PROTOCOL

THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

T van den Heever; B.Sc., MB.Ch.B., DA(SA)[1*]
MGL Spruyt; MB.Ch.B., M.Med (Surgery), Critical care[2]

[1]Department Critical Care University of the Free State, Universitas and Pelonomi Hospital, Bloemfontein, Free State, **researcher**.
[2]Head Department Critical Care University of the Free State, Universitas and Pelonomi Hospital, Bloemfontein, Free State; **Study leader**.

Declaration

I certify that the dissertation hereby submitted by me for the M.Med.Sc degree at the University of the Free State is my independent effort and had not previously been submitted for a degree at another university/faculty. I furthermore waive the copyright of the dissertation in favour of the University of the Free State.

Abstrak

Inleiding

Daar is huidiglik wynig studies gepubliseer oor die monitoring van ‘n deurlopende infuus van vancomycin. Hierdie studie bewys dat terapeutiese vlakke van 15 – 20 mg/L effektief is in die behandeling van gram positiewe infeksies. Gelykvlak in die weefsel word bereik as terapeutiese vlakke van 15 – 20 mg/L bereik word. ‘n Ladings dosering van
15 mg/kg word aanbeveel ongeag die nierfunksie. Vir pasïente met geen nierfunskie inkorting nie word ‘n instandhoudings dosering van 30 mg/kg aanbeveel. Hierdie studie is oor ‘n kort tydperk uitgevoer en geen nefrotoksisiteit is waargeneem nie.

Metodes

‘n Prospektiewe analitiese studie met 10 pasïente wat aan die insluitingskriteria voldoen het, is in die studie ingelsuit. Die studie is gedoen in die Multidissiplinere Intensiewe Sorg Eenheid te Universitas hospitaal. Resultate was opgesom met behulp van standaard deviasies of persentiele (numeriese veranderlikes), frekwensies en persentasies (kategoriese veranderlikes). Die distribusie volume was gebruik om die instandhoudings dosering van vancomycin aan te pas, in orde om ‘n terapeutiese plasma vlak van 15 – 20 mg/L te verkry.
Die ladingsdosereing wat gebruik is, is 15 mg/kg opgelos in 200ml 5% Dextrose water. Die ladingsdosering is oor ‘n tydperk van twee ure toegedien. Onmiddelik na die ladingsdosering is die instandhoudings infuus van 30 mg/kg in 200ml 5% dextrose water teen 8 ml per uur begin.

Resultate

Van die dertien pasïente het slegs tien aan die insluitingskriteria voldoen. Na die ladingsdosering was die gemiddelde vlak 34,9 mg/L. Die gemiddelde konsentrasie na die eerste, tweede en derde tydsinterval was tussen 15 – 20 mg/L. Die gemiddelde tydsduur om ‘n terapeutiese vlak van 15 – 20 mg/L te bereik was 21 uur. Die gemene elliminasie konstante van 0.150 was bewys om die mees effektiefste te wees in orde om terapeutiese vlakke te bereik. As die elliminasie konstante meer as 0.150 was dan moes die instandhoudings dosering verminder word, en vice versa. Die gemiddelde hoeveelheid vancomycin wat toegedien was om tereaputiese vlakke te bereik was 3 282 mg.

Doel

Om navolginswaardige riglyne te toets in orde om tereapeutiese vlakke van 15 – 20 mg/L te bereik.

Gevolgtrekking

Vir die optimalisering van behandeling van die kritiek siek pasïent is dit belangrik om navolginswaardige protokolle vir elke institusie op te stel en na te volg. Vir vancomycin word ‘n ladingsdosering van 15 mg/kg, opgelos in 200ml 5% dextrose water wat toegedien word oor ‘n tydperk van 2 ure aanbeveel. ‘n Instandhoudings infuus wat bestaan uit 30 mg/kg opgelos in 200ml 5% Dextrose water word aanbeveel. In orde om die regte dosering te bereken word ‘n distribusie volume van 0.72 l/kg aanbeveel as die kreatinine opruiming meer as 60 ml/min is. Vir ingekorte nierfunksie word ‘n distribusie volume van 0.89 l/kg aanbeveel as die kreainien opruiming 10 – 60 ml/min is. As die kreatinien opruiming minder as tien is dan word ‘n distrubusie volume van 0.9 l/kg aanbeveel. Die studie bewys dat dit moontlik is om met behulp van farmakodinamika en farmakokinetika parameters, gelykvlak te bereik en dat dit volhoubaar is. Dit het die gevolg dat tyd- en koste effektiewe behandeling van pasïente met sensitiewe gram positiewe infeksies vir vancomycin, moontlik is.

Abstract

Introduction

Studies on therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients are scant. It has been proven that therapeutic levels of 15 – 20 mg/L is effective in treating severe gram positive infections and if kept in this range the amount of drug entering in and out of the tissue are equal. A loading dose of 15mg/kg should be administered irrespective of the renal function. The maintenance infusion in non renal impaired patients should be 30mg/kg and adjusted on a daily basis according levels. This study was over a short period of time and no nephrotoxicity was detected.

Methods

A prospective analytical study of 10 consecutive patients meeting the inclusion criteria, admitted to the Multidisciplinary Intensive Care Unit at Universitas Hospital was applied. Results were summarised by means of standard deviations or percentiles (numerical variables), frequencies and percentages (categorical variables). The distribution volume was used to calculate the estimated dosage of vancomycin to be given in order to achieve a therapeutic plasma concentration, in the case of vancomycin 15 – 20 mg/L.

A loading does of 15mg/kg in 200ml 5% dextrose water over a 2 hour period was administered. Immediately after the loading dose a constant infusion of 30mg/kg in 200ml 5% dextrose water was started at a rate of 8ml/hr ivi.

Results

Of the thirteen patients only ten met the inclusion criteria. After the loading dose the mean concentration was 34,9 mg/L. The mean concentration after the first, second and third time interval was between 15 – 20 mg/L. The mean time to reach therapeutic levels of 15 – 20 mg/L was 21 hours. A mean elimination constant of 0.150 was shown to be the most effective in obtaining therapeutic levels whilst on a constant vancomycin infusion. If the elimination constant was more than 0.150 then the maintenance dosage had to be reduced and vice versa. The mean total Vancomycin administered to reach therapeutic levels was 3 282mg.

Aim

To test a feasible regimen for adjusting maintenance of vancomycin infusion in the critically ill patient in order to reach therapeutic vancomycin levels (15 – 20 mg/L) after commencement.

Conclusion

To optimise treatment of the critically ill patient institution-specific protocols need to be instituted. For vancomycin, a loading dose of 15mg/kg and a continuous infusion of 30mg/kg in 200ml 5% dextrose water are advisable to keep the concentration 15 – 20 mg/L. A distribution volume of 0,72 l/kg should be used for patients with a creatinine clearance above 60 ml/min. For patients with impaired renal function different distribution volumes are advisable. If the creatinine clearance is between 10 – 60 ml/min then a distribution volume of 0.89 l/kg is advisable. If the creatinine clearance is less than 10 ml/min then a distribution volume of 0.9 l/kg is advisable. These distribution volumes should be used to adjust the maintenance infusion accordingly. This study shows that with known pharmacodynamic and pharmacokinetic parameters it is possible to maintain a steady state with a continuous vancomycin infusion. This would lead to more time- and cost- effective treatment for patients with Vancomycin sensitive organisms.

INDEX

Abbreviations

ABW	Actual body weight
AUC	Area Under serum concentration-time Curve
B-HS	Beta haemolytic streptococci
BMI	Body Mass Index
BSA	Body Surface Area
BW_{adj}	Adjusted body weight
C_1	Concentration 5 minutes after completion of infusion
C_2	Concentration 60 minutes after completion of infusion
CA-MRSA	Community Acquired Methicillin Resistant *Staphylococcus aureus*
CEO	Chief Executive Officer
Cexp	Expected concentration
CL/f	Clearance constant fraction
Clcr	Creatinine clearance
CL_p	Plasma Clearance
Cl_{Vanco}	Vancomycin Clearance
CL_{vc}	Vancomycin Clearance
cm	centimetre
Cm	Measured concentration
Cmax	Maximum concentration
CL/F	Clearance constant fraction
Co	Concentration
CO-MRSA	Community Onset Methicillin Resistant *Staphylococcus aureus*
conc	Concentration
CoNS	Coagulase negative Staphylococcus
const	Constant
CrCl	Creatinine Clearance
Cr_s	Serum Creatinine
CSF	Cerebral spinal fluid
Css	Concentration of steady state

CVP	Central venous pressure
d	Dalton
IBW	Ideal body weight
ICU	Intensive Care Unit
HA-MRSA	Hospital Acquired Methicillin Resistant *Staphylococcus aureus*
hrs	hours
Ke	Elimination rate constant
kg	kilogram
kg /d	kilogram per day
ld	loading dose
l/kg	litre per kilogram
m	metre
m^2	square metre
MBC	Minimal bactericidal concentration
md	maintenance dose
meas	measured
mg/d	milligram per day
mg/L	milligram per litre
MIC	Minimal Inhibitory Concentration
min	minute
ml/min	millilitre per minute
mmol/l	millimol per litre
MSSA	Methicillin sensitive *Staphylococcus aureus*
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
no	number
PAE	Post-antibiotic effect
P_{Cr}	Plasma Creatinine
Pd	Pharmacodynamics
Pk	Pharmacokinetics
PVL	Panton-Valentine Leukocidin

R	Resistant
R_{inf}	Infusion rate
Ro	Infusion rate (dosing rate)
S	Sensitive
Suppl	Supplement
T	Time
t_0	time zero
t_1	time after 5 minutes
t_2	time after 60 minutes
$t_{1/2}$	Half life
t_{inf}	infusion time
$t_{p\text{-}inf}$	time to restart infusion
Van	Vancomycin
VAP	Ventilator associated pneumonia
VRE	Vancomycin resistant enterococci
VSE	Vancomycin sensitive enterococci
Vd	Distribution volume
U_{Cr}	Urine Creatinine
UFS	University of the Free State
µg/ml	micro gram per millilitre
w	weight or mass

RESEARCH PROPOSAL

THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

1. LITERATURE REVIEW

1.1. Introduction

Vancomycin was first isolated from *Streptomyces* (currently *Amycolaptosis*) *orientalis*[1] in the jungle of Borneo in 1950.

Vancomycin is a large glycopeptide antibiotic with a molecular weight of ~1450d (dalton) which is not absorbed orally [2]. Elimination is primarily renal with 80 – 90% being recovered unchanged in urine within the first 24 hours after a single dose[2]. Excretion is primarily through glomerular filtration without tubular reabsorption[3].

Studies on therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients are scant. Vancomycin is renally eliminated by glomerular filtration; vancomycin dosing in renal insufficiency can be accurately dosed based on the creatinine clearance (CrCl), (i.e. the daily dose of vancomycin should be reduced in proportion to the decrease in renal function)[4]. In those responding to vancomycin therapy and in those with a normal volume of distribution (Vd), vancomycin levels are unhelpful, expensive, and unnecessary for vancomycin dosing[4].

Evidence to date for a direct causal relationship between toxicity and specific serum concentrations is limited, and data are inconclusive because of confounding nephrotoxic agents, inconsistent and highly variable definitions of toxicity, and difficulty in assessing the time sequence of events regarding changes in renal function secondary to vancomycin exposure[5].

Rello and co-workers (2005) recently performed a retrospective analysis where patients were treated with Vancomycin for Oxacillin-resistant ventilator associated pneumonia (VAP)[6]. The study revealed that continuous infusion of vancomycin was independently associated with lower mortality than intermittent infusion (25% vs 54.2%, $p = 0.02$)[6]. This was the first clinical study supporting the potential usefulness of continuous infusion in enhancing the clinical efficacy of vancomycin, although caution was expressed because of the retrospective nature of the study and the small number of patients receiving such a regimen ($n = 16$).

1.2. Mechanism of killing

By inhibiting the peptidoglycan (structural polymer of the bacterial cell wall) the bactericidal effect is obtained[7].

Vancomycin binds with high affinity to the D-Ala-D-Ala C-terminus of the pentapeptide, thus blocking the addition of late precursors by transglycosylation to the nascent peptidoglycan chain and preventing subsequent cross-linking by transpeptidation. Vancomycin does not penetrate the cell wall and this leads to the translocation of the precursors on the outside surface[7]. Refer to figure 1.

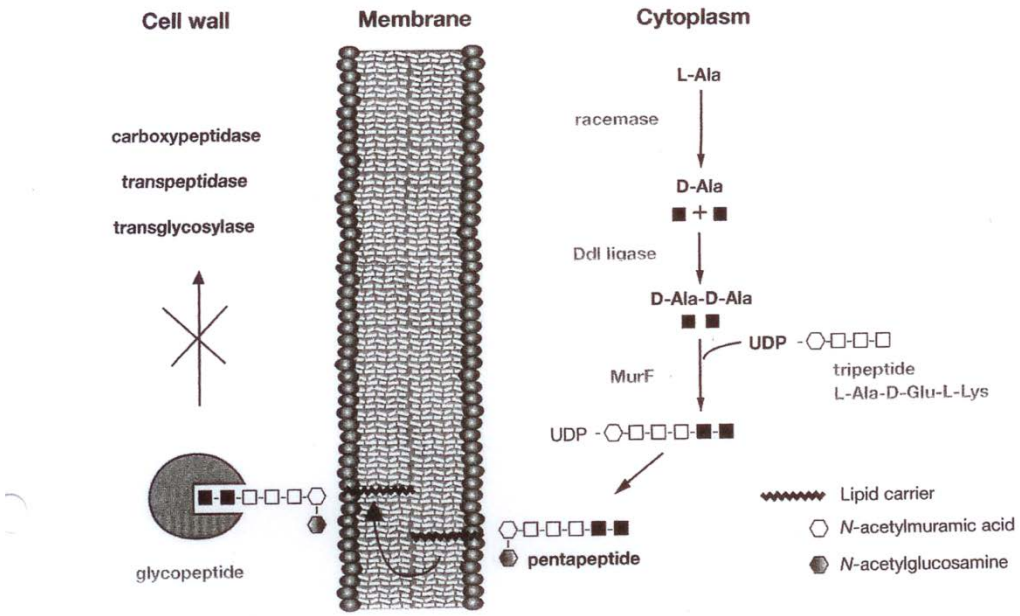


Figure 1. Peptidoglycan biosynthesis and mechanism of action of vancomycin. Binding of the antibiotic to the C-terminal D-Ala–D-Ala of late peptidoglycan precursors prevents reactions catalyzed by transglycosylases, transpeptidases, and the D,D-carboxypeptidases. Ddl, D-Ala:D-Ala ligase; MurF, a synthetase protein; UDP, uracil diphosphate.

Adapted from Courvalin, 2006[7].

Vancomycin has a slow bactericidal effect against dividing organisms and a bacteriostatic effect against *Enterococcus* and methicillin-resistant *Staphylococci*.
The first resistance was reported in 1986 in Europe (VRE – vancomycin resistance Enterococcus) [7].

Vancomycin is a concentration dependent antibiotic as well as a time-dependent antibiotic. However Vancomycin is regarded to have a time-dependent action and therefore the rationale for the use of a continuous infusion. Vancomycin obeys both concentration dependent kinetics > MIC and concentration independent kinetics < MIC[4]. The postantibiotic effect of vancomycin is dependent on the concentration[2]. As drug concentrations exceed the MIC by 2-4 fold, the postantibiotic effect has been reported to increase from 0.2 to 2 h for *Staphylococcus aureus* and from 4.3 to 6.5 h for *Staphylococcus epidermidis*[2].

1.3. Resistance

Resistance is due to the presence of operons that encode enzymes for:

1. The synthesis of low affinity precursors, C-terminal D-Ala residue which is replaced by D-lactate of D-serine (D-Ser) with the change in the vancomycin binding site.
2. Elimination of high affinity precursors that are produced by the host. Thus the binding site of vancomycin is removed[7].

Six resistant phenotypes have been identified: Vancomycin A – Vancomycin G (Van A - Van G). In vancomycin the resistant organisms' peptidoglycans are changed to D-alanyl-D-Lactate (Van A, Van B and Van D) or D-alanyl-D-serine (Van C, Van E and Van G) [8].

Van A confers inducible resistance to high concentrations of vancomycin with a minimum inhibitory concentration (MIC) $\geq$ 64 μg/mL. Van B confers inducible resistance to vancomycin (MIC 4 - > 1024 μg/mL). Van C is present in *Enterococcus casseliflavus* / *Enterococcus flavescens* and *Enterococcus gallinarum* with a low level of resistance to vancomycin (MIC 4 – 32 μg/mL)[8].

Van D is only found in certain isolates. Van E is acquired from Van A, Van B and Van D, and has a low resistance to vancomycin (MIC 16 μg/mL) and Van G (MIC 12 – 16 μg/mL)[8].

Another reason for resistance to vancomycin lies in cell-wall thickening of *S aureus* strains, of both methicillin-sensitive *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA)[4]. Vancomycin-mediated cell-wall thickening results in "permeability mediated" resistance to vancomycin as well as to other anti-MSSA and anti-MRSA antibiotics[4]. Vancomycin-induced "permeability-mediated" resistance is manifested microbiologically by increased minimum inhibitory concentrations (MICs) and clinically by delayed resolution or therapeutic failure in treating staphylococcal bacteraemias or acute bacterial endocarditis[4]. The size of the vancomycin molecule prevents it from penetrating the cell walls of gram-negative organisms[4].

To avoid the development of resistance, trough serum vancomycin concentrations should always be maintained at greater than 10 mg/L, based on evidence suggesting that exposure of *S aureus* to trough serum concentrations of less than 10 mg/L can produce strains with vancomycin-intermediately susceptible *S aureus*-like characteristics[5].

1.4. Three varieties of MRSA

The prevalence of MRSA has increased during the past several decades with three clinical variants recognised[4]. Two of these are hospital acquired (HA-MRSA) and community onset MRSA (CO-MRSA)[4]. CO-MRSA originates in hospitals, circulates in the community and subsequently has its onset in the community before being readmitted to hospital[4]. A third MRSA is community acquired (CA-MRSA), a term often mistakenly applied to CO-MRSA because both come from the community[4].

CA-MRSA has two distinctive clinical presentations readily differentiating them from CO-MRSA strains, which represent the majority of MRSA admitted from the community (community onset) to the hospital[4]. CA-MRSA usually presents with pyoderma or necrotising / haemorrhagic community acquired pneumonia[4]. Although rare, these two clinical CA-MRSA syndromes are recognizable by their clinical presentations[4]. Strains of CA-MRSA, with Panton-Valentine leukocidin gene (PVL positive), are unusually virulent with a high degree of cytotoxic activity[4]. This accounts for their extensive tissue destruction and two unique clinical presentations. Our hospital cannot test for PVL. In spite of the increased virulence of CA-MRSA PVL positive strains, these organisms are surprisingly sensitive to older antibiotics, eg. Clindamycin, doxycycline, trimetroprim-sulphamethoxazole (TMP-SMX), but these antibiotics are effective against a proportion of HA-MRSA strains[4].

Vancomycin, linezolid, daptomcyin, minocycline and tigecycline are active against HA-MRSA, CO-MRSA and CA-MRSA strains[4]. For CA-MRSA necrotising pyodermas, treatment with surgical debridement and a HA-MRSA/CO-MRSA antibiotic, such as vancomycin, linezolid, daptomcyin, or tigecycline is indicated. For

CA-MRSA with influenza like illness, treatment with influenza anti-virals and linezolid[4] is appropriate.

1.5. Coagulase negative Staphylococcus

Infections that involve indwelling prosthetic material are commonly due to Coagulase negative staphylococci[1]. Slime biofilms produced by these organisms may enhance bacterial persistence[1]. Although Coagulase negative staphylococcal bacteremia associated with indwelling Hickman or Broviac catheters usually can be eradicated with vancomycin alone, removal of the indwelling foreign body may be necessary for cure[1].

1.6. Enterococci

Because of the gradually increasing resistance of *E. faecium* to penicillin, vancomycin had become the only remaining therapeutic agent effective against increasing numbers of clinical strains of enterococci[1]. However 15% of enterococci in intensive care units currently exhibit vancomycin resistance[1]. Four resistant phenotypes, VanA, VanB, VanC and VanD, have been observed[1]. Genes determining VanA- and VanB resistance phenotypes are located on transmissible genetic elements that may be located on plasmids or may insert into chromosomes[1]. VanC resistance, which is associated with low-level vancomycin resistance and susceptibility to teicoplanin, is constitutive and chromosomally encoded and therefore not transferable[1]. The VanD-resistance phenotype is similar to VanB and has thus far been observed only in rare strains of *E. faecium*[1]. No consensus has emerged concerning treatment of van A VRE, which are frequently also ß-lactam and aminoglycoside resistant[1].

Enterococci, may develop tolerance to vancomycin[8]. "Tolerance" may be defined as a minimum bactericidal concentration (MBC) of ≥ 32 times the MIC of an antibiotic[8]. Vancomycin "tolerance" may account for some cases of delayed or blunted therapeutic response with enterococci or staphylococci[8]. Vancomycin is a heptapeptide and is bactericidal for most gram-positive organisms, including staphylococci but is bacteriostatic against enterococci[8]. Enterococci resistance to vancomycin may be of the high- or low-grade variety[8]. High-level (VanA)

vancomycin resistance (MIC ≥ 64 µg/ml) is mediated by plasmids and is inducible and transferable. Low-level (VanB) resistance (MIC: 32-64 µg/ml) is non-transferable and chromosomally encoded[8].

1.7. The minimum inhibitory concentration (MIC) of Vancomycin

"MIC-drift" is present in staphylococci with an increased cell wall thickness and a permeability gradient for vancomycin. Increased MIC values in the presence of vancomycin therapy are indicative of increased cell wall thickness[8].

Table 1.7.1. refers to the MIC of Vancomycin for various organisms.

Table 1.7.1 – MIC of Vancomycin for Various Organisms[1]

Organism	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% susceptible
S. aureus			
Oxacillin (S)	1.0	1.0	100.0
Oxacillin (R)	1.0	1.5	100.0
CoNS			
Oxacillin (S)	1.5	2.0	100.0
Oxacillin (R)	1.5	2.0	100.0
Enterococcus sp	2.0	>256	75.3

Abbreviations: CoNS Coagulase negative *Staphylococcus aureus*
S Sensitive
R Resistant
MIC Minimal inhibitory concentration

If the MIC is less than 1 mg/L, trough serum vancomycin concentrations of 15 to 20 mg/L should achieve an area under the curve/MIC of 1400 for most patients[5].

Pharmacokinetic and pharmacodynamic information has been reported for vancomycin, supporting the idea that the ratio of the area under the serum concentration-time curve (AUC) and the minimum inhibitory concentration (MIC) is the parameter best correlated to efficacy in vancomycin therapy[9]. Refer to figure 2[10].

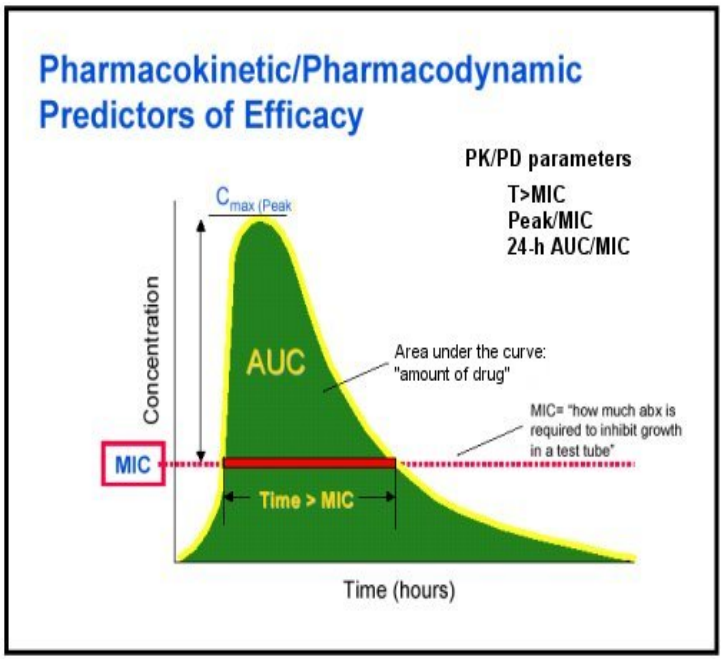


Figure 2. Adopted from rxkinetics 04/08/2009

Thus, the AUC/MIC ratio is currently accepted as the most relevant surrogate marker for this glycopeptide, and a value of 360 has been proposed as the recommended breakpoint for this parameter as referred to 24 h (AUC_{24h}/MIC)[9]. Refer to figure 3[10].

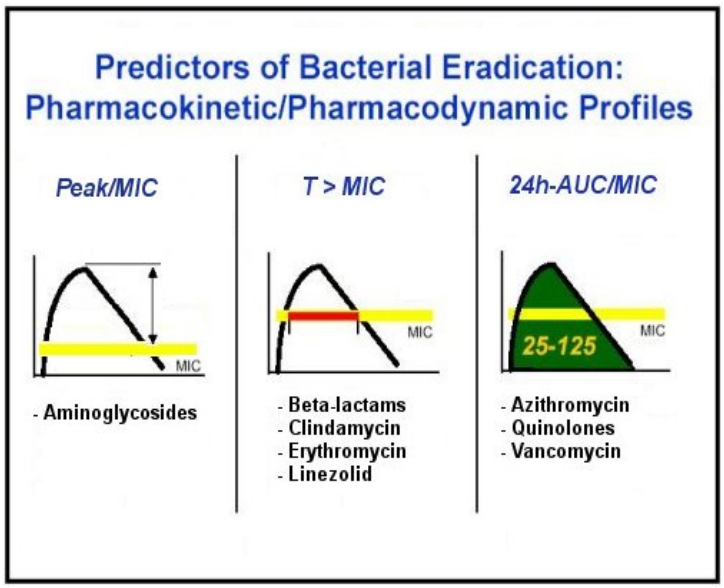


Figure 3. Adopted from rxkinetics on 04/08/2009.

1.8. Pharmacokinetics in the critically ill

Knowing how dosing methods perform for a given patient population can be helpful. One of the three methods will be applied when applicable.

The Lake-Peterson method typically provides the best vancomycin dosing estimated for individuals with a CrCl above 15ml/min, while the Matzke method was best for CrCl ≤ 15ml/min[11]. The CrCl is estimated more accurately by using with the actual body weight (ABW), ideal body weight (IBW) and the adjusted body weight (BW_{adj}) for each patient. In order to predict CrCl the BW_{adj} was used, ABW was used, instead of the BW_{adj}, if the ABW/IBW = 1.2. If the ABW/IBW = ≥ 1.2 the BW_{adj} will be used[11].

To prevent adverse effects, the infusion must be administered over a 2 hour period. Adverse effects include: "Red man syndrome" due to vasodilatation with histamine release, hypotension, ototoxicity, neurotoxicity, peripheral thrombophlebitis. A rare side effect includes a hypersensitivity maculopapillary rash, with a drug induced fever. Neutropenia only occurs in 2% of patients and is reversible[1]. With adverse effects the infusion should be discontinued.

Pharmacokinetic factors that influence the overall activity of vancomycin include its tissue distribution and protein binding effects[2]. Other factors that influence the serum concentration include creatinine clearance and body surface area (BSA)[2].

In the case of fully susceptible pathogens with a MIC of ≤ 1 mg/L, the strategy of targeting a steady-state vancomycin concentration of 15 mg/L during continuous infusion may simultaneously enable an area under the plasma concentration-time curve (AUC)/MIC ratio of ≥ 360, so that both pharmacodynamic efficacy targets may be optimised[6]. With the total daily dosage being the same, this approach may ensure higher and more sustained plasma steady-state trough concentrations than intermittent dosing, without causing higher total daily drug exposure in terms of the AUC from 0 to 24 hours (AUC_{24} being equal to $dose_{24h}$/clearance)[6].

The pharmacokinetic profile is characterised by a 2- to 3-compartment model. The distribution volume (Vd) is 0.4 – 1 l/kg[2]. In patients with a normal creatinine clearance the α-distribution phase lasts between 30 minutes and 1 hour, and the β-elimination half life ($t_{1/2}$) varies between 6 – 12 hours in serum in the presence of normal kidney function and 7 days in an anuric patient[2]. Refer to figure 4[2].

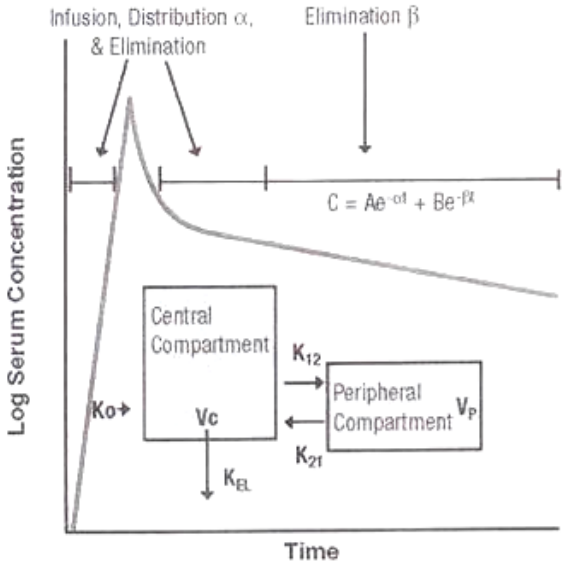


Figure 4. Schematic representation of a 2-compartment pharmacokinetic model, wherein C is the concentration, α and β are the respective elimination constants, e is the base of the natural logarithm, t is time, A and B are the retrospective zero time intercepts for α and β, Ko is the infusion rate constant, Vc is the volume of the central compartment, Vp is the volume of the peripheral compartment, K_{12} and K_{21} are intra compartmental rate constants, and K_{EL} is the elimination rate constant from the central compartment. Adopted from Rybak 2006[2].

The distribution volume is influenced by: fever, sepsis, burns, protein-binding capacity, drug interactions, lipid solubility and the pKa of the drug, pH of the environment, hydration and nourishment of the patient[2,12].

In the critically ill patient there is a constant change in the pH, due to respiratory failure, shock states and renal failure. Ionised drugs are influenced by the pH of the environment in that they do not easily penetrate the lipid membrane.

1.8.1. Renal

Nephrotoxicity has been associated with impure preparations of vancomycin[8]. Concomitant use of vancomycin and an aminoglycoside exacerbates the nephrotoxic effects of the aminoglycoside. The turning point was reached upon the discovery that Gram negative-bacilli could also be treated with aminoglycosides[8]. The combination of vancomycin and aminoglycosides leads to the release of an endotoxin, which in turn leads to an increase in creatinine[8].

1.8.2. Burn patients

Burn patients display two tendencies viz. either an increase in renal clearance or a variation in the renal clearance[13]. Burn patients have an increase in the renal clearance of drugs due to a hypermetabolic state[13].

1.8.3. Altered plasma protein concentration

In a study done by Benet & Hoener in 2002 it was thought that changes in carrier proteins in patients result in changes in unbound drug based on in vitro data, but this is no longer accepted – equilibrium is reached irrespective of concentrations of carrier proteins with the absolute concentration of unbound drug not affected except in rare cases[47]. However a study done by Boucher et al. showed that a decrease in the plasma protein concentration leads to a decrease in the concentration of the protein bound drug, resulting in an increase in the unbound fraction[13]. The unbound drug distributes to different tissues which in turn increase the distribution volume. The opposite is also true with an increase in the plasma protein concentration. However it must be remembered that our study was based on Boucher and that equilibrium is not reached in all critically ill patients.

Although most studies have shown that the binding of vancomycin to protein is moderate (≤50%), there are a number of *in vitro* assessments that have demonstrated a 1-8 fold increase in the MIC in the presence of albumin whereas it is normally measured in the presence of a serum[2].

1.8.4. Sepsis

In the septic patient fluid shifts are ascribed to an increased capillary leak associated with a decrease in the oncotic pressure[13]. The shifts are aggravated by the addition of crystalloids and colloids[13]. An increase in third space fluid loss due to an interstitial leak is experienced[13]. This becomes apparent as oedema, ascites and pleural effusions to which hydrophilic drugs such as vancomycin spread[13].

For fluid losses that involve water and electrolytes, replacement is effected by isotonic electrolyte solutions, also called replacement-type solutions[14]. Glucose administration maintains tonicity, preventing ketosis and hypoglycaemia[14].

1.8.5. Age

Organ function deteriorates with increasing age[14]. The older the patient, the lower the rate of clearance and the longer the elimination half-time of a neuromuscular blocking drug, even if it primarily undergoes organ-independent elimination[14].

1.9. Dosages

To achieve the recommended trough serum concentrations when the MIC is less than 1 mg/L, most patients with normal renal function should receive vancomycin dosages of 15 to 20 mg/kg (based on actual body weight)[5]. The bolus infusion period should be increased to 2 hours when individual doses greater than 1g are used[5].

A loadingdose of 15mg/kg[1] over a period of 1 hour with a maintenance infusion of 30 mg/kg in 200ml solution is used to obtain a level of 15 – 20 mg/L. With a MIC of ≤ 1 mg/mL a constant level of the area under the curve (AUC) in the serum plasma time curve (AUC/MIC) can be maintained.

Intravenous drug abusers require larger doses, as they have an increased renal elimination. Poor penetration in solid organs requires higher serum levels (30 – 40 mg/L) in order to have a therapeutic value[15].

Continuous infusion (30 mg/kg) is used for the optimisation and improvement of effectiveness in the critically ill patient[17]. The strategy of targeting a steady-state vancomycin concentration of 15 mg/L during continuous infusion may simultaneously enable an area under the plasma concentration-time curve (AUC/MIC ratio of ≥ 360, so that both pharmacodynamic efficacy targets may be optimised[6].

An initial loading dose of 15 mg/kg must always be administered, irrespective of the patient's renal function, with the continuous infusion starting immediately

afterwards[6]. Vancomycin is not removed by hemodialysis[4]. Dosages are then adjusted according to levels[4].

1.10. Therapeutic drug monitoring

1.10.1. Adjustment of dosing

When concentrations of drugs are used for purposes of adjusting dosage regimens, samples obtained shortly after administration of a dose are almost invariably misleading[18].

1.10.2. Timing of sampling

The point of sampling during supposed steady state is to modify one's estimate of clearance constant fraction (CL/F) and thus one's choice of dosage[18].

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of CL/F for the patient being treated, using the following equation:

CL/F (patient) = Dosing rate/C_{ss} (measured) [18].

Pharmacokinetic parameters are generally determined just as readily from constant-rate data as from i.v. bolus data. Certainly, this is so for an i.v. infusion - refer to figure 5 and 6.

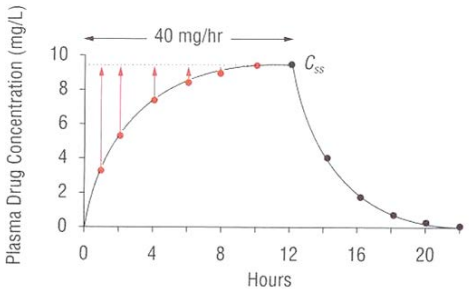


Figure 5. Estimation of pharmacokinetic parameters from plasma data during and after a constant infusion. The vertical arrows represent the differences between concentrations at plateau and observed during the infusion. Adopted from Rowland, Tozer; 1995[12].

At early times, a pronounced distribution phase is seen upon stopping an infusion, because distribution equilibrium has yet to be achieved between drug in blood and that in many tissues. With a more prolonged infusion more drug enters the tissues[12]. The drug distribution from blood to tissue is consequently reduced, and it appears that the distribution phase is much shallower upon stopping the infusion. At plateau, the rates of drug entry into and out of the tissues are equal. Upon stopping the infusion, elimination of drug from plasma, along with a subsequent fall in plasma concentration, creates a gradient for return of drug from tissues. Initially, the rate of elimination from plasma exceeds the rate of efflux from tissues, and plasma concentration falls rapidly. Eventually, however, the rate of return from tissues limits the rate of elimination from plasma. The body then acts, once again, as a single compartment; plasma concentration and amount in the tissues and hence in the body as a whole, fall with a half-life equal to that seen during the terminal phase following an i.v. bolus dose.

From figure 5 it is clear that the longer the infusion the closer the concentration is to the plateau value and the greater is the error in the difference measurement[12]. Generally, difference values calculated from concentrations beyond 90% of the plateau have excessive error. Consider the concentration data at and after the end of the infusion. Plotting these data on semi-logarithmic paper also gives a straight line, from which half-life can be determined, after stopping the infusion (refer to figure 6).

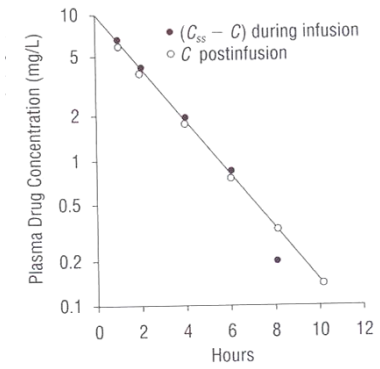


Figure 6: Semi-logarithmic plot of the difference (•) between plateau drug concentration and that observed during the infusion against time. Also plotted are the declining values of plasma drug concentration (○) against time after stopping the infusion. Adopted from Rowland, Tozer; 1995[12].

2. DRUG INTERACTIONS WITH VANCOMYCIN.

Table 2.1. Drug interactions with concomitant use of a vancomycin infusion[18,19].

Drugs	Nephrotoxicity	Clearance	Vancomycin Levels	**Other adverse effects**
Aminoglcyosides	⇧	▫	▫	▫
Amphoterocin B	⇧	⇩	▫	▫
Heparin	▫	▫	Sub-therapeutic	▫
Non-depolarising Muscle relaxants	▫	▫	▫	**Histamine Release**
Zidovudine	▫	▫	▫	**Myelotoxicity Neutropenia**

3. AIM OF THE STUDY AND PROBLEM STATEMENT

3.1. Problem statement

A need exists for therapeutic drug monitoring of vancomycin in critically ill patients to ensure adequate serum and tissue levels.

3.2. Aim of the study

The aim of the study is to test a feasible regimen for adjusting maintenance of vancomycin infusion in the critically ill patient, in order to reach the ideal therapeutic vancomycin levels of 15 – 20 mg/L. The study entails both the loading dose and the maintenance dose.

3.3. Relevance of the study

Vancomycin pharmacokinetic parameters may vary considerably among individuals, developing institution-specific, population-based dosing methods and monitoring approaches[11], could ensure accurate dosing for individual patients within a shorter time frame. This would lead to more time- and cost- effective treatment for patients with Vancomycin sensitive organisms.

An important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen[18]. If a sample is obtained too soon after dosage is begun, it will not accurately reflect clearance[18]. Simple guidelines can be offered[18].

The speed of recovery of the patient depends on the rate at which therapeutic levels are attained – the sooner the better consequently improving patient morbidity and mortality.

In order for the patient to reach a steady state as soon as possible the following are taken into account:

3.3.1. Patient factors

Age, sex, length, weight, distribution volume (Vd), body surface area and creatinine clearance[2,11].

3.3.2. Drug factors

Protein binding capacity, MIC/AUC, correct preparation and administration techniques, the taking of vancomycin levels 15 minutes[6] after the bolus dose and then the continuation of the infusion.

4. METHODOLOGY

4.1. Ethical aspects

Permission was obtained from the ethical committee as well as the Head of Clinical Services of Universitas Hospital prior to commencing the study (ETOVS nr 09/2010). Prior to commencing the study consent was obtained from the patient or his/her relatives and if they were not available then consent was obtained from the Head of Clinical Services (Appendix A).
No greater risk for the patient than that which normal examination entails is envisaged. The standard hospital consent form was used.

Target date for submission of research proposal was the 26th of January 2010.

4.2. Study design and location

A prospective analytical study of 10 consecutive patients meeting the inclusion criteria, admitted to the Multidisciplinary Intensive Care Unit at Universitas Hospital was applied.

4.3. Consent

Prior to commencing the study consent was to be obtained from the patient or his/her relatives and if they are not available then consent will be obtained from the Head of Clinical Services (Appendix A).

4.4. Confidentiality

Personal details of every patient participating in this particular study will be kept confidential.

4.5. Inclusion and exclusion criteria

4.5.1. Inclusion criteria.

1. Severe infections caused by prevalent Gram positive organisms namely, MRSA, CoNS, Enterococci.
2. Severe infections caused by *S. aureus*, enterococci or streptococci that are resistant to B-lactam antibiotics.

4.5.2. Exclusion criteria

1. Children younger than 12 years.
2. Two out of four positive blood cultures for CoNS, indicative of contamination.
3. The continued empirical use for infections which are negative for B-lactam resistant and gram-positive organisms.
4. Selective bowel decontamination with vancomycin.
5. Eradication of MRSA colonisation
6. Primary treatment of Clostridium difficle colitis.
7. Renal failure patients on dialysis.
8. Hypersensitivity to vancomycin.
9. Central nervous system infections.
10. Endocarditis.
11. Pregnancy.
12. Empirical use in neutropenic patients with a fever that is not attributable to gram-positive infections.
13. Neutropenia.
14. Thrombocytopenia.
15. Concurrent use with nephrotoxic drugs.
16. Topical application or irrigation.

4.6. Special investigations

4.6.1. Blood cultures

Four blood cultures, using aseptic techniques, will be taken. Two cultures will be taken peripherally and two when the insertion of the new central venous pressure line (CVP) takes place.

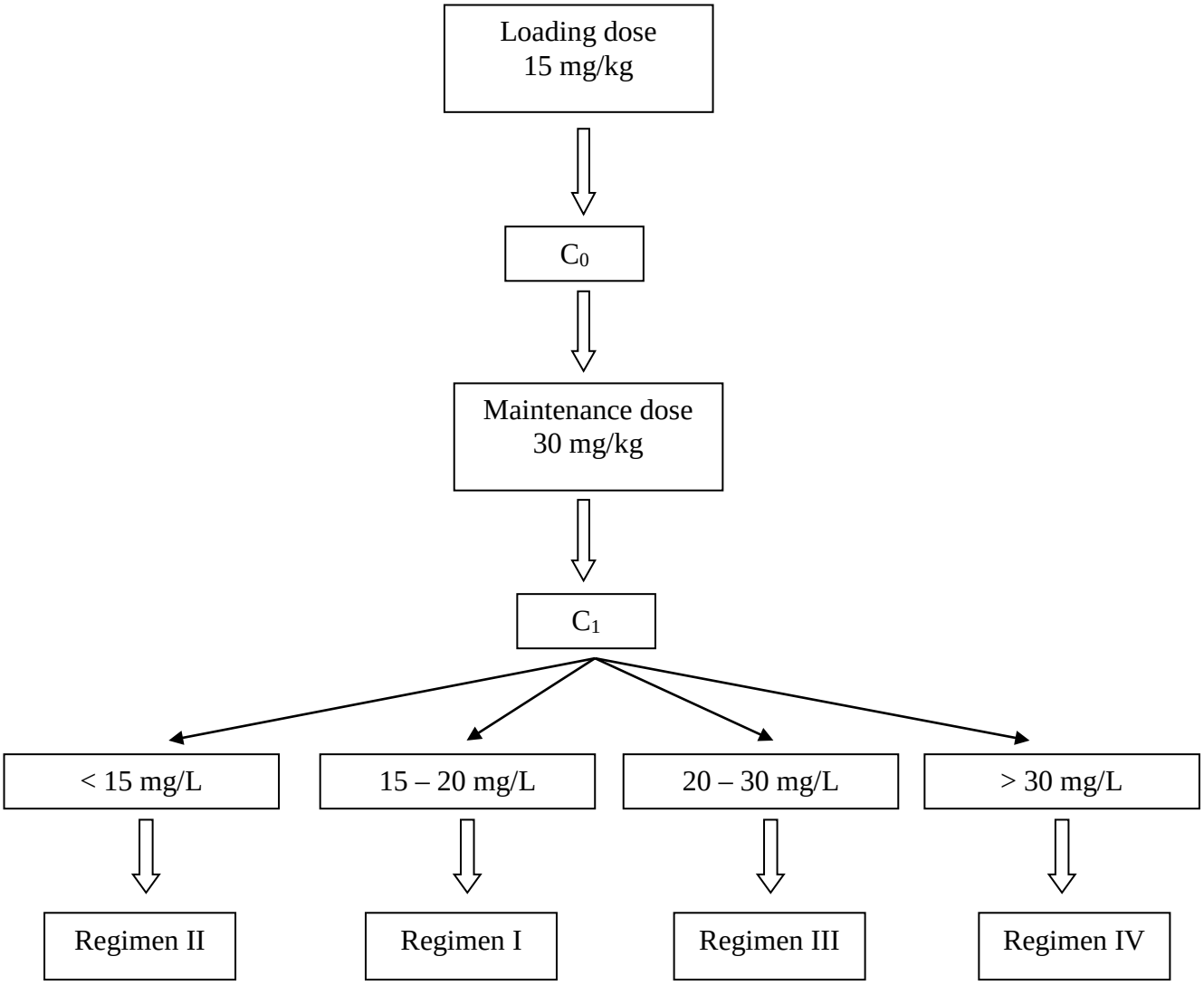
Aseptic technique involves the following: Mask, sterile gown, sterile pack containing: gauze, kidney bowls, towels, and 2 pairs of sterile gloves.
[One pair for taking blood from the peripheral site and the other pair for taking blood from the newly inserted central line (using the Seldinger technique)], 4 x 10 ml syringes with needles. Prior to use the blood culture bottle's expiry date will be assessed.

Cleaning of the peripheral area with an alcohol based cleaning solution. 10 ml of blood, filling the syringe, will be drawn for every blood culture.
The sterile needles and syringe are connected. The blood culture top is cleaned by the assistant. The needle with the syringe is then plunged into the bottle. Upon completion of the procedure the needle will be withdrawn and discarded. The blood culture bottles are sent to the laboratory immediately.

4.6.2. Vancomycin dosing

1. Calculate the creatinine clearance according to the Cockroft-Gault formula[20].
2. Calculate the loading dose (15 mg/kg).
3. Calculate the infusion rate of the loadingdose over two hours[5].
4. Draw C0 after completion of the loading dose infusion[21].
5. Start empirical maintenance dose of 30 mg/kg[4].
6. Draw C1 after six hours[21].
7. If the value of C1 is within the target range of 15-20 mg/L[4] follow regimen I.
8. If the value of C1 is less than the target level follow regimen II.
9. If the value of C1 is above 21 but less than 30 mg/L follow regimen III.
10. If the value of C1 is above 30 mg/L follow regimen IV stop the infusion.

Figure 7. Flow chart illustrating protocol



For regimen I is to be used if the measured concentration (Cm) is within the expected range (15-20 mg/L).

1. Continue with the maintenance dose infusion and there is no need to adjust the loading dose.
2. Check the level after 6 hours and adjust accordingly.

For regimen II an additional bolus dose is given as follows:

1. Expected concentration minus measured concentration x Vd [22].
2. The bolus dose should be administered over one hour[5].
3. Continue with original maintenance dose.
4. Repeat blood levels after 6 hours[5].

For regimen III the infusion is stopped and restart the original maintenance infusion rate.

1. Calculate the stopping time by using the following formula: Excess loading dose/rate of maintenance dose infusion + hours of stopping the infusion.
2. Continue with original calculated maintenance dose.
3. Repeat blood levels after 6 hours and if the levels are still unsatisfactorily repeat regimen III.

For regimen IV

1. Stop the infusion and note the time.
2. Draw a blood level after 5 minutes of discontinuation (C1) and again after 60 minutes (C2).
3. Use equation 4 to calculate T1/2.
4. Use T1/2 to calculate Ke by using formula 5[12].
5. Use Ke to calculate the true Vd by using equation nr 8.
6. Use the Vd from equation 8 to calculate CLp by using equation number 9.
7. Use CLp from equation number 9 to calculate R1 (the new infusion rate) by using equation number 10[12].
8. Use equation number 6 to calculate the new CO (concentration).
9. Use the new CO to calculate the time when the infusion should be restarted.

For formulas see end of this section.
Above-mentioned dosages have been proven to be safe in the critically ill patient[4].

4.7. Blood sampling

The site was the opposite arm from the infusion site using aseptic techniques. A lithium heparin tube was used. The tube was filled with 5ml of blood. The sample was personally delivered to the laboratory by the researcher.

4.8. Vancomycin monitoring

Vancomycin peak levels were taken 15 minutes after completion of the bolus dose[8] using a lithium heparin tube. Blood samples were analysed by using the AxSym Vancomycin II assay. This assay utilizes Fluorescence Polarization Immunoassay (FPIA) technology. Upon reaching the laboratory all samples were immediately centrifuged at 2 500 revolutions per minute.

Awaiting results the maintenance infusion was commenced at a dose of 30mg/kg/day in 200ml 5% dextrose at a flow rate of 8ml/hr. The flow rate was adjusted according to the result of vancomycin level. The desired serum vancomycin level is 18 – 20 mg/L, with a reference value of 15 – 20 mg/L[12].

The ultimate goal is a serum vancomycin reference value of 15 – 20 mg/L and a tissue level of 30 – 40 mg/L in solid organs[6].
Depending on the concentration the specific regimen for the levels was used.
The regimens are based on assumptions and the calculations are based on standard formulae used by Tozer[22].

4.9. Turnaround time

(Turnaround time is the time that lapses between sampling and analysing.)
The appropriate laboratory technician is to be alerted as soon as possible on commencement of vancomycin infusion.
The analysis of each sample will take approximately 20 min.

4.10. Rejection of samples

Responding to vancomycin levels of the previous days will lead to inaccuracy.
Inaccuracy could arise because of:

Time lapse for sample registration
Meditech system being out of order
Uncertainty of the time lapse between sampling
Analysis (longer than an hour)

4.11. Statistical analysis

This is a non-randomized sequential prospective cohort study done in a single centre unit.

The data collection sheets are displayed in table 8.11.1 – 8.11.6.
Results will be summarised by means, standard deviations or percentiles (numerical variables) and frequencies and percentages (categorical variables).

After completion of the table all relevant data will be analysed, i.e. infusion rate, calculated creatinine clearance, time period of infusion to reach therapeutic levels, mean concentration of infusion.

4.12. Outcome

The projected outcome will be to develop protocols for the administration of vancomycin in critically ill patients to maximise the serum levels and efficacy.

4.13. Completion of research proposal

Estimated time of completion of the research proposal will take approximately two months. Statistical analysis will be done by the Department of Biostatistics (University of the Free State), over a two month period.

4.14. Formulas

1. Vd = Dose / concentration expressed in litre per kilogram[20].
2. Cockroft-Gualt[20]: CrCl = (140 – age) x (IBW)(0.85 in females) / 72 x P_{CR}
3. Matzke method: Cl_{vanco}(ml/min) = (CrCL x 0.689) + 3,66;
   V = 0,72 l/kg if CrCl > 60 ml/min
   V = 0,89 l/kg if CrCl 10 – 60 ml/min
   V = 0,9 l/kg if CrCl < 10 ml/min[11].
4. IBW is calculated by using the Devine formulae[11].
   IBW_{males} = 50kg + 2,3($length_{inch}$ – 60kg)
   $IBW_{females}$ = 45,5kg + 2,3($length_{inch}$ – 60kg)
   1 inch = 2,54 cm
5. CrCL = U_{Cr} x V/P_{Cr}[20]
   U_{Cr} = urine creatinine
   V = volume
   P_{Cr} = Plasma creatinine
6. Jacobson formula for body surface area (BSA)[23].
   BSA (m^2) = length (m^2) + weight (kg) – 60 / 100
7. Body mass index (BMI) = weight (kg) / $length^2$ (m)

5. PITFALLS

1. Levels above 45µg/mL are to be avoided as this could lead to ototoxicity and nephrotoxicity especially in the presence of other drugs which could contribute to these adverse effects[11].

2. The clearance of many non-depolarizing neuromuscular blocking drugs is lower in women. Consequently a smaller dose could achieve a similar effect to that in men[14].

6. BUDGET

Accurate vancomycin dosing is readily achieved more quickly, simply, less expensively, and without risk of nephrotoxicity by dosing vancomycin based on calculated CrCl rather than by vancomycin levels[4].

A relatively low cost is anticipated as the department will only be responsible for the stationery.
Routine levels of serum vancomycin levels are done in the intensive care unit and this will not compromise the study financially, as this is part of the normal daily management.

Table 6.1. Cost analysis

ITEM	***PRICE PER UNIT***	***TOTAL***
Kit / 100	R 11,45	**R 1 145,00**
Binding of regimen (20 copies)	R 10	**R 200**
Binding of script (8 copies)	Plus minus R 30	**R 240**
Grand total		**R 1 585,00**

7. VANCOMYCIN MONITORING

When the goal of measurement is adjustment of dosage, the steady state sample should be taken within one minute of completion of the bolus dose.

REGIMEN

As adopted from Tozer[12].

As adopted from Healy[21].

PART 1: PREDICTING CONCENTRATION AT END OF LOADING DOSE INFUSION:

1. Obtain the following:

- Age
- weight (w)
- Serum creatinine (Cr_s)
- Dose of vancomycin (15 mg/kg) x 2 hrs
- Infusion rate (dosing rate)[Ro] = (Dose/2 hrs) mg/hr

2. Assumptions

- Vancomycin clearance (CLvc): Cl_{vanco}(ml/min) = (CrCL x 0.689) + 3,66;

$$\boxed{CL_{vc} = (CL_{cr} x 0.689) + (3.66)} \qquad \text{Eq. 1}$$

- Vancomycin obeys 2- to 3-compartment model kinetics.
- Volume of distribution for vancomycin:

V = 0,72 l/kg if CrCl > 60 ml/min

V = 0,89 l/kg if CrCl 10 – 60 ml/min

V = 0,9 l/kg if CrCl < 10 ml/min[24].

3. Calculate

- Derive vancomycin clearance from CrCl:

  - CrCl = (140 – age) x (IBW)(0.85 in females) / 72 x P_{CR} (Cockroft-Gualt[20])

Cl_{vanco}(ml/min) = (CrCL x 0.689) + 3,66;

- Obtain elimination rate constant (Ke) [Adopted from Bauer p225][25].

CLvc = Vd x Ke (Vd = 0.72 x w)

$$K_e = \frac{CL_{vc}}{V_d} \qquad \text{Eq. 2}$$

- Calculate expected concentration (C_{exp}) at end of the infusion (Rowland &Tozer p 301)

$$\left(C_{\exp}\right) = \frac{R_{o-\inf}}{CL_{vc}}\left(1 - e^{-K_e t_{\inf}}\right) \qquad \text{Eq. 3}$$

Where t_{inf} = time of infusion

4. Draw blood sample for concentration immediately (within 1 min) after end of the infusion (C_o)[20]. Take blood from the opposite arm from side of infusion.

5. Immediately, start the empirical maintenance dose (MD) of 30 mg/kg x 24 hrs, and run it for 2 hrs as you wait for results of blood level (must be within 1 hr)[4].

6. Get results of concentration within 1 hr and calculate patient's parameters using appropriate regimen as follows:

   - Use Regimen I if measured concentration (Cm) is within the expected range (15-20 mg/L).

- Use Regimen II if measured concentration (Cm) is equal or less than 15 mg/L

- Use regimen III if the measured concentration (Cm) is 21 - 30 mg/L (i.e., higher than Cexp or Css).

- Use regimen IV if the measured concentration is higher than 30 mg/L.

PART 2: REGIMEN I

Use Regimen I if measured concentration (Cm) is within the expected range (15 - 20 mg/L).

- Continue with the MD dose infusion and there is no need to adjust LD.

- Check level after 6 hours, and adjust accordingly[5].

PART 3: REGIMEN II

Use regimen II only if the measured concentration (Cm) is less than 15 mg/L (i.e., < Cexp or Css).

ii) If measured concentration is less than Css or expected concentration, e.g., 15 mg/L instead of 20 mg/L. (Cexp – Cm)Vd

- Then add dose of: (20-15) x Vd (the old Vd of 0.7L/kg x w)
- Then Dose to add is: 5 mg x Vd

ii) Administer the deficit over 1 hour in an infusion[5].

iii) Continue with original maintenance dose**:**

iv) Check concentration (Css) after infusion for 6 hrs[5]. If the concentration is not within the required range then repeat regimen II.

PART 4: REGIMEN III

Use regimen III only if the measured concentration (Cm) is 21 - 30 mg/L (i.e., higher than Cexp or Css).

i) If measured concentration is, e.g., 25 mg/L instead of 20 mg/L (Css or Cexp).

- Calculate excess L-Dose as: (25 - 20) x Vd (the old Vd of 0.72 L/kg x w)
- The excess L-Dose is: 5 mg x Vd

ii) Determine how long to interrupt the infusion.

- (Excess L-dose/rate of MD infusion) = hours for stopping the infusion.

iii) Recommence with **Maintenance infusion after the above time.**

iv) Check concentration (Css) after infusion for 6 hrs[5]. If the concentration is not within the expected range then repeat regimen III.

PART 5: REGIMEN IV

Use regimen IV only if the measured concentration (Cm) is greater than 30 mg/L.

1. Stop the MD infusion (note the time of stopping)

2. Take blood sample 5 min after stopping of the infusion (C_1) and again 60 min later (C_2)[5]. NB: For each, write the exact time blood was collected (t_1 and t_2). Refer to table 7.1. for sample time collection.

Table 7.1. Sample time collection

Sample nr	Date	Time of commencing infusion	Infusion time completion	Time 1	Time 2	Concentration for time 1	Concentration for time 2

3. Get results of concentration and calculate patient's parameters (within 1 hr).

4. Use the results to calculate new infusion rate:

a) Calculate half life:

$$t_{1/2} = \frac{(t_2 - t_1)}{(C_1 - C_2)} \text{ x } (\frac{C_1}{2}) \qquad \text{Eq. 4}$$

b) Calculate the real Ke

$$K_e = \frac{0.693}{t_{1/2}} \qquad \text{Eq. 5}$$

c) Obtain concentration (**Co**) at end of infusion (to) by:

$$Co = (\frac{C_1}{t_{1/2}})(t_1 - t_0) + C_1 \qquad \text{Eq. 6}$$

d) Calculate time to restart infusion (t p-inf.)

Start infusion when concentration (Css) is 20 mg/L.

$$C_o = C_{ss} e^{-K_e t_{p-\text{inf}}} \qquad \text{Eq. 7}$$

e) Estimate the volume of distribution (Vd) from:

$$V_d = \frac{R_{\text{inf}} (1 - e^{-K_e t_{\text{inf}}})}{K \text{ x } C_o} \qquad \text{Eq. 8}$$

NB: This equation is derived from equation 1

f) Estimate vancomycin clearance from:

$$CL_p = (K) \, x \, (V_d)$$ Eq. 9

6. Estimate actual maintenance dose and adjust accordingly

$$(R_o) = (Css) \, x \, (CLp)$$ Eq. 10

7. Start the new infusion after the calculated time of post infusion under 5 d). That is when concentration is = Css

8**. C**heck concentration after 6 hrs (Css).

8. RESULTS

One patient was used in the pilot study. Of the thirteen patients only ten met the inclusion criteria and were enrolled for the study, over a period from February 2010 to February 2011.

For demographic and pharmacokinetic data refer to tables 8.11.1 – 8.11.6.

Table 8.11.1. Demographic and pharmacokinetic data

Pt no	Age (yrs)	Sex	Weight (kg)	Serum creatinine Cr_s (mmol/L)	Dose = 15 x *w* Total dose (15mg/kg)	Time of Infusion (t; hrs)	Ro = Dose / t_{inf} Infusion Rate (Ro; mg/hr)
1	19	F	70	0.06	1000	2	500
2	35	F	70	0.423	1000	2	500
3	23	F	50	0.03	750	2	375
4	58	M	80	0.058	1200	2	600
5	26	M	70	0.047	1000	2	500
6	58	M	65	0.05	1000	2	500
7	70	F	95	0.105	1425	2	712.5
8	65	F	70	0.036	1000	2	500
9	41	M	100	0.067	1500	2	750
10	47	M	68	0.045	1000	2	500
11*	37	M	100	0.085	1500	2	750

Table 8.11.2. Demographic and pharmacokinetic data

Pt no	$Cl_{cr} = \frac{(140\text{-age}) \times w}{814 \times Cr_s}$ Creatinine Clearance (CLcr; ml/min)	$CLvc = \frac{(CLcr \times 0{,}689) + 3{,}66}{1000} \times 60$ Vancomycin Clear (CLvc; L/hr)	$Vd = 0{,}72 \times w$ Distribution Volume (0,72 L/kg) Vd	$K_e = \frac{CL_{vc}}{Vd}$ Elimination Const (Ke; hr-1)	Sex
1	173	7.32	50.4	0.290	F
2	21.34	1.102	62,3	0.018	F
3	239.56	10.123	36	0.281	F
4	138.948	5.964	57.6	0.104	M
5	208.584	8.842	50.4	0.175	M
6	130.958	5.633	46.8	0.120	M
7	77.805	3.436	68.4	0.050	F
8	179	7.6	50.4	0.151	F
9	181.52	10.89	72	0.151	M
10	173	7.37	48.96	0.150	M
11*	148.865	6.374	72	0.089	M

For patient number 2 the distribution volume was calculated as follows:

Vd = 0.89 X 70 = 62,3 L/kg.

Table 8.11.3. Demographic and pharmacokinetic data

Pt no	(Ke x tinf)	$Cexp = \frac{R_{o\text{-}inf}}{CLvc}(1\text{-}e\text{-}K_e t_{inf})$ Expected conc (Cexp;mg/L)	Measured concentration (mg/L) after loading dose	Maintenance Dose (30mg/kg)	Ro-inf mg/hr	$Cexp = \frac{R_{o\text{-}inf}}{Clvc}$ Expected conc (Cexp;mg/L)
1	0.290	17.21	37.5	2000	83.33	11.38
2	0.036	8.167	37.3	2000	83.33	75.6
3	0.562	15.92	34	1500	62.5	6.174
4	0.208	18.99	23.5	2400	100	16.77
5	0.35	16.68	26.5	2000	83.33	9.424
6	0.240	18.90	14.3	2000	83.33	14.42
7	0.1	19.69	39	2850	119	34.63
8	0.302	17.126	23.6	2000	83.33	10.96
9	0.302	17.91	29.2	3000	125	11.47
10	0.301	20.00	43	2000	83.33	11.5
11*	0.178	19.18	53.3	3000	125	19.61

Table 8.11.4 Demographic and pharmacokinetic data

Pt No	Measured Conc after 6 hours (mg/L)	Regimen	Dosage Adjustment +/- (mg)	Time (hrs)	Measured Conc	Regimen	Dosage Adjustment +/- (mg)
1	12.4	2	+383	7	18.3	1	0
2	26.6	3	-411	11	22.5	3	+156
3	16	1	0	6	20.0	1	0
4	26	3	-380	10	17	1	0
5	14.4	2	+282	7	16	1	0
6	13	2	+327	7	16.3	1	0
7	29	3	-615	11	35	4	PT DIED
8	12.8	2	+403	7	16.7	1	0
9	14.0	2	+423	7	19	1	0
10	18	1	0	6	26	3	-196
11*	25	3	-360	9	23	3	-216

Table 8.11.5 Demographic and pharmacokinetic data

Pt no	Time (hrs)	Measured Conc mg/L	Regimen	Dosage Adjustment +/- (mg)	Time (hrs)	Dosage Adjustment +/- (mg)
1	6	15.3	1	-	-	-
2	8	19.9	1	0	6	0
3	-	-	-	-	-	-
4	6	17.1	1	-	-	-
5	6	16	1	-	-	-
6	6	19.3	1	-	-	-
7	PT DIED	PT DIED	-	-	-	-
8	6	15.4	1	-	-	-
9	6	16	1	-	-	-
10	8	17	1	0	STOPPED	-
11*	7	20	1	0	DIED	-

Study stopped once therapeutic and therefore (-)

Table 8.11.6 Demographic and pharmacokinetic data

Pt no	Time to Therapeutic Conc (hours)	Total Vancomycin (mg) till therapeutic	Serum creatinine Cr_s (mmol/L) After 24 hrs	$Cl_{cr} = \frac{(140\text{-age}) \text{ w}}{814 \text{x} Cr_s}$ Creatinine Clearance (CLcr; ml/min) after 24 hrs
1	21	3383	0.054	192.69
2	33	2433	0.474	19.05
3	14	2250	0.038	189.12
4	24	3220	0.102	79.009
5	21	3282	0.045	217.854
6	21	3277	0.035	187.083
7	-	3659	0.257	31.788
8	21	3403	0.035	184.275
9	21	4932	0.063	193.050
10	16	2804	-	-
11*	24	3924	0.085	148.865

(-) Too much Vancomycin was administered and the dosage had to be reduced according to the appropriate regimen.
(+) Too little Vancomycin and a calculated dosage had to be added.
Patient number 7 died whilst on the study.
Patient 10 the study was stopped as the vancomycin vials ran out of stock.
The levels were considered therapeutic if two consecutive therapeutic levels were obtained ranging 15 – 20 mg/L.
Patient 11* was used for the pilot study.

Five patients were female and 6 were male. The mean weight was 76kg.

Two patients were in the therapeutic range, with a creatinine clearance ranging from 173.239 – 239,560 ml/min.

Five patients, with a creatinine clearance range from 130 – 208.6 ml/min, had subtherapeutic Vancomycin levels, and the maintenance dosage was adjusted accordingly.

Four patients' Vancomycin levels were too high, with a creatinine clearance range of 21.3 ml/min – 148 ml/min and the maintenance dosage was adjusted accordingly.

A mean loading dose of 1 000 mg was used to aim for therapeutic levels of 15 – 20 mg/L.

The mean creatinine clearance was 173 ml/min; the mean Vancomycin clearance was 7.3 L/hr. The mean creatinine clearance after 24 hours was 185.679 ml/min.

The mean distribution volume was 50.4 l/kg.

The mean elimination constant was 0.150.

The mean expected concentration after loading was 17.9 mg/L, but the mean measured concentration after loading was 34.9 mg/L.

A mean maintenance dosage of 2 000 mg was started.

The mean expected concentration during the maintenance infusion was 11.5 mg/L and the mean measured concentration after 6 hours of the maintenance infusion was 16.00mg/L.

The mean concentration after the first maintenance dose was 19.0 mg/L; after the second time interval during the maintenance dose it was 17.0 mg/L and after the third time interval during the maintenance dose was 15.0 mg/L.

The mean time to reach therapeutic levels of 15 – 20 mg/L was 21 hours.

The mean total Vancomycin administered to reach therapeutic levels was 3 282mg.

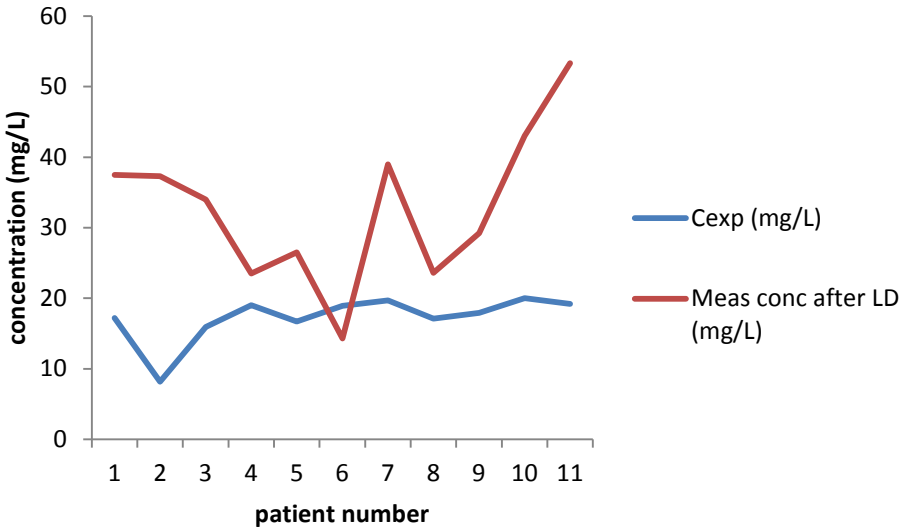


Figure 8: The expected concentration versus measured concentration after the loading dose.
There is a marked difference between the expected and the measured concentration and therefore the Vancomycin concentration is not predictable after a loading dose.

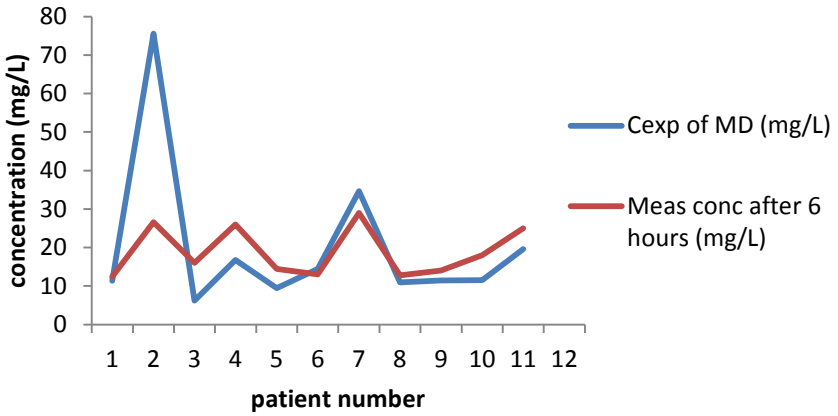


Figure 9: Expected concentration versus measured concentration after 6 hours.
Patient number 2 has a high expected concentration but the measured concentration is far less. If the Vancomycin clearance is low and the distribution volume is large then the half life is longer than expected, and a longer rate of elimination is seen[12], refer to table 8.11.2 and 8.11.3. It is possible to predict the Vancomycin concentration for a maintenance infusion by using the formulas of Rowland and Tozer.

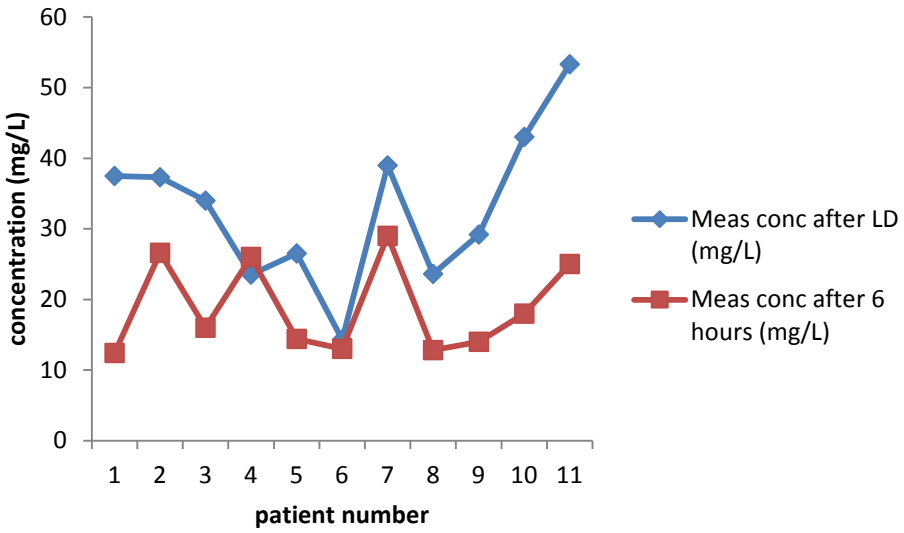


Figure 10: The measured concentration after loading dose versus the measured concentration after 6 hours. Six of the eleven patients remained in the therapeutic range after 6 hours. For patient 7 refer to tables 8.11.1 – 8.11.4. The creatinine clearance in this patient was less than 80 ml/min. The vancomycin clearance was low with a high distribution volume therefore the half life is longer than expected, and a longer rate of elimination is seen[12]. Declining renal function is associated with a marked reduction in the elimination of vancomycin, and dosage adjustment will therefore be required[34,35]. Patient number 11 had a measured concentration of above 50 after loading, (refer to tables 8.11.1 – 8.11.4) and had a slow rate of elimination constant of 0.089 hr^{-1} meaning that less of the drug is eliminated.

9. DISCUSSION

In this study it became evident that the five female patients had a body mass lower than the six male patients and thus had a greater distribution volume for their weight. It is a well known fact that women have greater fat stores than men, which may account for greater volumes of drug distribution[26,27](refer to tables 8.11.1 – 8.11.2). The distribution volume is used to calculate the estimated dosage of a drug to be given in order to achieve a therapeutic plasma concentration, in the case of vancomycin 15 – 20 mg/L. Lipid-soluble drugs penetrate adipose tissue and therefore have a large distribution volume[28]. The distribution volume is also increased in oedema, with sepsis, trauma, pleural effusions, ascites, mediastinitis, fluid therapy or indwelling post-surgical drainage[29]. In order to calculate the estimated distribution volume, 0.72 l/kg was used, the normal distribution volume for vancomycin being 0.4 – 1 l/kg[2]. In our study the loading dose was 15 mg/kg (refer to table 8.11.1) although in another study done by Bergman et al. the distribution volume was used to calculate the loading dose[30]. The equation that was used in this study was: Vd = (0.72 x w), except in patient number 2 (Vd = 0.89 x w). Then the elimination rate constant (Ke) was calculated using equation number 2 (refer to table 8.11.2 and 8.11.3). The elimination rate constant is the rate at which drugs are removed from the body[31]. A mean elimination constant of 0.150 was shown to be the most effective in obtaining therapeutic levels whilst on a constant vancomycin infusion. If the elimination constant was more than 0.150 then the maintenance dosage had to be reduced and vice versa (refer to tables 8.11.2, 8.11.3, 8.11.6).

In a prospective multicentre randomized study by Wysocki, et al. a continuous vancomycin infusion was compared with an intermittent vancomycin infusion; it was demonstrated that target concentrations (20 – 25 mg/l) were achieved faster with a continuous infusion than intermittent infusion (mean 36 versus 51 hours). In his study levels were taken daily and the infusion was adjusted daily by 500mg according to levels[32]. In our study the mean time to therapeutic levels was 21 hours. Levels were

taken according to the appropriate regimen and the dosage was adjusted within 1 hour from receiving the new levels.

In a study done by Murphy et al. seven methods were studied for estimating vancomycin pharmacokinetic parameters that varied widely in predicting vancomycin trough concentrations compared with measured serum concentrations. The conclusion of Murphy's study was that there is no sufficiently reliable formula in predicting trough concentrations and therefore therapeutic monitoring of Vancomycin serum concentrations is advocated[33]. In our study the Matzke method was used to calculate Vancomycin clearance (refer to equation 1[11]). The concentration after the loading- and maintenance dose was predicted using equations 2[25] and 3[12] and the creatinine clearance was calculated with the Cockroft-Gault formula[20]. The formula used was unreliable for the loading dose (refer to figure 8), but reliable for the maintenance dose (refer to figure 9).

According to this study the measured concentration halved within eight hours from administering the loading dose, although the maintenance infusion was started immediately after the loading dose (refer to figure 10). The pharmacokinetic profile is characterised by a 2-3-compartment model. In patients with a normal creatinine clearance the α-distribution phase lasts between 30 minutes and one hour, and the β-elimination half life varies between 6 – 12 hours in the presence of a normal kidney function and may even be as long as 7 days in the anuric patient[2]. The sampling done immediately after completion of the loading dose is not a true reflection of the α-distribution phase because the equilibrium between tissues and blood has not been reached yet. In steady state the equilibrium is reached[36]. According to figure 13, steady state was reached as early as 21 hours in 50 % of the cases; these patients had normal renal function.

Sepsis is a hyperdynamic state[13,29,37], with an increase in cardiac output and the blood flow is redistributed away from high-flow tissue beds[37]. (Refer to figure 11.) This hyperdynamic state can be associated with an increase in the glomerular filtration rate[13,38]. In shock the glomerular filtration rate will be less[38]. During fluid resuscitation in sepsis the extracellular volume expands[38] and therefore vancomycin is

given in dextrose as it distributes through all the compartments[39]. With worsening sepsis extravasation of fluid occurs which leads to a decrease in the serum concentrations[40]. Patients number 1, 5, 6, 8, 9 had sub-therapeutic levels within 8 hours after commencement of the constant vancomycin infusion, which suggests that the sepsis might have worsened and more extravasation of fluid took place (refer to table 8.11.4). This is demonstrated by an increase in the creatinine clearance after 24 hours (refer to tables 8.11.2 and 8.11.6). During sepsis aggressive fluid loadings which are given may lead to dilution of vancomycin and a dosage adjustment is required. In this study all patients were septic and oxidative stress plays a major role in the worsening of organ function.

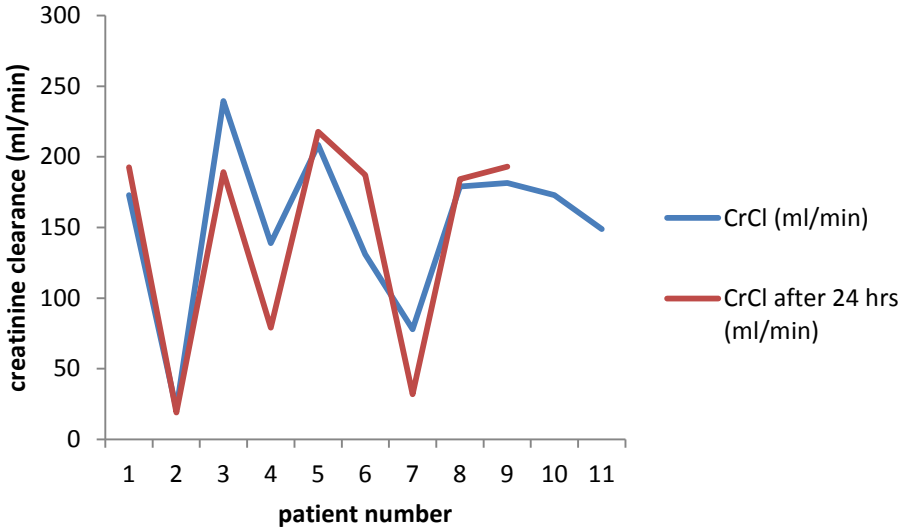


Figure 11: Comparison of creatinine clearance over 24 hours.
Patient numbers 2, 4 and 6 had a creatinine clearance of less than 100 ml/min. Even after 24 hours their creatinine clearance did not deteriorate with more than 50%.
Patients number 4 and 7 had a more than 50% increase in creatinine from the baseline before the start of vancomycin which is suggestive of nephrotoxicity. However a study done by Jeffres et al. discussed the possibility that an increase in vancomycin concentrations was markers of renal toxicity rather than causative factors[42].

Nephrotoxicity is more likely in patients with a trough concentration of 15mg/L or more and those who receive vancomycin for longer than 14 days[41]. Our study period was too short to demonstrate nephrotoxicity and worsened renal function could be attributed to other disease effects.

Unfortunately patient number 7 died and it was uncertain if the renal failure worsened due to the underlying disease process or drugs (refer to figure 11).

A study done by Dailly et al. showed that there was a significant relationship between vancomycin clearance and creatinine clearance for burn patients. This relationship does not exist for all patients, suggesting that renal tubular secretion might be most prominent[43]. (Refer to figure 12, table 8.11.2.)

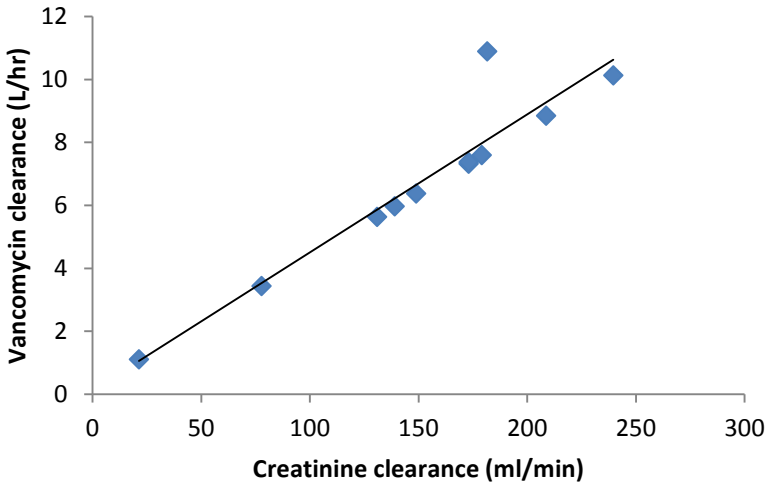


Figure 12: The relationship between Vancomycin clearance and creatinine clearance, estimated by means of the Cockroft and Gault formula. It clearly reflects the correlation between creatinine clearance and Vancomycin clearance, Rotshafer et al. reported that creatinine clearance correlated poorly with Vancomycin clearance and suggested there would be a significant deviation in the creatinine clearance. Declining renal function is associated with a marked reduction in the elimination of vancomycin, and dosage adjustment will therefore be required[34,35]. Thus there is a strong correlation between Vancomycin clearance and creatinine clearance as seen in the graph.

As there is a strong linear correlation between vancomycin clearance and creatinine clearance in patients with impaired renal function, it is possible to calculate the daily dose of vancomycin[35]. The formula used in our study was

Clcr = 140-age(w) / 814xCr_s. Clvc = (Clcr x 0.689) + 3.66 then multiply by 60 and divide by 1000. This showed that there is a linear correlation for renal impaired as well as non renal impaired patients, and this correlates with a study done by Kees et al.[44]. This allows for the correct estimation of the Vancomycin dosages needed to reach therapeutic drug levels. For patients number 2 and 7 it is clear that the lower the elimination rate of vancomycin the lower the vancomycin clearance, (refer to table 8.11.2) and this reflects a linear correlation (refer to figure 12). A higher vancomycin clearance can be attributed to drugs that improve the cardiac output and the renal blood flow[45]; this is clearly reflected in figure 12. The linear correlation still exists for

an increase in the vancomycin clearance and the creatinine clearance and the correct vancomycin dosage can still be calculated.

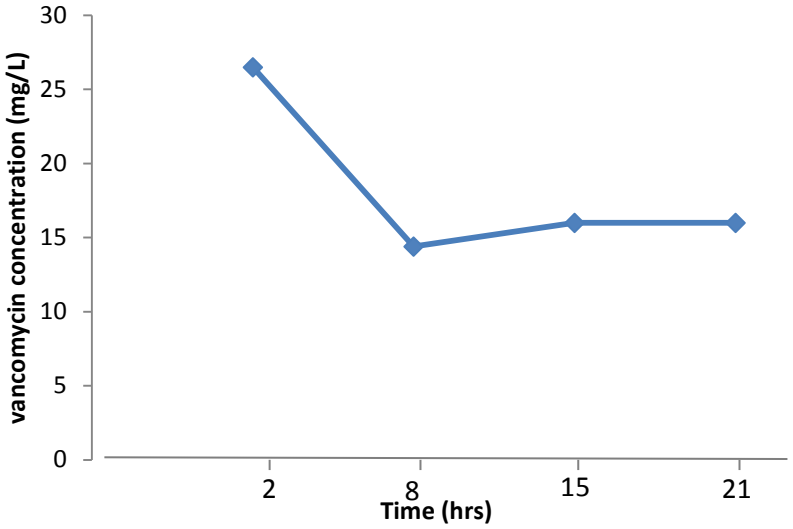


Figure 13: Graph reflecting Vancomycin concentration level (until therapeutic level of 15 – 20mg/L). Data of patient number 5, refer to tables 8.11.1 – 8.11.6, illustrating the plateau concentration 21 hours from commencement of the infusion. According to this graph it is possible to maintain a therapeutic plateau level of 15 – 20 mg/L.

In a study done by Craig it was shown that the concentrations in serum are much better predictors of interstitial fluid levels than are tissue homogenate concentrations. Tissue homogenate concentrations might be under- or over estimated[40]. In our study serum levels were taken.

There is considerable debate on when to measure vancomycin concentrations[46].
From figure 13 it is evident that levels can be measured 21 hours after commencement of the continuous vancomycin infusion and this should be in the therapeutic range if the renal function is normal, in about 50% of cases. Measuring peak concentrations after the loading dose should be avoided as these levels are most variable and the curve of the slope is greatest[46]. Vancomycin is a hydrophilic antibiotic, with frequent plasma concentration variations that need dosage adjustment on a daily basis, as the renal function varies daily[29] (refer to table 8.11.3 – 8.11.6). More regular measured plasma concentrations are advisable for patients with renal function impairment and the dosage should be adjusted accordingly. A proposed interval would be 6 hours. A therapeutic steady state can be achieved with a continuous vancomycin infusion. This implies that the concentration is 4 to 5 times the MIC and is of great benefit to the patient.

No adverse effects were noticed during the study.

10. CONCLUSION

Vancomycin is a well known antibiotic for the use of severe life-threatening gram positive infections.

Our study was based on a bolus dose vancomycin of 15mg/kg in 200ml 5% dextrose water over a 2 hour period, followed by a calculated maintenance dose of 30 mg/kg in 200ml 5% dextrose water until therapeutic levels of 15 – 20 mg/L were obtained.

In 50% of cases the therapeutic level was reached within 21 hours. However in the other 50% of patients therapeutic levels were reached within 33 hours.

The dosage adjustment was based on the distribution volume. The distribution volume of 0,72 l/kg was used when the creatinine clearance was above 60 ml/min. When the creatinine clearance was less than 60 ml/min but still above 10 ml/min then the distribution volume of 0,89 l/kg was used and 0,9 l/kg upon being less than 10 ml/min. Consequently a continuous infusion of vancomycin is efficacious in order to maintain a therapeutic level of 15 – 20 mg/L, which is 4 to 5 times above the MIC.

As a result of the study we have developed a protocol to be used in our ICU to manage vancomycin infusions and levels. For this protocol refer to appendix H.

Limitations

1. Due to strict inclusion criteria not all patients that were started empirically on Vancomycin were included in the study.
2. Time from sample drawn at Pelonomi Hospital to analysis was unreliable and therefore a single centre study was conducted at Universitas Hospital.
3. A small number of patients were used for the study. A multicentre prospective analytical study should be conducted.
4. The time it took to finish the study was prolonged due to various practical problems.
5. To obtain therapeutic levels the actual body weight must be used. Currently there is no perfect system in place in our hospital to measure the actual body weight of a patient whilst in the intensive care unit.

6. Estimation of the creatinine clearance using the Cockroft-Gault are validated in stable outpatients. The estimation of glomerular filtration in acute settings is very difficult. Therefore it is difficult to interpret in the critically ill patient.

Acknowledgements

A heartfelt thanks to Professor A Walubo for assistance in compiling the formulae.

A heartfelt thanks to Dr J du Plessis for assistance in laboratory analysis.

APPENDIX A

Pharmacokinetic parameter prediction methods

1. Vd = Dose/concentration[20] in litre per kilogram (l/kg)

2. Cockroft-Gault[20] (140 – age) x [IBW/72 x P_{Cr}]
   In females: IBW x 0,85

3. Matzke method: Cl_{vanco} (ml/min) = (CrCl x 0,689) + 3,66; Vd = 0,72 l/kg if CrCl is > 60 ml/min; Vd = 0,89 l/kg if CrCl is 10-60 ml/min; Vd = 0,9 l/kg if CrCl < 10 ml/min[11].

4. IBW is calculated using the formula of Devine[23]
   IBW (males) = 50 kg + 2,3(height[inch] – 60 kg)
   IBW (females) = 45,5 kg + 2,3(height[inch] – 60 kg)
   1 inch = 2,54 cm

5. CrCl = U_{Cr} x V/P_{Cr}[20]
   U = Urine Creatinine
   V = Volume
   P_{Cr} = Plasma Creatinine

6. Jacobson formula for body surface area (BSA)[23].
   BSA (m^2) = length (m^2) = mass (kg) – 60/100
   m^2 = Square metre

7. Body Mass Index (BMI) = Mass (kg) / (length in metre)^2.

APPENDIX B

Information Guide

Therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients.

To whom it may concern

We, the Department of Critical Care are doing research on therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients. Research is the process of learning the answer to a question. In this study we want to prove that it is possible to obtain therapeutic drug levels of vancomycin infusion in the critically ill patient within twenty four hours of commencement. An infusion is an induction of a solution of vancomycin in dextrose, administered in a vein.
Therapeutic is a practical branch of medicine concerned with the treatment of a disease.

We are asking you to participate in a research study or asking your permission to include your family member in a research study. This study will be conducted in the Multidisciplinary Intensive Care Unit at Universitas Hospital Bloemfontein.

What is involved in the study: You or your family member will receive a vancomycin infusion with regular blood sampling for vancomycin levels to be taken. This study will only be done till therapeutic levels are obtained within 24 – 48 hours. You/relative will be one of ten patients meeting the inclusion criteria will partake in this study.

Inclusion criteria: All critically ill patients with life threatening infections caused by the following micro organisms - Methicillin resistant Staphylococcus aureus), Coagulase Negative Staphylococcus (CoNS) and enterococci.

Benefits: Partaking in this study will assure that you/relative/other patients will be treated successfully.

Study design: A prospective analytical study.

Method: According to weight a bolus dose (15 mg/kg) will be administered over a period of two hours. Blood sampling will be done immediately after cessation of the bolus infusion. Not more than 5ml of blood will be taken per sample. A continuous infusion (30 mg/kg Vancomycin) will be commenced immediately after cessation of the bolus infusion. The continuous infusion will be started at a rate of 8 ml/hr. Depending on the level obtained one of four regimens will be used. Blood sampling will then be done every six hours till the desired level (15 – 20 mg/L) is reached. As soon as the desired level is reached blood sampling will be done on a daily basis, whilst on the continuous infusion.

Risks If adverse events should arise immediate cessation of the infusion will be done.

Adverse effects include the following: Hypotension, ototoxicity (if the level is above 40mg/l), neurotoxicity, peripheral thrombophlebitis, flushing due to vasodilatation and a skin rash.

Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled: the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality can not be guaranteed. Personal information may be disclosed if required by law. Organisations that may inspect and / or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee, for Medical Research and the Medicines Control Council (where appropriate).

If results are published, this may lead to individual / cohort identification.

Contact details of researcher – for further information / reporting of study related adverse events: Dr T van den Heever, Department Critical Care UFS, telephone number 051 405 3314.

Contact detail of REC Secretariat and Chair of the Ethics Committee of the Faculty of Health Sciences, UFS – for reporting of complaints / problems: (051) 405 2812.

APPENDIX C
Informed consent by patient or family member

You have been asked to participate in a research study.

You have been informed about the study by Dr T van den Heever.

You may contact Dr T van den Heever at 051 405 3314 any time if you have a question about the research or if you are injured as a result of the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 405 2812 if you have questions about your rights as a research subject.

Your participation in the research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____	_____
Signature of Participant	Date
_____	_____
Signature of witness	Date
_____	_____
Signature of translator (Where applicable)	Date

APPENDIX D

Informed consent to be used if family members or patient unable to give consent

HJ 117

CONSENT FOR SURGERY, ANAESTHESIA AND OTHER MEDICAL SERVICES

Patient details (or pre-printed label)

Patient Sticker

Patient's Name ..... Gender ..... Age .....

Institution ..... Ward ..... Number (or other identifier) .....

TO BE COMPLETED BY PATIENT / MANDATE

Date ..... Time ..... AM/PM

1. I consent to the performance upon .....
(Myself or Name of Patient)

For the following surgery or other medical procedure/investigation/treatment .....
(State Nature and Extent of Operation/procedure/investigation/treatment)

I understand that this surgery or other procedure is to performed under the direction of Dr .....

2. I understand that during the course of the surgery or other procedure the Doctor named in paragraph 1. or his her associates may consider it necessary or advisable to perform procedures or to render medical treatment in addition to that named in paragraph 1. because of conditions which may not be presently forseeable. I therefore consent to performances of such additioal surgery or treatments and procedures as are deemed necessary or advisable.
3. I consent to the administration of such anaesthetic as may be considered necessary or advisable by the person authorised to administer anaesthesia (cross out if anaesthesia is not to be used)
4. I consent that tissue or parts of my body removed at surgery, body fluids, x-ray films, and other materials, as well as medical information concerning me may be used in teaching and training.
5. The nature and purpose of the surgery, treatment or procedure and the reasonable (1) alternative methods of treatment, (2) risks, (3) benefits, (4) possible uotcomes, (5) possibility of complications, (6) consequences of not consenting (6) the knowledge that I may withdraw consent at any time have been fully explained to me. **No guarantee or assurance has been given by anyone as to the results that may be obtained.**
6. I have read and understand the above authorisation and the reasons why the surgery, treatment, or procedure is necessary.
7. I agree to the presence of the appropriate health trainee observers during my procedure/operation/treatment for the advancement of medical education and care.

Iunderstand the contents of this consent.

Signed at ..... on ..... day ..... 20 .....

....
Name of person giving consent in print Signature of person giving consent

☐ Patient/Mandate ☐ Spouse ☐ Common Law Partner ☐ Parent Witness .....

☐ Grand Parent ☐ Guardian ☐ Adult child ☐ Sister ☐ Brother .....
Print Name

Reason for signing in representative capacity

.....

AFFIRMATION OF INFORMED CONCENT BY RESPONSIBLE HEALTH CARE PROFESSIONAL

I ..... have informed the above named patient or the person authorised to extend consent on the patient's behalf of the medical surgical treatment and/or the further diagnostic procedures referred to above. I have explained, consistent with accepted medical judgement, the nature and purpose of the treatment or procedures, the reasonable (1) alternative methods of treatment, (2) risks, (3) benefits, (4) possible outcomes, (5) possibility of complications, (6) consequances of not consenting (6) and the knowledge that the consent may be withdrawn at any time.

Dr. ..... Name in Print .....
(Responsible Health Care Practitioner)

Date ..... Time .....

AFFIRMATION BY RESPONSIBLE MEDICAL PRACTITIONER PROVIDING ANAESTHESIA

I ..... have informed the above named patient or the person authorised to extend consent on the patient's behalf, of the anaesthesia proposed for the procedures referred above. I have explained, consistent with medical judgement, the nature and purposes of the anaesthesia, the reasonable (1) alternative anaesthetic methods, (2) risks, (3) benefits, (4) possible outcomes, (5) possibility of complications, (6) consequences of not consenting (6) and the knowledge that the consent may be withdrawn at any time. In addition, I have explained that the anaesthetic which is proposed to be used is a ..... anaesthetic but that a alternative form of the anaesthesia may be used if required by unexpected conditions arising before or during the procedure.

Dr. ..... Name in Print .....
(Anaesthetist)

Date ..... Time .....

TELEPHONIC CONSENT

Telephonic consent was obtained from .....

☐ Mandate ☐ Spouse ☐ Common Law Partner ☐ Parent Witness .....

☐ Grand Parent ☐ Guardian ☐ Adult Child ☐ Sister ☐ Brother .....
Name in Print

....
Physician/Social Worker Name in Print Date

DECLARATION BY SOCIAL WORKER IF CONSENT IS NOT AVAILABLE

Telephonic consent could not be obtained from .....

CONSENT BY THE HEAD OF CLINICAL SERVICES / CLINICAL MANAGER ON CALL / HEAD OF HEALTH ESTABLISHMENT

Considering that this is an emergency treatment /

Irreparable damage can result if not attended to and:

☐ Patient's age less than 14 years (medical) or 18 years (surgical) if parents / guardian not available

☐ According to the Children's Amendment Act (43 of 1976 art 8A)

☐ According to the Mental Health Act (Act 17 0f 2002)

☐ Patient /mandate uable to give consent for the above procedure

I hereby give consent to this procedure

..... Name in Print .....
Head of Clinical Services / Clinical Manager on Call

If telefonically discussed, Ihereby give consent to this procedure*

I, Dr ..... Date ..... Time .....

Discussed the case and obtained consent from Dr. ..... Witness .....

Name in Print .....

NB! Before presenting a case to the Head of Clinical Services / Clinical Manager on Call, documented attempts must have been made to trace relatives or the social worker must have bee employed to trace family

* Must be signed by Head of Clinical Services / Clinical Manager on Call as soon as possible

STATEMENT OF INTERPRETER (WHERE APPROPRIATE)

I have interpreted the information above to the patient to the best of my ability and in a way I believe he/she can understand

Signed ..... Date .....

Name in Print ..... Job Title .....

INFORMED REFUSAL

I hereby refuse to give consent for the following surgery or other medical procedure/investigation/treatment .....

.....
(State Nature and Extend of Operation/procedure/investigation/treatment)

The nature and purpose of the surgery, treatment or procedure and the reasonable (1) alternative methods of treatment, (2) risks, (3) benefits, (4) possible outcomes, (5) possibility of complications, (6) consequences of not consenting have been fully explained to me.

Signed at ..... on day of ..... 20.....

....
Name of person refusing consent in Print Signature of person refusing consent

☐ Patient/Mandate ☐ Spouse ☐ Common Law Partner ☐ Parent Witness .....

☐ Grand Parent ☐ Guardian ☐ Adult child ☐ Sister ☐ Brother .....
Print Name

Reason for signing in representative capacity

APPENDIX E
Correspondence

January 2010

Dr N R J van Zyl
CEO: Universitas Hospital
Bloemfontein 9300

Dear Dr van Zyl

Re: Therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients

I would like to apply for approval of the above project (protocol available if requested) and provide the following details for your perusal:

1. I am the chief researcher for this project.
2. This is a study to evaluate therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients.
3. This study will take place within the domain of critical care and related diagnostic departments.
4. Ten patients will be included in the study.
5. Consent will be obtained from family members / patient / or CEO if no family are available.
6. Personal information will be kept confidential.
7. Duration is estimated at six months to a year.
8. The results will be published and presented.
9. There is no additional cost to either patient or the hospital.

Regards

…….
Dr Théa van den Heever
Department Critical Care
University of the Free State
Cellphone no: 082 77 55 723

health
Department of
Health
FREE STATE PROVINCE

Ref. no.: 13/2

15 December 2009

Dr T van den Heever
Department Critical Care
Universitas Academic Hospital

Dear Dr van den Heever

RESEARCH PROJECTS: THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

Herewith permission for the mentioned project to be done at Universitas Academic Hospital on condition that approval is obtained from the Ethics Committee.

The Chief Executive officer must be notified if the findings of the project will be published.

Yours sincerely

DR NIC R J VAN ZYL
HEAD: CLINICALSERVICES
UNIVERSITAS ACADEMIC HOSPITAL

DR NRJ VAN ZYL
2009 -12- 15
HEAD: CLINICAL SERVICES
UNIVERSITAS ACADEMIC HOSPITAL

HEAD: CLINICAL SERVICES: DR NRJ VAN ZYL
Private Bag X20660, Bloemfontein, 9300. Tel. No.: 051-4052866,
Fax: 051-4053500, Room 1077, First Floor, Universitas Academic Hospital
E-mail: vanzylnr@fshealth.gov.za

APPENDIX F
Laboratory consent

January 2010

Professor Walubo
Head Pharmacology Department
Bloemfontein
9300

Dear Professor Walubo

Re: Therapeutic drug monitoring for continuous infusion of vancomycin in critically ill patients.

I would like to apply for approval of the above mentioned project, (protocol attached), which we would like to do with the help of your laboratory.

The following details are for your perusal

1) I am the chief researcher for this project.

2) This study is to test a feasible regimen, for adjusting maintenance of vancomycin infusion in the critically ill patient in order to reach therapeutic vancomycin levels (18-20 mg/L) after commencement.

3) This study will take place within the domain of critical care.

4) Ten patients meeting the inclusion criteria (protocol – page 18) will be used.

5) Vancomycin levels will be taken as stipulated in the protocol (pages 19 - 21).

6) The duration of the study is estimated over a period of six months to a year.

7) Consent will be obtained from the patient, family members or CEO of Universitas Hospital prior to commencing the study.

8) All results will be kept confidential as far as possible.

9) The results will be published and presented.

10) There is no additional cost to either the patient or the hospital.

Regards

……..
Dr Théa van den Heever
Department Critical Care

University of the Free State
Cellphone no: 082 77 55 723

Date: Fri, 8 Jan 2010 13:20:18 +0200
From: waluboa@ufs.ac.za
To: tornatios@hotmail.com
CC: gnfmjbdp@ufs.ac.za
Subject: Re: letter

Dear Thea,
I have seen you protocol.
If you got permission from the director of clinical services, then you are free to start with pharmacology. Please organize with Dr. du Plessis.

Regards

Prof. Walubo
Head, Pharmacology

APPENDIX G
Consent from Ethics Committee

04/01/2011

EXTENSION OF ETHICAL APPROVAL

ETOVS NR 09/2010
Re: THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

I hereby wish to apply for extension of the above research project for the following study year. Due to a lack of patients qualifying for the study the project is taking longer than expected.

Kind regards

Dr Thea van den Heever
Department Critical Care
University of the Free State
Bloemfontein
Cell: 082 775 5723
E-mail: theavdheever@gmail.com

UNIVERSITEIT VAN DIE VRYSTAAT
UNIVERSITY OF THE FREE STATE
YUNIVESITHI YA FREISTATA

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences

Research Division
Internal Post Box G40
☎(051) 4052812
Fax (051) 4444359

E-mail address: StraussHS.md@ufs.ac.za

Ms H Strauss

2010-02-12

DR T VAN DEN HEEVER
DEPARTMENT OF CRITICAL CARE
FACULTY OF HEALTH SCIENCES
UFS

REC Reference number: REC-230408-011

Dear Dr Van den Heever

ETOVS NR 09/2010
PROJECT TITLE: THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

- You are hereby kindly informed that the Ethics Committee approved the above study at the meeting held on 09 February 2010.
- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
- The Committee must be informed of any serious adverse event and/or termination of the study.
- A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.
- Kindly refer to the ETOVS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

.....
CHAIR: ETHICS COMMITTEE

339, Bloemfontein 9300,RSA ☎ (051) 405 2812 StraussHS.md@ufs.ac.za
Republiek van Suid-Afrika / Republic of South Africa

UNIVERSITEIT VAN DIE VRYSTAAT
UNIVERSITY OF THE FREE STATE
YUNIVESITHI YA FREISTATA

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences

Research Division
Internal Post Box G40
☎(051) 4052812
Fax (051) 4444359

E-mail address: StraussHS@ufs.ac.za

Ms H Strauss

2011-01-27

DR T VAN DEN HEEVER
DEPT OF CRITICAL CARE
FACULTY OF HEALTH SCIENCES
UFS

REC Reference number: REC-230408-011

Dear Dr van den Heever

ETOVS NR 09/2010
PROJECT TITLE: THERAPEUTIC DRUG MONITORING FOR CONTINUOUS INFUSION OF VANCOMYCIN IN CRITICALLY ILL PATIENTS

- You are hereby kindly informed that the Ethics Committee approved the following at the meeting held on 25 January 2011:
  - ***Extension of the study for a year.***
- Committee guidance documents: Declaration of Helsinki, ICH, GCP and MRC Guidelines on Bio Medical Research. Clinical Trial Guidelines 2000 Department of Health RSA; Ethics in Health Research: Principles Structure and Processes Department of Health RSA 2004; Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, Second Edition (2006); the Constitution of the Ethics Committee of the Faculty of Health Sciences and the Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines.
- Kindly refer to the ETOVS reference number in correspondence to the Ethics Committee secretariat.

Yours faithfully

.....
CHAIR: ETHICS COMMITTEE

APPENDIX H
Proposed protocol for Vancomycin continuous infusion

1. Obtain the following:

- Age
- Actual body weight (w)
- Serum creatinine (Cr_s)
- Loading dose of vancomycin (15 mg/kg) over 2 hrs in 200ml 5% D/W.
- Infusion rate after loading dose (dosing rate)[Ro] = (Dose/2 hrs) mg/hr
- Maintenance dose = 30mg/kg in 200ml 5% D/W start at 8ml/hr.
- Infusion rate for the maintenance dose [Ro-inf] = (Dose/24 hr) mg/hr

2. Draw Vancomycin sample from the A-line at 06:00 in a green top tube.

3. Adjust the vancomycin dosage on receiving the levels according to number 4, 5 if the levels are not in therapeutic range (18 – 20 mg/L).

4. **Calculate the Creatinine Clearance using the Cockroft-Gault formula**

CrCl = (140 – age) x (IBW)(0.85 in females) / 72 x P_{CR}

5. Calculate the distribution volume using the appropriate value for the calculated creatinine clearance:

Vd = weight x V

V = 0,72 l/kg if CrCl > 60 ml/min

V = 0,89 l/kg if CrCl 10 – 60 ml/min

V = 0,9 l/kg if CrCl < 10 ml/min

6. Aim of the levels is 18 – 20 mg/L
7. Use regimen 1 if the level is therapeutic
8. Use regimen 2 if the level is less than 18 – 20 mg/L
9. Use regimen 3 if the level is 21 – 30 mg/L.
10. If level is above 31 mg/L stop the infusion and draw levels on a daily basis (06:00) and adjust the vancomycin dosage accordingly.

REGIMEN I

Use Regimen I if measured concentration (Cm) is within the expected range (18-20 mg/L).

- Continue with the MD dose infusion and there is no need to adjust LD.

Draw blood at 06:00 and adjust according to the appropriate regimen.

REGIMEN II

Use regimen II only if the measured concentration (Cm) is less than 18 mg/L (i.e., < Cexp or Css).

ii) If measured concentration is less than Css or expected concentration, e.g., 15 mg/L instead of 20 mg/L.

- Then add dose of: (20-15) x Vd (the old Vd of 0.72 L/kg x w)
- Then Dose to add is: 5 mg x Vd

ii) Administer the deficit over 1 hour in an infusion.

iii) Continue with original maintenance dose**:**

iv) Check concentration (Css) the following morning at 06:00. It is expected that this will be within the required range. If the concentration is not within the required range then repeat regimen II.

v) Adjust maintenance dose for the next 24 hours with the adjusted dosage.

EXAMPLE:
If the level is 15mg/L in a normal 70kg patient with a Vd of 0.72 L/kg then:
70 x 0.72 = 50.4 L/kg.
50.4 x 5 (deficit per kg) = 252 mg/24 hrs.
Add 250 mg Vancomycin. If the solution contains 2 000mg then the Rate of infusion over a 24 hour period is 83,3 mg/hr. The solution contains 10mg Vancomycin / ml. Increase the infusion with 25 ml extra. Remember to add this to the 8 ml. Increase this infusion to 33 ml for 1 hour then continue at 8 ml/hr. In next vancomycin infusion add an extra 250 mg and keep infusion at 8 ml per hour.

REGIMEN III

Use regimen III only if the measured concentration (Cm) is 21 - 30 mg/L (i.e., higher than Cexp or Css).

i) If measured concentration is, e.g., 25 mg/L instead of 20 mg/L (Css or Cexp).

- Calculate excess L-Dose as: (25 - 20) x Vd (the old Vd of 0.72L/kg x w)
- The excess L-Dose is: 5 mg x Vd

ii) Determine how long to interrupt the infusion.

- (Excess L-dose/rate of MD infusion) = hours for stopping the infusion.

iii) Continue with **Maintenance dose after the above time.**

iv). It is expected that this will be within the required range. If the concentration is not within the expected range then repeat regimen III.

EXAMPLE:

If the level is 25mg/L. If the patient weighs 70kg and the Creatinine clearance is within normal range then calculate the distribution volume.
Vd = 70 x 0.72 = 50.4 l/kg.
The excess dosage: 50.4 x 5 = 252 mg.
Calculate the Rate of infusion if the bag contains 2 000 mg = 83 mg/hr. The dosage is 10 mg/ml.
Now calculate the time needed to stop the infusion (excess loading dose/ rate of infusion).
252/83.3 = 3 hours. To convert to minutes multiply by 60 = 180 min.
Stop the infusion for 180 minutes then continue at 8 ml per hour.
Remember when mixing the new solution to subtract 252 mg from the maintenance. Continue at 8 ml/hour.
Take the next sample at 06:00 and adjust accordingly.

REMEMBER TO ADJUST THE MAINTENANCE DOSAGE ON A DAILY BASIS TO ENSURE CORRECT TREATMENT

REFERENCES

1. Mark P. Wilhelm, Lynn Estes. Vancomycin. Symposium on antimicrobial agents – part xii Mayo Clin Proc 1999: 74: 928-935.
2. Rybak MJ. The pharmacokinetic and pahrmacodynamic properties of vancomycin. CID 2006: 42 (Suppl 1): S35-S39.
3. Cunha BA, Mohan SS, Hamid N, McDermott BP, Daniels P. Cost-ineffectiveness of serum vancomycin levels. European journal of clinical microbiology infectious disease. 2007: (26): 509-511.
4. Cunha BA. Vancomycin revisited: A reappraisal of clinical use. Critical care Clinics.2008: (24): 393 – 420
5. Guidelines issued for monitoring of vancomycin treatment in *S aureus* infection: Available from: http://www.medscape.com/viewarticle/706367. As cited on 26/07/2009.
6. Pea F, Viale P. Should the currently recommended twice-daily dosing still be considered the most appropriate regime for treating MRSA ventilator-associated pneumoniae with vancomycin. Clinical pharmacokinetics. 2008: 47 (3): 147-152.
7. Courvalin P. Vancomycin resistance in gram-positive cocci. CID 2006: 42 (Suppl 1): S25-S34.
8. Levine DP. Vancomycin: A history. CID 2006: 42 (Suppl 1): S5-S12.
9. Fernández Maria del Mar, et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Medicine. 2007: (33): 279-285.
10. A PK/PD approach to antibiotic therapy: Available from http://www.rxkinetics.com/antibiotic_pk_pd.html as cited on 04/08/2009.
11. Murphy JE, Gillepsie DE, Bateman C. Predictability of vancomycin trough concentrations using seven approaches for estimating pharmacokinetic parameters. American journal health system pharmacology. 2006; 63 (23): 2365-2370. Available from: http://www.medscape.com/viewarticle/549091.
12. M Rowland, T.N, Tozer. Clinical pharmacokinetics concepts and applications. Third edition. Willin and Wilkins. 1995: 21, 23, 24, 78, 114-116, 137-155, 179, 299, 301, 323.
13. Boucher BA, Wood CG, Swanson JM. Pharmacokinetic changes in critical illness. Critical care clinics 22. Elsevier Saunders. 2006: 255 – 271.

14. Morgan GE, Mukhail MS, Murray MJ. Clinical Anaestehsiology. Fourth edition McGraww Hill. 2006: 233, 693.
15. Amari EBE, Vuagnat A, Stern R, Assal M, Denormandie P, Hoffmeyer P, et al. High versus standard dose vancomycin for osteomyelitis. Scandanavian journal of infectious disease. 2004: 36: 712-717.
16. Stevens DL. The role of vancomycin in the treatment paradigm. CID 2006: 42 (Suppl 1): S51-S57.
17. Rybak M, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-system pharmacists, the infectious disease society of America, and the society of infectious diseases pharmacists. American journal Health-system Pharm. 2009: 66: 82-98.
18. Hardman Joel G, et al. Goodman and Gilman's The pharmacological basis of therapeutics. Ninth edition McGraww Hill. 1996: 26.
19. Stockley IH, Sweetman SC. Stockley's drug interactions. Eighth edition Pharmaceutical Press. 2008: 127, 291, 351, 377, 645, 809, 832, 943, 1080.
20. Krishan V, Murray P. Pharmacological issues in the critically ill. Clinics in chest medicine 24. Elsevier Saunders. 2003: 671 – 688.
21. Healy DP, et al. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. Antimicrobial agents and chemotherapy. 1987: March: 393-397.
22. Rowland M and Tozer T. (Ed). Chapter 6, constant-rate regimens. In: Clinical Pharmacokinetics, concepts and applications. Third edition. 1995. William and Wilkins.
23. Marino PL. The icu book. Third edition; Lippincott Williams and Wilkins. 2006: 994.
24. Watanakunakorn C, Guerriero JC. Interaction between Vancomycin and Rifampin against Staphylococcus aureus. Antimicrobial agents and Chemotherapy. June 1982: 1089-1091.
25. Bauer LA. Applied clinical pharmacokinetics. New York: McGraw Hill, Medical publishing division. 2001: 180 – 261.
26. Whitley HP, Lindsey W. Sex-based differences in drug activity. American family Physician. 2009: December 1, volume 80, number 11: 1254 – 1258.

27. Schwartz, JB. The influence of sex on pharmacokinetics. Clinical Pharmacokinetics. 2003: 42(2): 107-121.
28. Brenner. Brenner and Rector's the kidney, eighth edition. Available from http://www.mdconsult.com/books/page.do?sid=1150352940&eid=4-ul.0-B978-1- 416. As cited on 24/04/2011.
29. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients. A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clinical pharmacokinetics. 2005: 44(10): 1009-1034.
30. Bergman S, Speil C, Short M, Koirala J. Pharmacokinetic and pharmacodynamic aspects of antibiotic use in high-risk populations. Infectious disease clinics of North America. 2007: (21): 821-846.
31. Hermsen ED. Pharmacokinetic training packet for pharmacists. The Nebraska medical centre. Available from http://www.nebraskamed.com/careers/education/asp/pdfs/pk_trainingpacked.pdf As cited on 13-04-2011.
32. Wysocki M, et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: Prospective multicenter randomized study. Antimicrobial agents and chemotherapy. 2001: September: 2460 – 2467.
33. Murphy J, Gillespie DE, Bateman CV. Predictability of vancomycin through concentrations using seven approaches for estimating pharmacokinetic parameters. American Journal Health-System Pharmacists. 2006: December: 63(23): 2365-2370.
34. Matzke GR, McGory RW, Hastenson E, Keane WF. Pharmacokinetics of Vancomycin in patients with various degrees of renal function. Antimicrobial agents and Chemotherapy. 1984 April: 433-437.
35. Rodvold KA, Blum RA, Fischer JH, Zokufa HZ, Rotschafer JC, Kent B, Crossley, Riff LJ. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrobial agents and Chemotherapy. 1988: June: 848-852.
36. Pharmacokinetic modelling. Available from: http://www.rxkinetics.com/pktutorial/1_5.html . As cited on 29/04/2011.
37. Hofer JE, Nunnally ME. Taking the septic patient to the operating room. Anesthesiology clinics. 2010: (28): 13-24.
38. Kumar A. Optimizing antimicrobial therapy in sepsis and septic shock. Critical care clinics. 2009: (25): 733 – 751.

39. Infusion of is-osmolar fluids. Available from http://www.anaesthesiamcq.com/fluidbook/fl8_1.php. As cited on 25/04/2011.
40. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for Antibacterial dosing of mice and men. Clinical infectious diseases. 1998: 26: 1-12.
41. Hazlewood KA, Brouse SD, Pitcher WD, Hall RG. Vancomycin-associated nephortoxicity: Grave concern or death by character assassination? The American journal of medicine. 2010: (123), 182.el- 182.e7
42. Jeffres MN, Isakow W, Joshua A, Doherty BS, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. Clinical therapeutics. 2007: volume 29, number 6: 1107-1114.
43. Dailly E, Le Floch R. Deslandes G, Pannier M, Jolliet P. Influence of glomerular filtration rate on the clearance of vancomycin administered by continuous infusion in burn patients. International Journal of Antimicrobial Agents; 2008: (31): 537-539.
44. Kees M. et al. Clearance of vancomycin during continuous infusion in intensive care unit patients: correlation with measured and estimated creatinine clearance and serum cystatin C. International journal of antimicrobial agents. 2010/07/15.
45. Llopis-Salvia P, Jiménez-Torres NV. Population pharmacokinetic parameters of vancomycin in critically ill patients. Journal of clinical pharmacy and therapeutics. 2006: (31): 447-454.
46. Healy DP, et al. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. Antimicrobial agents and chemotherapy: 1987: March: 393-397.
47. Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance. Clinical pharmacology and therapeutics. 2002: (71): 115-121.

DEFINITIONS

Active transport – The transport of substance against their electrical and chemical gradients by carriers.

Actual body weight – The measured body weight during time of examination, expressed in kilogram.

Adjusted body weight – A weight adjustment is generally thought necessary only if the weight of an individual differs by more than 30% from the average adult weight (70 kg). Adjustments are therefore made if the patient is petite, emaciated, or obese.

Amino acid – An organic acid in which one of the hydrogen atoms on a carbon atom has been replaced by NH_2.

Antibody – An immunoglobulin molecule produced by B lymphoid cells with a specific amino acid sequence.

Antigen – Any substance that, as a result of coming in contact with appropriate cells, induces a state of sensitivity and/or immune responsiveness after a latent period (days to weeks) and that reacts in demonstrable way with antibodies and/or immune cells of the sensitized subject in vivo or in vitro.

Area under the serum concentration-time curve – A plot of concentration against time after drug administration. Usually a trapezoid shape with the area given by the product of average concentration and time interval.

Atom – The smallest part of a chemical element, consisting of a positively charged nucleus (containing protons and typically also neutrons) surrounded by a negatively charged electrons.

Authorisation – Giving permission to the investigator to partake in the study.

Bacteraemia – The presence of viable bacteria in the circulating blood as a result of infection.

Bactericidal – Causing the death of bacteria by an antibiotic.

Bacteriostatic – The inhibition of the multiplication of bacterial by antibiotics.

Biofilm – The accumulation of micro-organisms and their extracellular products, forming a structured community on a surface.

Blood – The "circulating tissue" of the body. The fluid and its suspended formed elements that are circulated through the heart, arteries, capillaries and veins. Blood is the means by which oxygen and nutritive materials are transported to the tissues and carbon dioxide and various metabolic products are removed for excretion. It consists of pale yellow or gray-yellow fluid, plasma, in which are suspended red blood cells (erythrocytes), white blood cells (leukocytes) and platelets.

Blood pH – pH of arterial blood, normal is 7.4 (normal range 7.36 – 7.44).

Blood pressure – The fluctuation in the arterial pressure in the systemic circulation. This differs with each heartbeat. The maximum value is the systolic pressure during cardiac systole and the minimum value is the diastolic pressure during cardiac diastole. The mean is known as the mean arterial pressure and the difference is the pulse pressure.

Body mass index – An approximate measure of whether someone is over- or underweight. The body weight in kilograms, divided by the square length in metre.

< 20 = underweight
20 – 25 = optimal weight
25 – 30 = over weight
30 – 40 = obese
> 40 = morbidly obese

Body surface area – The calculated total surface of the human body.

Calorie – The amount of energy that is required to raise the temperature of one millilitre water with one degree Celsius, from 15°C to 16°C. One kilocalorie equal 1000 calories. One calorie equals 4, 184 kilojoules.

Capillary – Relating to a small blood vessel.

Cardiac output – Output of the heart per unit time. In a normal physiological man weighing 70 kg this would be 5 litres.

Chromosome – Containing the genetic material in the nucleus.

Clearance – Removal of a substance from the blood e.g. by renal excretion.

Clearance constant fraction (CL/F) – The dosing rate divided by the measured concentration at steady state.

Clearance plasma (Clp) – Total clearance of a drug from the plasma expressed in L/hr.

C0 – Concentration taken after completion of the loading dose which is infused over a 2 hour period. This is denoted as time zero.

C1 – Concentration taken six hours after time zero.

Cockroft-Gault - The calculated creatinine clearance based on age, weight and plasma creatinine at a given time.

Compartment – Different section of a body within which the concentration of a drug is assumed to be uniformly equal.

Concentration – The relative amount of a substance contained per unit volume or weight within a solution.

Constant rate – The same amount of drug infused during a consecutive time period.

Correlation – The interdependence between variable quantities.

Creatinine – A breakdown product of creatinine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). Creatinine is filtered by the kidneys and excreted in urine.

Creatinine clearance (CrCl) – The amount of creatinine cleared almost entirely with a rate similar to the glomerular filtration rate. Calculated by the Cockroft-Gault formula.
CrCl = (140 – age) x (IBW)(0.85 in females) / 72 x P_{CR}

> 90 ml/min = normal
60 – 90 ml/min = Mild renal impairment
30 – 60 ml/min = moderate renal impairment
15 – 30 ml/min = severe renal impairment
≤ 15 ml/min = renal failure

Critical – Denoting a morbid condition in which death is possible.

Cytoplasm – The substance of a cell, exclusive of the nucleus, which contains various organelles and inclusions with colloidal protoplasm.

Cytosol – Cytoplasm exclusive of the mitochondria, endoplasmic reticulum, and other membranous components.

Cytotoxic – Detrimental or destructive to cells.

Data – Facts and statistics used for analysis or reference.

Data analysis – A process of inspecting, cleaning, transforming and modelling data with the goal of highlighting useful information, suggesting conclusions and supporting decision making.

Depolarize – To deprive of polarity.

Devine formula – The calculation of ideal body weight based on pre-determined weight and length measured in inches.

$$IBW_{males} = 50kg + 2{,}3(length_{inch} - 60kg)$$
$$IBW_{females} = 45{,}5kg + 2{,}3(length_{inch} - 60kg)$$

Detoxify – To diminish or remove the toxic effects of a substance.

Dextrose – A hypotonic solution containing 50 gram of glucose in 1 litre water for infusion, and provides 170 calories per litre.

Distribution equilibrium – The amount of drug distributed equally between all compartments. This rate depends upon the ratio of the perfusion of the tissue to the partition of the drug into tissue.

Distribution volume – Relates to the amount of drug in the body to the concentration of the drug in blood or plasma. This volume does not necessarily refer to an identifiable physiological volume; but merely to the fluid volume that would be required to contain all of the drug in the body at the same concentration as in the blood or the plasma. Expressed in litre per kilogram.

Elimination half time – This is the time necessary for the plasma concentration of a drug to fall to 50% during the elimination phase, after terminating an infusion of particular duration.

Elimination phase – When the drug in the plasma and the tissue reaches equilibrium, the decline of the plasma concentration is driven by the elimination of the drug from the body.

Elimination rate constant (Ke) – The rate at which drugs are removed from the body.

Expected concentration (Cexp) –The expected calculated concentration taking into account the elimination rate constant, rate of infusion and vancomycin clearance.

Excess loading dose – An excess calculated loading dose administered as a bolus over a pre-determined time period.

Extracellular volume – Fluid volume outside the cells. It is divided into two components, the interstitial fluid and the circulating blood plasma.

Fever – A complex physiologic response to disease mediated by pyrogenic cytokines and characterised by a rise in the core temperature (above 38,3°C), generation of acute phase reactants, and activation of immune systems.

Figure – A shape defined by one or more lines in two dimensions.

Formula – A mathematically relationship expressed in symbols.

Genotype – The genetic constitution of an organism.

Glomerular filtration rate – The amount of blood filtrated by the glomerulus. The average glomerular filtration for a 70kg man is 125mL/min. Its magnitude correlates well with surface area. The value for women is 10% less than for men when correcting according the surface area.

Glomerulus –A tuft formed of capillary loops at the beginning of each nephric tubule in the kidney; this tuft with its capsule (Bowman capsule) constitutes the corpusculum renis (malphigian body).

Graph – A diagram showing the relation between variable quantities, typically of two variables measured along a pair of axes at right angles.

Half-life – The time period it takes for the plasma concentration to be reduced by 50%.

Heptapeptide – A compound of seven amino acids linked with peptide bonds.

Homogenate – The process where fat droplets are emulsified and a suspension is obtained.

Hour – A time period containing 60 minutes.

Hydrophillic – Tendency to dissolve in water.

Hyperdynamic state – A state which is recognised by an increase in the cardiac output, low peripheral vascular resistance, fever, and an increased protein influx.

Hypotension – When the systolic blood pressure is less than 90 mmHg; mean arterial pressure less than 70 mmHg, or a systolic blood pressure reduction more than 40 mmHg from the baseline, or less than 2 of the Standard deviation below normal for age.

Hypotonic solution – A solution having a lower effective osmole concentration than the cytosol.

Ideal body weight – The calculation of ideal body weight based on pre-determined weight and length measured in inches. Calculated by using the Devine formula.

Immunoassay – The detection and assay of substances by serological (immunological methods); in most applications the substance in question serves as an antigen, both in antibody production and measurement of antibody by the test substance.

Immunoglobulin – A large Y-shaped protein used by the immune system to identify and neutralise foreign objects such as bacteria and viruses.

Inclusion criteria – The inclusion of a patient to partake in a study if certain criteria are met.

Infusion –The induction of a solution intravenously.

Infusion rate – Time period it takes for the infusion to be infused.

Interlobular arteries – Pertaining to arteries between the lobules.

Interstitial fluid – The part of the extracellular fluid that is outside the vascular system, bathing the cells.

In vitro – An artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media.

In vivo – In the living body, referring to a process or a reaction occurring therein.

Ion – An atom or a group of atoms carrying an electric charge by virtue of having gained or lost one or more electrons.

Isotonic fluid – Denoting to solutions with the same osmotic pressure, which is limited to solutions where cells don't shrink or swell.

Joule – A unit of energy. It is an approved multiple of the SI fundamental unit of energy, the erg, and is intended to replace the calorie (4.184J).

Kilogram – The SI unit of mass, 1000 gram.

Kilo-joule – A unit of energy, work, or quantity of heat equal to 10^3 joules.

Linear correlation – Involving directly proportional change in two related quantities.

Lipid-soluble drugs – "Fat-soluble" drugs which is insoluble in water.

Litre – This is a metric system unit of volume equal to 1 cubic decimetre (dm^3), to, 1 000 cubic centimetres (cm^3) and to 1/1000 cubic metre. There is two SI unit symbols, the Latin letter L in lower and upper case (l and L).

Loading dose – A calculated dose based on weight in order to achieve more rapidly therapeutic levels, usually given as a bolus over a certain time period.

Macromolecule – A molecule containing a very large number of atoms, e.g. protein.

Maintenance dose – A calculated dose usually smaller than the loading dose. The maintenance dose is administered through a continuous infusion in order to maintain therapeutic levels.

Mass – One of the seven fundamental quantities in the SI system, its unit is the kilogram.

Matzke method – The calculated clearance of vancomycin based on the creatinine clearance. A predetermined distribution volume are used for the applicable calculated creatinine clearance.

Mean – The average between a set of quantities.

Mean arterial pressure – A function of the cardiac output and the systemic vascular resistance.

Measured concentration (Cm) – The concentration measured after a calculated time period. Expressed in mg/L.

Millilitre – One-thousandth of a litre.

Milligram – One-thousandth of a gram.

Minute – A period of time equal to sixty seconds.

Minimum inhibitory concentration – The lowest concentration of an antibiotic that completely inhibits the growth of an organism in vitro.

Molecule – A group of atoms bonded together, representing the smallest fundamental unit of a compound that can partake in a chemical reaction.

Motor end plate – The terminal arborization of a motor axon on a muscle fibre.

Nephrotoxicity – If the creatinine clearance increases by 50% from the baseline after 24 hours of commencement of vancomycin.

Neutron – An electrically neutral particle in the nuclei of all atoms with a mass slightly more than a proton.

Neutropenia – The neutrophil count is less than 2.5 x 10^9/L except in black people where it is less than 1.5 x 10^9/L.

Non-depolarizing neuromuscular blocking drugs – A neuromuscular blocker that do not depolarize the motor end plate.

Nuclei – Pleural for nucleus.

Nucleus – The positively charged central core of an atom.

Organ – Any part of the body exercising a specific function, as of respiration, digestion or secretion.

Organelle – One of the specialised parts of cell tissue.

Ototoxicity – Toxic reactions to structures of the inner ear, including the cochlea, vestibule, semicircular canals, and otoliths.

Oxidative stress – An imbalance between the production and manifestation of reactive oxygen species and a biological system's ability to detoxify the reactive intermediates or to repair the resulting damage.

Participating – Partaking in the study.

Patient – One who is suffering from an illness and is being treated for it.

Pentapeptide – A peptide consisting of five linked amino acids.

Peptide – A compound of two or more amino acids in which a carboxyl group of one is united with an amino group of another, with elimination of a molecule of water; thus forming a peptide bond.

Perfusion – To supply blood to an organ or tissue by circulating it through blood vessels.

Peripheral vascular resistance – The sum of the resistance of all peripheral vasculature in the systemic circulation.

Peritubular capillaries – The short afferent arterioles are straight branches of the interlobular arteries. Each divides into multiple capillary branches to form a tuft of vessels in the glomerulus. The capillaries coalesce to form the efferent arteriole, which in turn breaks up into capillaries that supply the tubules before draining into the interlobular veins.

Peroxide – The 0_2^{2-} ion.

pH – Symbol for the negative decadic logarithm of the H^+ ion concentration (measured in moles per litre); a solution with a pH 7.00 (1×10^{-7} g molecular weight of hydrogen per litre), is neutral at 22°C (i.e. $[H^+] = [OH^{-l}]$), one with a pH value of more than 7.00 is alkaline, one with a pH of less than 7.00 is an acid. At a temperature of 37°C, neutrality is at a pH value of 6.8.

Plateau - The rates of drug entry into and out of the tissues are equal.

Pharmacodynamics – The uptake, movement, and interactions of pharmacologically active molecules at their tissue site of action.

Pharmacokinetics – Movements of drugs within biologic systems, as affected by uptake, distribution, binding, elimination and biotransformation.

Pharmacology – The science concerned with drugs.

Phenotype – The observable characteristics, at the physiological, morphologic, or biochemical level, of an organism as determined by the genotype and the environment.

Plasmid – A genetic particle physically separate from the chromosome of the host cell (chiefly bacterial) that can stably function and replicate and usually confer some advantage to the host cell; not essential to the cell's basic functioning.

Protein - Macromolecules consisting of long sequences of α-amino acids in peptide linkage.

Protocol – The exact procedure for administering medical treatment.

Protoplasm – The total cell material, including cell organelles.

Proton – The positively charged unit of a nuclear mass.
Post-antibiotic effect – The persistent suppression of bacterial growth following antibiotic exposure.

Reactive oxygen species – Chemically reactive molecules containing oxygen, examples are oxygen ions and peroxides.

Regimen – A set of recommended guidelines on how to achieve therapeutic levels with a drug.

Researcher – An individual that is systematically investigating a study or sources in order to establish facts and reach new conclusions.

Sample – A small blood specimen that will not be detrimental to the patient.

Sepsis – The invasion of microorganism or their toxins into the bloodstream, together with the host response to that invasion.

Septic – Relating to or caused by sepsis.

Serum creatinine (Cr_s) – This reflects the balance between creatinine production and creatinine excretion by the kidney, which is dependent on the glomerular filtration rate. Creatinine generation varies with muscle mass, physical activity, and catabolism. However, when these processes are in equilibrium and renal function is stable the serum creatinine is a useful marker of the glomerular filtration rate.

Shock – The condition in which the cells of the body receive inadequate amounts of oxygen secondary to changes in perfusion; most commonly secondary to blood loss or sepsis.

SI – The International System of Units, abbreviated SI from French: Système international d'unités, is the modern form of the metric system and is generally a system of units of measurement devised around seven base units and the convenience of the number ten.

Stable outpatient – Patient outside the hospital not deteriorating in illness.

Steady state (Css) – The drug elimination (the product of clearance and concentration) will equal the rate of drug availability during a constant rate infusion. Expressed in mg/L.

Standard deviation – The square root of the average deviation from the mean.

Stroke volume – The amount of blood pumped out by each ventricle during a single beat.

Study – Research, detailed examination, and/or analysis of an organism, object, or phenomena.

Sub-therapeutic levels – Measured vancomycin concentration less than 15mg/L.

Renal – relating to the kidney

Renal tubular secretion – The active transport of material from peritubular capillaries to renal tubular lumen.

T >MIC (Time above MIC) – The percentage of a dosage interval in which the serum level exceeds the MIC.

Table – A set of facts displayed in columns.

Therapeutic level – Measured concentration as per se 15 – 20 mg/L.

Thrombocytopenia – A platelet count below 150,000/μL, but the ability to form a hemostatic plug is retained until the platelet count falls below 100,000/ μL.

Time of infusion (t_{inf}) – The allowed time period for an infusion to be administered.

Tolerance - Minimum bactericidal concentration (MBC) of ≥ 32 times the MIC of an antibiotic.

Treatment – Medical management of a patient.

Trough concentration – The plasma level measured just before the next dose, Cmin.

Turnaround time - The time that lapses between sampling and analysing.

Vancomycin clearance - Elimination of vancomycin through the blood per unit of time, expressed in ml/min.

Vessel – Relating to an artery or a vein.

Virulence – The disease-evoking severity of a pathogen; numerically expressed as the ratio of the number of cases of overt infection to the total number infected, as determined by immunoassay.

Voluntary – Acting out of free will.

Volume of distribution (Vd) - Dose / concentration expressed in litre per kilogram.

Weight – The product of the force of gravity, defined internationally as 9.80665 m/s^2, times the mass of the body.