only (odds ratio = 3.12; 95% CI = 1.81 to 5.37), which would reflect the impact of LD on nephrotoxicity risk.[24]

The minimal incidence of nephrotoxicity associated with LD use observed in this systematic review may be attributable to the exclusion of patients with renal impairment in the majority of trials. Conceptually, it is unlikely that a single LD of vancomycin would contribute significantly to increasing nephrotoxicity in patients who do not have any underlying risk factors for renal impairment. In light of the conflicting evidence, patients on prolonged vancomycin therapy (ie, >1 week) should have renal function monitored via serum creatinine 2 to 3 times weekly with regular urine output monitoring.

The incidence of red-man syndrome with vancomycin LDs did not appear to be increased in adult studies; however, 1 pediatric trial observed a non–statistically significant increase of this adverse reaction with LD administration in children.[8] It is important to be aware of the potential for red-man syndrome when considering using LDs in pediatric patients.

Obesity

Morbidly obese patients were excluded from most trials. Vancomycin is a moderately lipophilic molecule and has a V_d of 0.4 to 1 L/kg in nonobese adults.[1] In obesity, both adipose tissue and lean muscle mass are increased, resulting in increased vancomycin V_d. Studies report significant variability in vancomycin V_d in obese patients, with values up to 1.25 L/kg.[25] Although not prospectively studied yet, it is hypothesized that a direct relationship between LDs and V_d exists, which suggests that larger vancomycin LDs on a mg/kg basis may be required to account for physicochemical changes in obese patients. All studies in our review that used a weight-based LD used actual body weight. One trial without weight restrictions found, in a small subset of patients (n = 8), weighing >150% of their ideal body weight, that initial trough concentrations were similar to those of nonobese patients. Obese patients were, however, more likely to exhibit second trough concentrations >20 mg/L. Maximum doses in this trial were 20 mg/kg of ideal body weight or 1.5 g/dose, whichever was less.[11] In most obese

patients, a 1.5-g LD would be below the usual 25- to 30-mg/kg LD range and, thus, 1.5 g would not be considered a true LD. Another study used a 2-g vancomycin LD in all patients, regardless of weight, and found that a higher proportion of patients achieved therapeutic trough concentrations compared with those not receiving an LD. The mean weight for LD patients was 73.0 ± 18.8 kg; consequently, use of fixed LDs may lead to subtherapeutic or supratherapeutic concentrations at extremes of weight.[9] Institutions that use maximum vancomycin dose restrictions may inadvertently underdose obese patients. Further clinical trials are required to clarify the appropriate approach for vancomycin LDs in obesity.

Future Research

The goal of LD administration is to achieve rapid high trough concentrations, which may be beneficial in seriously ill patients. Future studies should focus strictly on patients with severe infections, such as those with bacteremia, infective endocarditis, hospital-acquired pneumonia, meningitis, osteomyelitis, or confirmed MRSA infections. This would assist clinicians in determining attributes of LDs on patient outcomes.

Despite consensus guidelines that recommend higher vancomycin target trough concentrations and LD administration for serious infections, published, validated nomograms are lacking. One study of a nomogram designed to target vancomycin troughs of 15 to 20 mg/L did not include an LD recommendation and found that it took ≥2 days to achieve target.[26] Development of future vancomycin dosing nomograms should incorporate clear guidance regarding administration of standardized LDs in the severely ill to attain more rapid target troughs.

Use of single or divided LDs needs to be clarified. In 2 trials,[11,13] this approach appeared to minimize exposure to supratherapeutic concentrations in patients who were vulnerable to toxicities (ie, unstable renal function) while still reaching therapeutic concentrations. Given the observational nature of these studies and lack of comparator arms, further studies are required to determine the utility of and potential benefits of divided LDs.

Current studies have largely excluded patients at extremes of weight and those with chronically impaired renal function. Vancomycin dosing in these patients poses a particular challenge because of altered pharmacokinetics; thus, trials enrolling these populations would further clarify LD efficacy and safety.

Limitations

This systematic review has several limitations. The review included only articles published in English; however, all abstracts from identified articles (English and non-English) were screened, and no non-English abstracts met inclusion criteria. Because of the paucity of available data, we included abstracts in our review; however, it is not possible to critically evaluate the quality of these data, and greater emphasis should be placed on published trials rather than on abstracted data.

In general, studies assessed were of varying methodological quality, with the majority of data derived from small, observational trials. Although high vancomycin target trough concentrations are advocated for patients with serious infections, many studies did not clearly identify these patients in their recruitment. Most trials involved only a single center and reflected highly variable local vancomycin dosing practices, which precludes extrapolation to other patient populations and institutions. Furthermore, clinical efficacy was not assessed, and study end point was the attainment of target trough concentration, which lacks definitive prospective evidence to support its use as a surrogate marker for clinical outcome.[2,5] Finally, studies were not powered to adequately assess nephrotoxicity and other adverse effects associated with LDs.

Conclusions

Currently, high-quality data to guide the use of vancomycin LDs are lacking. The available literature suggests that vancomycin LDs are inconsistent in rapidly attaining trough concentrations of 15 to 20 mg/L in adults, and the data do not support their routine use in children. The published studies have small sizes, heterogeneous populations, variable dosing practices, and differences in timing of trough concentration measurements. These limitations make determination of overall effectiveness of vancomycin LDs difficult. There is no good evidence to support or discourage the use of vancomycin LDs in obesity and renally impaired patients. We have proposed further studies that are required to determine the benefit of vancomycin LDs on clinical outcomes.

Declaration of Conflicting Interests

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