REVIEW ARTICLE

Vancomycin and Linezolid dosing in Obese and Overweight Patients: Is There a Universally Accepted Dosing Protocol to Improve their Efficacy?

Wada Yusuf[1,2], Mustapha Sagir[3,4], Irekeola Adebayo Ahmed[1,5], Muhammad Suwaiba Ladan[6], Harun Azian[1,7], Chan Yean Yean[1], Zaidah Abdul Rahman[1,7]

[1] Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan Malaysia.
[2] Department of Zoology, Faculty of Life Sciences, Ahmadu Bello University, Zaria Nigeria
[3] Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kota Bharu, Malaysia
[4] Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Kaduna, Nigeria
[5] Microbiology Unit, Department of Biological Sciences, College of Natural and Applied Sciences, Summit University Offa, Offa PMB 4412, Nigeria.
[6] Department of Chemical Science, Federal University of Kashere, Gombe PMB 0182, Gombe State, Nigeria
[7] Hospital Universiti Sains Malaysia, Universiti Sains Malaysia 16150 Kubang Kerian, Kelantan Malaysia

ABSTRACT

Vancomycin is used to manage methicillin-resistant *Staphylococcus aureus* (MRSA) and other bacterial infections that are Gram-positive in nature. Linezolid belongs to the oxazolidinone class of antibiotics, which is primarily used to treat vancomycin-resistant *Enterococcus* (VRE), MRSA, diabetic foot, soft tissue, and skin infections. Here, we discuss vancomycin and linezolid dosing in obese patients, their mechanism of actions, pharmacokinetics, problems with dosing and evaluation of several dosing protocols in the obese patient population. There is no generally accepted dosing protocol for linezolid and vancomycin. Evidence suggests that using trough concentrations alone is insufficient for estimating vancomycin and linezolid exposure accurately as many researchers have revised protocol guidelines, developed more rigorous dosing and monitoring guidelines, or developed novel dosage strategies to meet the needs of overweight patients. Peaks and troughs measurement should be considered because it improves precision and reduces the area under the curve (AUC) estimate bias. To provide better dosing guidelines in this vulnerable group, obese patients must be included in all phases of drug design.

Keywords: Obesity, Overweight, Vancomycin, Linezolid, Trough concentration

Corresponding Author:
Zaidah Abdul Rahman, PhD
Email: drzaidah@usm.my
Tel: +60-169227344

INTRODUCTION

Adults are categorized as either overweight or obese by using the Body Mass Index (BMI) which is a measure of weight over height with the unit in kg/m^2 (1,2). As outlined by World Health Organization (WHO), an overweight adult has a BMI of ≥ 25 while an obese adult weighs ≥ 30 (3). Further, an overweight child under the age of five has a weight over height measure > 2 points above the WHO Child Growth Standards while obese children of the same age have a weight over height measure > 3 points above WHO standards. Similarly, overweight children between 5-19 years have a weight over height measure > 1 point and obese children within the same age have a weight over height measure > 2 points above WHO standards (20). Obesity was once thought to be a problem for only developed countries but available data suggests otherwise. There are reports of obesity in less developed countries and as it stands, no one is free from obesity especially in the urban areas. About 38.2 million children around age 5 were obese or overweight in 2019 alone. For instance, in about a decade, 25% of children around 5 years are overweight in Asia and Africa and they have the highest count of overweight children in 2019 under age 5 (2). In 2016 however, the number of teenagers and children between 5 - 19 years that are overweight was more than 340 million. Further, a significant jump in the occurrence of overweight and obesity from 4-18% between 1975-2016 among 5-19 years children and young people has been observed. This jump was also seen in teenagers so much so that in 2016, 124 million children and young people making up about 6% and 8% of young boys

and young girls respectively were obese as compared to under 1% in 1975. Contrary to popular belief, underweight has caused far fewer deaths than obesity and overweight as data has proven that a considerable large number of people worldwide excluding African-Sub Sahara and Asia are obese than underweight (1,2). The categorization of BMI according to WHO is seen in Table I.

Table I: Body Mass Index categorization according to World Health Organization

BMI (kg/m^2)	WHO categorization
≥ 40.00	Obese class III (other terms: morbidly obese, extremely obese)
35.00–39.99	Obese class II
30.00–34.99	Obese class I
25.00–29.99	Overweight
18.50–24.99	Normal weight
< 18.50	Underweight

Obese individuals have not only been documented to be worse-off in clinical outcomes as obesity is known to have a direct relationship with hypertension, cardiovascular illness and diabetes but are also a potential risk for infectious agents (4). Because of these risks, sufficient antimicrobial dosing is required to effectively treat obese patients even though information on dosing guidelines of several antibiotics in obesity is scarce or lacking (5). Several reasons exist for the difficulty observed in antimicrobial dosing in obese individuals among which is the differential volume and clearance of drugs. This can be caused by characteristics of the antimicrobial and the type and extent of obesity (6).

Vancomycin is used to treat methicillin-resistant Staphylococcus aureus (MRSA) and other Gram-positive bacterial infection (7, 8). It was recommended that vancomycin be given every 8-12 hours at 15 to 20 mg/kg/dose by the Infectious Diseases Society of America (IDSA) MRSA protocol in 2011 and in a normal renal functioning patient, at least 2g per dose should be given (9). The same protocol suggested the observation of vancomycin concentrations at the highest levels and that vancomycin dosing is largely dependent on trough concentrations. More so, vancomycin dosing relying on actual body weight especially in obesity has its own complications as it could cause nephrotoxicity (10, 11). Linezolid belongs to the group of antibiotics called oxazolidinone majorly used in treating vancomycin-resistant Enterococcus (VRE), MRSA, diabetic foot, soft tissue and skin infections seen in obese patients (12, 13). Linezolid is given orally or intravenously with a 12-hourly dosage of 600mg (14). There seems to be no protocol for linezolid dosing in obese patients as regards weight, however, its concentration might be low in obese patients prompting a dose increment as described in some research (15).

In this review, we highlight vancomycin and linezolid dosing in obese patients. These include descriptions of their mechanism of actions, pharmacokinetics, problems with dosing and evaluation of several dosing protocols in the obese patient population.

MECHANISM OF ACTION OF VANCOMYCIN AND LINEZOLID

Vancomycin, which is only effective against Gram-positive bacteria prevents the polymerization of peptidoglycans in the bacteria cell wall which is made up of complex structures called N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) placed in a firm layer (16). The binding of vancomycin to D-alanyl D-alanine inhibits the fusion and polymerization of NAM and NAG by blocking the carrier's glucosyltransferase and P-phospholipid. Because of this, intracellular elements sip outward of the weakened cell wall and cause the dissolution of the bacteria cell wall (17).

Linezolid on the other hand, through the integration of the ribosomal unit of 50S and 30S rRNA, prevents the synthesis of bacteria protein (18, 19), and stops the progression of the initiation complex thereby decreasing the pace at which translation occurs. It helps lowers the toxins produced by bacteria that are Gram-positive by stopping the virulent element from emerging (20, 21). Linezolid has an exclusive inhibition spot which permits the multi-directional flow of resistant factors to other protein production inhibitors (21, 22). Also, the initiation process at this spot takes place first before that of other protein production stoppers (19).

PHARMACOKINETICS OF VANCOMYCIN AND LINEZOLID

Different antibiotics interact in the body in almost entirely different ways. Linezolid's absorption is unaffected by food availability (18, 23) and has a 100% bioavailability (24, 25). Linezolid can be given orally or intravenously, and it is sometimes given in conjunction with antacids because it has no effect when taken orally (13, 26). Aside from its ease of absorption, it has a 31% plasma protein aggregating level, a 3.4-7.4 half-life that metabolizes into hydroxyethyl glycine and aminoethoxy-acetic acid (26, 27), and a volume of circulation of the protein equivalent to 40-50 L. After distribution, clearance is carried out by the renal and other mechanisms at a rate of 80±29 mL/min. In most cases, unchanged linezolid is discharged through the urine, though reabsorption might take place in the renal tubules (28, 29).

Vancomycin, on the other hand, which is less bactericidal, is given intravenously, orally and via rectal (30). When administered orally, it has a 10% bioavailability or less, while activity begins immediately following a serum peak concentration after infusing vancomycin intravenously (31). Vancomycin has a protein-binding level of 55%

and a large volume of protein circulation in fluids and tissues, excluding normal meninges and cerebrospinal fluid (CSF) (32). Furthermore, unlike linezolid, it has no obvious metabolism, and in individuals with healthy renal tubules, it has clearance rates ranging from 0.71 mL/min/kg to 1.31 mL/min/kg and a bi-phasic elimination half-life of 4 to 6 hours at the terminal end, with a rapid initial half-life. Because of the elimination half-life, patients with renal dysfunction should be monitored around the clock (31). Furthermore, unlike linezolid, vancomycin infused intravenously is excreted 75% through urine and 25% through the glomeruli, whereas those administered orally are excreted primarily through feces (30, 33).

ADMINISTRATION STRATEGIES AND THEIR ATTENDANT PROBLEMS IN OBESE AND OVERWEIGHT PATIENTS

There has been some debate about whether vancomycin dosing should be based on AUC or trough concentration because AUC only represents total drug exposure over a given time administered to a patient (34, 35). Many investigations have been performed in an attempt to address the complexities associated with medicating in obesity when it is centered on weight. (36–38). One thing is certain: vancomycin administration has a pharmacokinetic target of 400 mg/L AUC and 15 to 20 mg/L trough concentration. This is a problem in obese patients because the trough concentration produces a different AUC (6, 37).

In the United States of America, for example, studies assessing the pharmacokinetics of antibiotics are scarce because they are not required for drug approval by the US Food and Drug Administration, even though approximately one-third of its adult population is overweight according to Halpern et al. (39), and that there are over 1.9 billion obese people worldwide (2). Currently, vancomycin administration and monitoring allow for dosing of 15–20 mg/kg every 8–12 hours based on real body weight, but more research is needed to recommend ideal administration of these antibiotics in obese individuals regardless of BMI (32).

As several studies have argued on the appropriate strategy for vancomycin dosing in obese patients, different vancomycin dosing guidelines have been used in different practices (40–46). Hall et al. (44) and Rybak et al. (47) describe a specific study in which 25% of obese patients were given vancomycin doses of ≥10 mg/kg per dose and 1% were given doses of ≥15 mg/kg per dose. The effectiveness of vancomycin in these obese patients is dependent on serum concentration, as they are hampered by elevated clearance and distribution, as well as a short half-life. As a result, some practices have advocated for regular dosing to reduce drug toxicity and improve efficacy (5, 35).

The case is however different for morbidly obese individuals. The peculiar interactions of several antibiotics are affected by morbid obesity (48). These antibiotics include vancomycin (32, 49) and aminoglycoside (48, 50). In the early 1980s, prior to the utilization of steady-state peak and trough target concentrations (40), vancomycin administration guidelines in normal renal functioning morbidly obese patients were developed. It was determined by the total body weight (TBW), which was 23.4 mg/kg/d-1 at the time. This measurement was thought to be the most effective in achieving steady-state concentrations of 15μg/ml-1 on average (51, 52). The fact that vancomycin exhibited bactericidal tendencies that varied with time, as well as the significance of the antibiotic in maintaining suitable steady-state trough concentrations, was not fully understood (53, 54).

Physiological changes influence antibiotic interactions in morbidly obese patients. These physiological changes may include increased adipose tissue availability, which, in addition to large organs, may increase slim body mass and blood quantity (55, 56). Because the quantity of distribution of a drug is directly proportional to the quantity of blood, organs, and drug interaction in the blood and organs, adipose tissue, which is mostly made up of fats, allows for easy drug dispersal through extracellular fluids, and the pace and volume of this dispersal for most drugs is increased, particularly in morbidly obese individuals (57). Drugs such as digoxin and cimetidine do not percolate deeply into fatty tissue because their quantity may be the same in normal-weight and morbidly obese individuals (58, 59). On the other hand, aminoglycosides with high polarity disperse easily through large extracellular spaces in adipose tissue (60–62), resulting in a significant increase in the volume of distribution in morbidly obese patients (42). Furthermore, when a drug like diazepam, which is highly lipid-soluble, is administered, the quantity of dispersal may be significantly elevated.

Creatinine clearance is another physiological change that is higher in morbidly obese patients compared to patients of normal weight when given the same concentration of serum creatinine (6). It is frequently employed as a surrogate for glomerular filtration rate, which is assumed to be higher in morbidly obese patients due to the existence of more effective nephrons and larger kidneys. (63). As a result, vancomycin and linezolid, which are excreted renally, are cleared quickly in morbidly obese individuals (40, 41). Because conventional techniques for measuring creatinine clearance in morbidly obese persons, such as the Cockcroft-Gault formula, are insufficiently exact, (64-66) a new method of determining creatinine clearance was established.

The concept of therapeutic drug monitoring (TDM) has been demonstrated to be important in the context

of obesity. In their studies, Cattaneo et al. (67) and Pea et al. (68) demonstrated the variability of linezolid minimum trough concentrations, particularly after receiving a linezolid dosage of 600mg every 12 hours in a large patient population. They also stated that with the proper treatment schedule, there is a 10- to 20-fold variation in linezolid minimum trough concentrations between patients. Taubert et al. (69), Tsuji et al. (70) and Minichmayr et al. (71) demonstrated the need for TDM-based linezolid administration in their studies. However, the lack of resources for effective and efficient use by most specialists is a disadvantage, and in this case, a substitute measure that promotes the best linezolid dosing is used, which is mostly based on renal function and body size. Linezolid's physiological pathway, like vancomycin's, is dependent on its pharmacokinetics according to Hanley et al. (72). For example, Bhalodi et al. (73) found a rather strain association between linezolid and body size in their small cohort study of moderately to morbidly obese patients. Another study, Hanley et al. (72), clearly demonstrated the relationship between linezolid pharmacokinetics with body size.

DOSING AND MONITORING PROTOCOLS

This section will go over vancomycin and linezolid dosing and monitoring protocols. However, based on the literature we have, we don't know much about different linezolid monitoring protocols. As a result, we would attempt to discuss the vancomycin protocol in the hope that it would suffice for linezolid. Because vancomycin dosing guidelines are not explicit enough, and there are differences in pharmacokinetic parameters in obese people, the need for a comprehensive dosing protocol cannot be overstated. Several researchers have developed different vancomycin dosing protocols to improve its efficacy in obese patients.

Wesner et al. (74) are one such group of researchers who conducted a prospective study to compare the performance of their new dosing strategy to that of a well-known strategy. Although their study did not report the performance of their new strategy for obese patients and excluded subjects weighing more than 120kg, vancomycin trough concentrations based on weight dosing protocols of the patients enrolled were the goal. In their investigation, a P value of 0.190 was attained by 49% of normal patients and 39% of obese subjects. Dosing was 30% over ideal body weight (IBW) for obese subjects and total body weight (TBW) for non-obese subjects. Subjects with trough targets of 15 to 20 µg/mL and 10 to 15 µg/mL were given a loading dose of 24 mg/kg and 22 mg/kg, respectively, and a maintenance dose of 13 mg/kg was given to the subjects at intervals based on creatinine clearance.

Reynolds et al. (75), concerned about high and irregular vancomycin trough levels in obese individuals visiting their clinic, decided to conduct a retrospective study to develop a new dosing strategy. In their study, 74 and 64 patients were given vancomycin using the new and standard protocols, respectively, and all subjects had a creatinine clearance rate of ≥60 mL/min. Unlike Wesner et al. (74), subjects in Reynolds et al. (75) studies were given a vancomycin initial dose of 20 to 25 mg/kg, trailed by a conservation dose of 10 mg/kg or 15 mg/kg every 12 or 24 hours, respectively. Furthermore, the new dosing strategy had vancomycin trough with the highest frequency 59% (P = 0.006) at 10 to 20 µg/mL target point, a >20 µg/mL trough concentration supratherapy occurring at a reduced rate (18% vs 55%, P = 0.001), and <10 µg/mL trough concentration subtherapy occurring at an increasing rate (23% vs 9%, P = 0.033). It is important to note that, even though all conditions were the same, subjects given the new dosing strategy had significantly lower TBW.

Similarly, after observing that the rate of supratherapeutic trough levels in obese individuals is increasing following standard dosing, Kosmisky et al. (76) developed a drug administration strategy for obese individuals in a retrospective study analogous to that of Reynolds et al.(75). In this strategy, initial doses of 20 to 25 mg/kg and preservation doses of 10 mg/kg were given, with the preservation dose given 12 to 24 hours after the initial dose, both based on TBW. The preservation dose, on the other hand, is determined by creatinine clearance. However, the intermediate initial and preservation doses were 19.4 mg/kg and 9.9 mg/kg given every 12 hours, respectively. Finally, a therapeutic trough level of 10 to 14.99 µg/mL and 15 to 20 µg/mL was observed in 23.5% and 76.5% of subjects respectively, while 56.3% and 8.3% of subjects experienced subtherapeutic and supratherapeutic trough levels respectively.

Hong et al. (77) attempted to determine effective dosing in obese patients using a calculation method based on agreed-upon drug pharmacokinetics. On the one hand, it included the addition of maintenance and loading doses, as well as an elimination rate constant calculated using the Matzke method (78), and on the other, it included the calculation of creatinine clearance using the Cockcroft-Gault equation and the determination of a volume of distribution of 0.8 L/kg dependent on the TBW. Unlike the standard guideline, which assesses trough concentration, Hong et al. (77) employed a two-sample peak and trough observation method for the intervention subjects. Furthermore, their strategy included loading doses of 30 to 40 g/mL and 10 to 15 g/mL, or 15 to 20 g/mL, indication-based maintenance doses respectively.

Finally, Denetclaw et al. (79) developed an elaborate vancomycin administration strategy in obese patients that involves dividing loading doses. This strategy was devised to attain a targeted trough concentration of ≥15 µg/mL within 24 hours while avoiding trough concentrations of ≥20 µg/mL or <10 µg/mL. First day,

the total initial dose was 60 mg/kg and 45 mg/kg or 30 mg/kg divided into 15 mg/kg every 6 hours and 15 mg/kg every 8 or 12 hours, with the highest dose at 20 mg/kg/dose. This strategy appears to be the most effective, but it requires a significant amount of labor due to its complexity.

Table II shows the suggested antibiotic dosing modifications in obesity for different antibiotic groups (80).

Table II: Some Antibiotic Dosage Modifications in Obese Patients

Antibiotics	Observations
Vancomycin	Doses do not seem linear to body weight; decreases in weight-based doses are needed
	Single levels, as well as two-point observations (peak and trough), might improve the accuracy of AUC estimates if software capable of Bayesian analysis was used.
Linezolid, ceftaroline, ceftolozane/tazobactam, ceftazidime/avibactam, doripenem, ertapenem, imipenem, meropenem, moxifloxacin, tedizolid, dalbavancin, oritavancin, and tigecycline	Do not seem to necessitate dose adjustments solely based on obesity. In some cases, prolonged infusions of meropenem and doripenem may be explored.
Gentamicin, tobramycin and amikacin, polymyxin B, trimethoprim-sulfamethoxazole, and daptomycin	To reduce the danger of toxicity, use $ABW_{0.4}$ as the dosage weight index.
β-lactams	Additional dose strategies, especially for severe infections or for patients with fluctuating renal function should be considered, e.g. prolonged or continuous infusions.
Amoxicillin, nafcillin, piperacillin/tazobactam, cefazolin, cephalexin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, clindamycin	Data are insufficient and/or contradictory; in severe and/or latent infections, dosing at the topmost end of the normal dosing range would be sensible.
Various antimicrobials (e.g., fluoroquinolones)	The importance of TDM in advancing antimicrobial dosing in obese, critically ill, and other special populations is becoming increasingly important.
Telavancin	Dosing modifications may be required (e.g., fixed-dose and a dose cap at 1000 mg).

CONCLUSION

The answer to the preceding question is no. To improve vancomycin and linezolid administration and target trough achievement, several researchers have made protocol adjustments, devised more intense administration and surveillance protocols, or developed new administration techniques to accommodate the needs of the obese individuals for which they offer care. The majority of these creative approaches, however, failed to meet expectations. Evidence suggests that using trough levels alone is inadequate for estimating vancomycin and linezolid interactions accurately. Peaks and troughs should still be well-thought-out because it facilitates precision and reduces AUC estimate bias. To provide better antibiotic administration guidelines in such vulnerable group, obese patients must be included in all phases of the drug design.

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