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Clinical Pharmacokinetics of Vancomycin

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Summary

Vancomycin utilisation has increased dramatically in the last 10 years due to the increasing clinical significance of infections with methicillin-resistant staphylococci. Recent studies have focused on characterising the disposition of vancomycin in patients and assessing the relationship between serum concentrations and therapeutic as well as adverse effects.

Although vancomycin is not appreciably absorbed from the intact gastrointestinal tract, several recent case reports have documented the attainment of therapeutic and potentially toxic vancomycin serum concentrations following oral administration to patients with pseudomembranous colitis. The disposition of parenterally administered vancomycin has been best characterised by a triexponential model. The half-life of the initial phase ($t_{½\alpha}$) is approximately 7 minutes, that of the second phase ($t_{½\beta}$) is approximately 0.5 to 1 hour, while the terminal elimination half-life ($t_{½\beta}$) ranges from 3 to 9 hours in subjects with normal renal function. The volume of the central compartment (Vc) in adults is approximately 0.15 L/kg while the steady-state volume of distribution (Vd_{ss}) ranges from 0.39 to 0.97 L/kg. More than 80% of a vancomycin dose is excreted unchanged in the urine within 24 hours after administration, and the concentration of vancomycin in liver tissue and bile has been reported to be at or below detection limits. Vancomycin renal clearance approximates 0.5 to 0.8 of simultaneously determined creatinine or ^{125}I-iothalamate clearances, suggesting that the primary route of renal excretion is glomerular filtration. Recently, non-renal factors such as hepatic conjugation have been proposed as an important route of vancomycin elimination. However, these data are difficult to reconcile with other studies showing minimal non-renal clearance of vancomycin in subjects with end-stage renal disease. As yet, the disposition of vancomycin in patients with hepatic disease has not been adequately defined.

Only limited data are available regarding the concentrations of vancomycin in biological fluids other than plasma. The penetration of vancomycin into cerebrospinal fluid (CSF) in patients with and without meningitis has been quite variable. Although early studies suggested that adequate CSF concentrations may not be achieved in subjects with uninflamed meninges, more recent investigations have reported contradictory results. Therapeutic concentrations of vancomycin, i.e. greater than 2.5 mg/L, have, however, been reported in ascitic, pericardial, pleural and synovial fluids. Tissue concentrations of vancomycin have exceeded simultaneous serum concentrations in heart, kidney, liver and lung specimens.

The disposition of vancomycin in paediatric and geriatric patients appears to be primarily related to the degree of renal function. However, there is some evidence of altered tissue binding and/or tissue distribution in geriatric patients. Since significant interpatient variability has been reported, further investigation will be required to substantiate dosing recommendations for these patient populations. Vancomycin clearance is decreased and the elimination half-life progressively prolonged in association with declining glomerular

filtration rate, but the volume of distribution at steady-state is not significantly correlated with declining renal function. Although marked variability in vancomycin clearance within a defined range of renal function has been observed, highly significant relationships between vancomycin clearance and creatinine clearance have been reported and may be utilised for the adjustment of dosage in this patient population. Haemodialysis provides no significant contribution to total body clearance of vancomycin, while haemoperfusion has produced prompt and sharp declines in vancomycin serum concentrations. Peritoneal dialysis clearances of vancomycin are markedly lower than those observed during haemodialysis or haemoperfusion. However, due to the longer course of this mode of dialysis, contribution to total body clearance may be significant for some patients.

Although early reports suggested that vancomycin therapy was frequently associated with adverse events, several recent reports have indicated that vancomycin is extremely safe. Nephrotoxicity has been observed in approximately 5% of patients and is associated with trough serum vancomycin concentrations of 30 mg/L or greater. The combination of an aminoglycoside and vancomycin may significantly increase the risk of nephrotoxicity. A causal relationship between attainment of peak vancomycin serum concentrations of 25 to 50 mg/L and/or trough concentrations of 13 to 32 mg/L and ototoxicity has been reported. Ototoxicity may be reversed, if not prevented, by close monitoring of vancomycin serum concentrations. The remaining adverse reactions which have been reported do not appear to be related to vancomycin dosage or serum concentrations.

The prospective design of vancomycin dosage regimens would appear to be warranted in adults with impaired renal function, elderly patients, morbidly obese patients, and paediatric patients. Although the pharmacokinetic profile of vancomycin is best described by a 2- or 3-compartment model, the collection of a sufficient number of serum concentrations to perform these characterisations in individual patients is not practical or cost-justified in routine clinical practice. Therefore an approach similar to that used for the aminoglycoside antibiotics would appear to be most practical.

Vancomycin, a bactericidal glycopeptide antibiotic produced by *Streptomyces orientalis*, was introduced in 1956 to treat emerging strains of penicillinase-producing staphylococci (McCormick et al. 1956). Early batches of vancomycin were referred to as 'Mississippi mud' because of the coloration imparted by impurities (Griffith 1981). Early reports of toxicity, apparently due to the product's impurities (Cunha & Ristuccia 1983; Griffith 1981; McHenry & Gavan 1983), coupled with the introduction of the antistaphylococcal penicillins and cephalosporins in the 1960s, resulted in a significant decline in the parenteral use of vancomycin. Resurgence in parenteral vancomycin use in the last few years may be attributed to the increasing clinical significance of methicillin-resistant staphylococci and the introduction of a more purified product which exhibits a relatively benign toxicity profile (Cook & Farrar 1978; Cunha & Ristuccia 1983; Esposito & Gleckman 1977; Griffith 1981).

This article reviews pharmacokinetic data derived from the use of vancomycin in man during the last 30 years. The resultant compilation and critique of the world literature is designed to facilitate rational dosage regimen design and therapeutic drug monitoring of vancomycin therapy.

1. Physicochemical Properties

Vancomycin (MW 1448) is a glycopeptide molecule consisting of a 7-membered peptide chain formed by parts of 3 phenylglycine systems, 2 chlorinated tyrosine units, aspartic acid and N-methylleucine. A disaccharide composed of glucose and vancosamine is also present but is not part of the cyclic structure (fig. 1). The pharmaceutical preparation currently marketed is a white solid amphoteric substance which is very soluble in water (over 100 g/L), moderately soluble in aqueous methanol, and insoluble in organic sol-

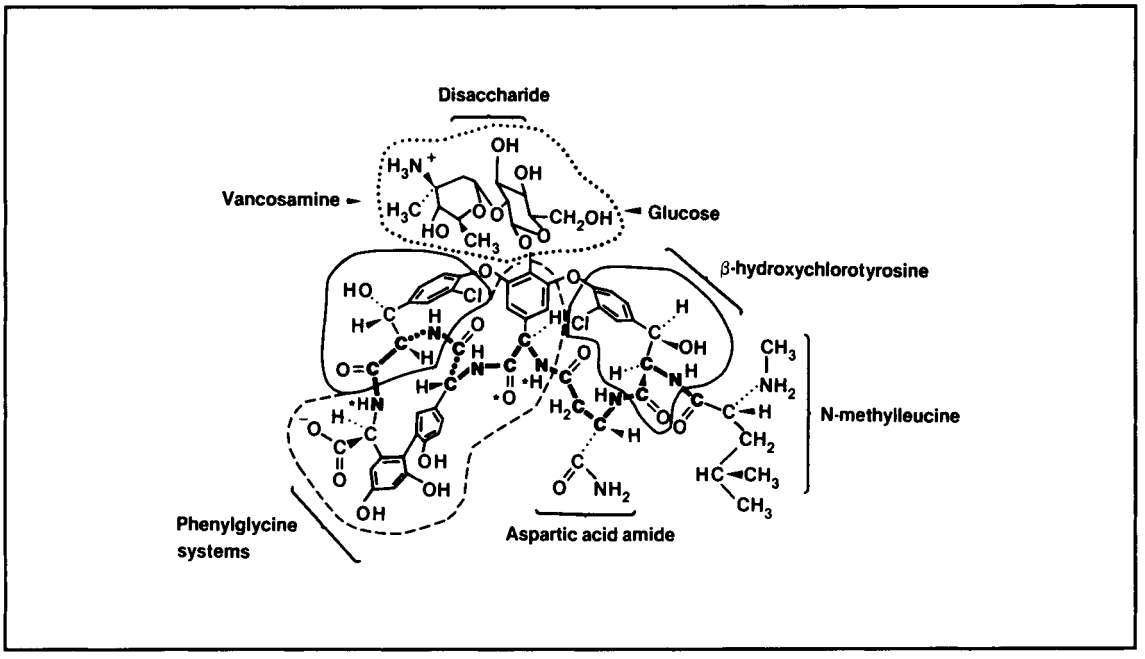

Fig. 1. Structural formula of vancomycin (after Pfeiffer 1981).

vents such as acetone and ether (Alexander 1974; Geraci & Hermans 1983; McCormick et al. 1956).

Vancomycin is an extremely stable antibiotic. Although the manufacturer indicates that reconstituted solutions are stable for 96 hours under refrigeration, other investigators have documented that the reconstituted solution is stable for 14 days at room temperature. Vancomycin admixed in either dextrose or saline solutions retains its potency for at least 7 days at both 5 and 25°C. In addition, vancomycin is physically compatible with dextran, sodium bicarbonate, and Ringer's lactate solutions. Vancomycin is incompatible with aminophylline, barbitone sodium, chloramphenicol sodium succinate, heparin sodium, methicillin sodium, pentobarbitone, phenobarbitone and quinalbarbitone (secobarbital) sodium, and warfarin sodium intravenous additives (Alexander 1974; Trissel 1983). Unlike many other antimicrobial agents, the activity of vancomycin is not significantly influenced by the pH of biological fluids (Geraci & Hermans 1983; Ziegler et al. 1956).

2. *Analytical Procedures*

Methodologies available for quantitation of vancomycin in biological fluids include microbiological, radioimmunoassay (RIA), fluorescence polarisation immunoassay (FPIA), fluorescence immunoassay (FIA), and high-performance liquid chromatographic (HPLC) techniques.

Although microbiological assays have proven relatively simple to perform, turnaround time is relatively long (2 to 18 hours), adequate reproducibility (coefficients of variation less than 10%) and accuracy (less than 10% error) are obtained over a relatively narrow concentration range (0.8 to 25 mg/L), and interferences from other antimicrobials may occur (Sabath et al. 1971; Walker 1980; Walker & Kopp 1978). The disadvantages of microbiological assays for vancomycin have been circumvented by the development of more sensitive, specific and rapid analytical procedures.

Recently, RIA, FPIA, FIA and HPLC techniques have been developed (Hoagland et al. 1984). In general, these methods have equivalent sensi-

tivity (lower limits of detection of less than 0.6 mg/L), specificity, and reproducibility (coefficients of variation less than 10%) over a broad concentration range (0.6 to 128 mg/L). Excellent correlations have been noted between microbiological assay and RIA (Crossley et al. 1980; Fong et al. 1981; Pfaller et al. 1984), microbiological assay and FPIA (Filburn et al. 1983; Pfaller et al. 1984; Pohlod et al. 1984; Ristuccia et al. 1984), microbiological assay and HPLC (Filburn et al. 1983; McClain et al. 1982; Pfaller et al. 1984; Ristuccia et al. 1984; Uhl & Anhalt 1979), RIA and FPIA (Ackerman et al. 1983; Pfaller et al. 1984; Schwenzer et al. 1983), RIA and HPLC (Jehl et al. 1985; Pfaller et al. 1984), and FPIA and HPLC (Filburn et al. 1983; Jehl et al. 1985; Pfaller et al. 1984; Ristuccia et al. 1984; Schwenzer et al. 1983). However, relatively poor correlations between FIA and other methods were noted by Pfaller et al. (1984).

In both clinical laboratory and research use, RIA and FPIA may be superior due to the smaller sample volume requirements, easier sample preparation and shorter turnaround time compared with HPLC, and their superior precision compared with FIA.

3. Fundamental Pharmacokinetic Properties

3.1 Absorption

Vancomycin is not appreciably absorbed from the gastrointestinal tract when administered orally (Geraci et al. 1957; Griffith 1957). However, vancomycin concentrations of 0.4 to 110 mg/L have been found in the urine of patients with normal renal function, suggesting that minimal absorption does occur (Geraci et al. 1957; Griffith & Peck 1956). Geraci et al. (1957) noted vancomycin stool concentrations of 400 to 24,000 mg/kg in 8 normal subjects after four 500mg oral doses administered 6-hourly.

Although measurable vancomycin serum concentrations are not usually attained, even in patients with severe renal impairment (Bryan & White 1978), recent case reports have documented therapeutic and potentially toxic vancomycin serum concentrations after administration of the drug orally to patients with severely impaired renal function and/or pseudomembranous colitis (Dudley et al. 1984; Halstenson et al. 1985; Spitzer & Eliopoulos 1984; Tedesco et al. 1978; Thompson et al. 1983). Although the risk of ototoxicity and nephrotoxicity due to vancomycin therapy is low, and the serum concentration-toxic effect relationship unclear, periodic monitoring of serum vancomycin concentrations in patients with pseudomembranous colitis or severe renal impairment receiving oral vancomycin therapy is recommended.

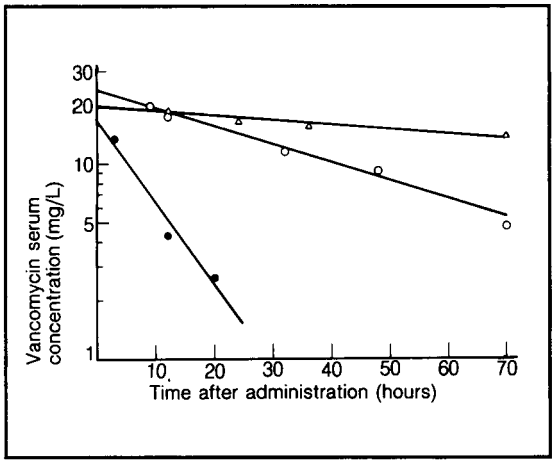

Fig. 2. Serum concentration time profiles for representative patients having creatinine clearances of 76 (●), 51 (○), and 3.6 (△) ml/min (reproduced with permission from Matzke et al. 1984).

Intramuscular injection of vancomycin results in severe pain; therefore it is usually administered only via the intravenous route for the treatment of systemic infections. Although vancomycin may be reconstituted in normal saline and administered as a slow intravenous bolus injection, it is recommended that the dose be reconstituted in 100 to 250ml of 5% dextrose or normal saline and administered at a rate not exceeding 15 mg/min (Geraci & Hermans 1983; Krogstad et al. 1980; Matzke et al. 1984).

3.2 Distribution

The vancomycin serum concentration *versus* time profile initially reported by Geraci et al. (1957)

was biphasic in nature. Subsequent studies of the disposition of vancomycin following intravenous administration have characterised the serum concentration *versus* time profile as being mono-, bi-, or triexponential in subjects with normal renal function (table I) [Blouin et al. 1982; Brown et al. 1983; Krogstad et al. 1980; Matzke et al. 1984; Rotschafer et al. 1982; Schaad et al. 1980]. The serum concentration *versus* time profile has been described as being mono- or biexponential in patients with renal impairment (Cunha et al. 1981; Dunn et al. 1984; Lam et al. 1981; Matzke et al. 1984) [figs 2 and 3].

Following the completion of an early distributive phase (half-life of approximately 7 minutes), a second phase of serum concentration decline begins (half-life in adults of approximately 0.5 to 1 hour). Although the early distributive phase has not been characterised in subjects with renal impairment, the second phase of serum concentration decline does not appear to be significantly altered in subjects with end-stage renal disease. The half-life of the third phase of serum concentration decline ($t_{1/2\beta}$) has ranged from 2.9 to 9.1 hours in subjects with normal renal function. This third phase $t_{1/2}$ increases in proportion to the decline in creatinine clearance (Matzke et al. 1984; Moellering et al. 1981a,b).

The volume of the central compartment (Vc) in adults has ranged from 0.10 to 0.15 L/kg with volumes of distribution at steady-state (Vd_{ss}) in adult and paediatric subjects ranging from 0.39 to 0.92 and 0.45 to 0.97 L/kg respectively (table I). These values approximate or slightly exceed total body water.

3.2.1 Protein Binding

Discrepancies have been noted in studies of vancomycin protein binding. Lindholm and Murray (1966) and Matzke et al. (manuscript in preparation) have reported protein binding of 10 to 30% while Krogstad et al. (1980) and Cutler et al. (1984) have reported substantially higher protein binding of 44 to 82%. It is likely that methodological differences (ultracentrifugation *vs* equilibrium dialysis) may have contributed to these disparate results. Further studies are necessary to resolve this issue.

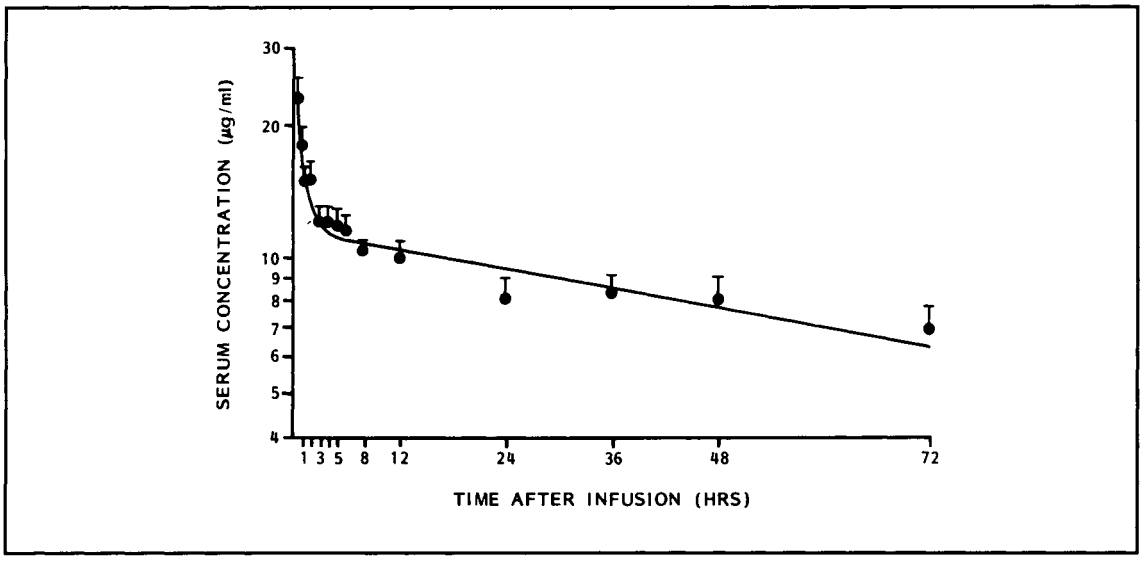

Fig. 3. Serum concentration-time profile (mean values ± SD) of vancomycin in patients undergoing continuous ambulatory peritoneal dialysis (reproduced with permission from C.V. Mosby Co., Bunke et al. 1983).

3.2.2 Distribution into Body Fluids

Therapeutic concentrations of vancomycin (greater than 2.5 mg/L) have been reported in ascitic, pericardial, pleural, and synovial fluids in patients with normal renal function after administration of single or multiple intravenous doses (table II). Since only low concentrations of vancomycin are noted in aqueous humour and bile after parenteral administration, the drug may not be useful for the treatment of ocular and biliary tract infections (Geraci et al. 1957; MacIlwaine et al. 1974). Therapeutic faecal concentrations of the drug have been detected after both oral and intravenous administration (Bryan & White 1978; Geraci et al. 1957; Schaad et al. 1980).

In the few multiple-dose studies that have been conducted, it is notable that concentrations in ascitic, pericardial and pleural fluid have been higher than in the single-dose studies (Geraci et al. 1957). This would suggest that drug accumulation in these fluids will occur with usual therapeutic regimens of vancomycin.

Potentially therapeutic concentrations of vancomycin have been observed in peritoneal dialysis fluid after intravenous dosing in patients undergoing intermittent and continuous ambulatory peritoneal dialysis (Blevins et al. 1984; Glew et al. 1982; Harford et al. 1984; Magera et al. 1983). Concentrations in dialysate fluid have ranged from 0 to 96% of simultaneous serum concentrations. This large degree of variability most likely reflects differences in patients (infected *vs* uninfected), drug administration schedules (single dose *vs* steady-state) and assay sensitivity.

3.2.3 Distribution into Tissues

Engineer et al. (1981) have documented high vancomycin concentrations in the kidney, liver, and spleen of rats with normal renal function. The concentrations of vancomycin in these same tissues were 4-fold higher in rats with end-stage renal disease. There is a paucity of similar tissue distribution data in humans. In a report of tissue and serum concentrations achieved after multiple doses in three patients, Torres et al. (1979) reported higher concentrations in aortic, heart, kidney, liver, and lung tissues than in simultaneous serum samples (table III). The very high concentrations achieved in the kidney were probably due to the presence of urine in the tissue samples (Torres et al. 1979). Concentrations of vancomycin in abscess exudate approximated those of serum.

3.2.4 Distribution into Central Nervous System

The cerebrospinal fluid (CSF) penetration of vancomycin in patients with and without meningitis has been quite variable (table IV) [Congeni et al. 1979; Geraci et al. 1957; Kirby & Divelbiss 1957; Moellering et al. 1981b; Nolan et al. 1980; Odio et al. 1984; Redfield et al. 1980; Schaad et al. 1980; Schaad et al. 1981; Spears & Koch 1960; Sutherland et al. 1981]. Although early studies suggested that inadequate CSF concentrations may be achieved following intravenous administration in subjects with uninflamed meninges (Geraci et al. 1957; Kirby & Divelbiss 1957; Spears & Koch 1960), some subjects with meningitis may attain adequate concentrations with this route (Redfield et al. 1980; Schaad et al. 1981). Due to the variability of vancomycin CSF penetration, intrathecal or intraventricular administration of 0.075 to 20 mg/day (Arroyo & Quindlen 1983; Congeni et al. 1979; Sutherland et al. 1981) has been recommended. However, the available information is insufficient to draw conclusions regarding the safety and efficacy of these routes of administration or the optimum dosage regimens.

3.3 Elimination

3.3.1 Metabolism

Lee et al. (1957) documented vancomycin concentrations to be less than 3 mg/kg and below assay sensitivity in liver tissue and bile, respectively, in dog and rat studies. These researchers concluded that vancomycin was not metabolised to any great extent. Kirby and Divelbiss (1957) reported that 80 to 100% of 1g and 2g intravenous doses were excreted unchanged in the urine in the first 24 hours after administration, suggesting that vancomycin undergoes minimal metabolism in humans.

Table I. Summary of results of pharmacokinetic studies of intravenous vancomycin in subjects with normal renal and hepatic function[a]

References	Subjects	No. of subjects	Mean age/ gestational age	Pharmaco-kinetic model[b]	CL_{CR} (ml/min)	CL (ml/min/kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Vc (L/kg)	Vd_{ss} (L/kg)
Gross et al. (1985)	Premature infants	3[c]	29 days/30 wk	One	NR	1.10 ± 0.29			9.92 ± 2.59		0.970[e] ± 0.426
	Premature infants	6[d]	39.5 days/33 wk	One	NR	1.03 ± 0.21			5.35 ± 0.77		0.453[e] ± 0.116
Schaible et al. (1984)	Infants	9	NR/27-40 wk	Two	NR	0.53-8[f]			3.5-9.6	NR	0.44-2.48
Schaad et al. (1980)	Infants	7	3.3 days/32 wk	Two	NR	0.85[g]		0.15	9.8	NR	0.736[e]
	Infants	7	4.7 days/34 wk	Two	NR	2.41[g]		0.05	5.9	NR	0.706[e]
	Infants	7	2.6 days/40 wk	Two	NR	2.05[g]		0.26	6.7	NR	0.690[e]
	Infants	12	3.1 mo	Two	NR	2.86[g]		0.27	4.1	NR	0.595[e]
	Infants	4	4.3 mo	Two	NR	4.67[g]		0.49	4.1	NR	0.964[e]
	Children	5	3.9 y	Two	NR	6.84[g]		0.23	2.4	NR	0.818[e]
	Children	7	5.8 y	Two	NR	5.11[g]		0.50	3.0	NR	0.764[e]
	Children	6	7.8 y	Two	NR	4.82[g]		0.31	2.2	NR	0.538[e]
Krogstad et al. (1980)	Adults	4	36.3 y	Three	120 ±12.5	1.19 ± 0.13	7.3 ± 0.9	1.02 ± 0.44	8.9 ± 2.92	0.12 ± 0.01	0.92 ± 0.32
Blouin et al. (1982)	Adults	4	27.0 y	Three	138.3 ±28.1	1.09 ± 0.07	6.7 ± 4.1	0.97 ± 0.20	4.79 ± 0.43	0.11 ± 0.03	0.39 ± 0.06
Rotschafer et al. (1982)	Adults	13	40.2 y	Two	184.1 ±52.6	1.26 ± 0.59		0.50 ± 0.33	5.6 ± 1.8	0.14 ± 0.08	0.62 ± 0.40
	Adults	11	43.9 y	Two	85.2 ±11.6	0.96 ± 0.34		0.50 ± 0.30	6.1 ± 3.1	0.10 ± 0.05	0.54 ± 0.41
Brown et al. (1983)	Adults	6	36.0 y	Two	153.7 ±54.9	2.45[g]		NR	2.6 ± 1.3	0.15[g]	0.48[g]
Matzke et al. (1984)	Adults	7[h]	46.5 y	One	87.6 ± 22.3	0.92 ± 0.36			9.1 ± 2.8		0.72 ± 0.35
Cutler et al. (1984)	Elderly	6	68.5 y	Three	97.7 ± 8.3	0.89 ± 0.06	7.8 ± 1.7	1.92 ± 0.30	12.1 ± 0.77	0.11 ± 0.02	0.76 ± 0.06

a Values expressed as means (± SD or SEM, if available).
b Number of exponentials that best describe the data.
c Patient weight ≤ 1kg.
d Patient weight > 1kg.
e Vd_{area}.
f ml/min.
g Mean value divided by mean weight; individual patient weights not reported.
h 11 observations.

Abbreviations: CL_{CR} = creatinine clearance; CL = total body clearance; $t_{1/2\alpha}$ = half-life of the initial (rapid) distribution phase; $t_{1/2\beta}$ = half-life of the slow distribution phase; $t_{1/2\gamma}$ = elimination half-life; Vc = volume of the central compartment; Vd_{ss} = volume of distribution at steady-state; NR = not reported.

Table II. Vancomycin concentrations in body fluid[a]

References	Body fluid	No. of subjects (observations)	Dose (no. of doses)	Route of admin.	Time to sample (h)	Serum conc. (mg/L)	Fluid conc. (mg/L)	Fluid/ serum ratio (%)
Geraci et al. (1957)	Ascitic							
	single-dose	10 (11)	500mg	IV	1.5 ± 0.4	6.9 ± 0.6	3.5 ± 1.4	52
	multiple-dose	2	500mg (3 or 4)	IV	2.2 ± 1.6	14.9 ± 8.1	10.7 ± 2.5	72
MacIlwaine et al. (1974)	Aqueous humour	5	500mg	IV	1.0 ± 0.2	13.8 ± 2.3	0.8	
Geraci et al. (1957)	Bile[b]	7	500mg	IV	1.0	7.6 ± 1.7	3.2 ± 0.6	42
Geraci et al. (1957)	Pericardial							
	single-dose	11	500mg	IV	2.6 ± 1.3	6.2 ± 1.2	2.3 ± 1.6	37
	multiple-dose	3	500mg (3 or 4)	IV	3.0 ± 0.5	8.6 ± 1.4	6.7 ± 1.3	78
Geraci et al. (1957)	Pleural							
	single-dose	8	500mg	IV	1.8 ± 1.1	7.2 ± 1.9	2.4 ± 1.9	33
	multiple-dose	4	500mg (4)	IV	3.0 ± 0.1	7.9 ± 2.2	4.3 ± 3.5	54
Geraci et al. (1957)	Stool	9[c]	500mg	Oral	6-40	NR	80-20,800	
Schaad et al. (1980)	Stool	2[d]	15-20 mg/kg/day	Oral	NR	0.9-1.05	85-540	85-540
	Stool	5 (6)[d]	10-15 mg/kg/day	IV	NR	NR	4.1-35.8	
Geraci et al. (1957)	Synovial	6	500mg	IV	1.3 ± 0.2	7.0 ± 1.3	5.7 ± 0.9	81
Moellering et al. (1981b)	Synovial	3	NR	IV	NR	8.0 ± 3.6	10.3 ± 2.5	129
Geraci et al. (1957)	Urine	8	500mg	IV	0-3	3.3-40.0	823 ± 411	20.6-249
					12-24	0.7-1.5	98.8 ± 35.8	66-141

a Values expressed as means (± SD or SEM, if available) or ranges.
b Data analysis excludes 1 patient who had a biliary concentration of 25 mg/L.
c Adults.
d Children.
Abbreviations: IV = intravenous; NR = not reported.

Table III. Vancomycin concentrations in body tissues following multiple-dose intravenous administration in 3 subjects[a] (data from Torres et al. 1979)

Body tissue	No. of subjects	Dose (mg/day)	Time to sample (h)	Tissue conc. (mg/L)	Serum conc. (mg/L)	Tissue/serum ratio (%)
Abscess	1	2000	NR	5	5.3	94
Aorta	1	2000	NR	34	5.3	640
Heart	1	2000	NR	7	5.3	132
Kidney						
normal renal function	1	2000	NR	243	5.3	4584
renal failure[b]	2	1000[c]	NR	7.2 ± 8.9	15.4 ± 8.7	46.9
Liver	1	2000	NR	20	5.3	377
Lung	1	2000	NR	13	5.3	245

a Values expressed as means (± SD or SEM, if available).
b Patients with oliguric chronic renal failure.
c Dose in mg/week.
Abbreviation: NR = not reported.

In contrast, two recent studies have suggested that vancomycin may be metabolised to a significant extent. Rotschafer et al. (1982), in a pharmacokinetic study of 28 patients with serious staphylococcal infections, concluded that non-renal factors may have an important influence on vancomycin elimination. These investigators demonstrated that only 50% of the variance in elimination half-life ($t_{½\beta}$) and total body clearance (CL) could be explained by renal function, age, weight, gender, and volume of distribution (calculated using β). These investigators postulated that non-renal factors, possibly hepatic conjugation, could account for these findings.

Brown et al. (1983) extended these observations in a pharmacokinetic study conducted in 15 cancer patients with normal and abnormal hepatic function (table V). These workers also concluded that vancomycin pharmacokinetics are influenced by hepatic function. Although the mean (± SD) elimination half-life in the 9 patients with abnormal hepatic function of 37.0 ± 74.3 hours (range 3.9 to 231 hours) was significantly greater than the 2.6 ± 1.3 hours (range 1.4 to 4.3 hours) observed in the 6 patients with normal hepatic function, 6 of the 9 patients with abnormal hepatic function had a $t_{½\beta}$ in the range reported for normal subjects. The accuracy of the $t_{½\beta}$ determination in this study is severely compromised by the short sampling interval of 6 hours. The data of Rotschafer et al. (1982) and Brown et al. (1983) are difficult to reconcile with those of other investigators who have found minimal non-renal clearance of vancomycin (approximately 5 ml/min) in subjects with end-stage renal disease (Cunha et al. 1981; Dunn et al. 1984; Lam et al. 1981; Matzke et al. 1984).

In summary, it appears that some non-renal clearance of vancomycin may occur in humans (approximately 5% of total body clearance). However, dosage adjustment of vancomycin in patients with hepatic impairment alone does not appear to be warranted. Since renal function may be altered in some patients with hepatic impairment, monitoring of serum creatinine concentrations is essential, and monitoring of vancomycin serum concentrations is recommended (if possible) with dosage adjustments made accordingly.

3.3.2 Excretion

Kirby and Divelbiss (1957) demonstrated 80 to 100% 24-hour urinary recovery of vancomycin fol-

Table IV. Vancomycin concentrations in cerebrospinal fluid[a]

References	Patients	No. of pts (observations)	Dose	Route of admin.	Time to sampling (h)	CSF conc. (mg/L)	Serum conc. (mg/L)	CSF/serum ratio (%)
Patients with meningitis								
Congeni et al. (1979)	Infants	2	10-15 mg/kg	IV	2	2.0-4.2	NR	
Schaad et al. (1980)	Infants	3 (12)	10-15 mg/kg	IV	NR	1.2-4.8	NR	7-21
Schaad et al. (1981)	Children	10 (23)	10-15 mg/kg	IV	NR	1.0-12.3	NR	7-37
Moellering et al. (1981b)	Adults	5 (23)		IV	NR	2.7 ± 2.5	2-51	1-7.0
Redfield et al. (1980)	Adults	2	40 mg/kg/day	IV	1-3	3.8	NR	0.1-8.2
Nolan et al. (1980)	Adults	3 (6)	1000-1500 mg/wk	IV	48-96	0.9 ± 0.4	15.9 ± 5.6	6.0 ± 1.8
Sutherland et al. (1981)	Adults	1	2000 mg/day	IV	2.0	1.2	32	3.8
		1	0.075 mg/day	Inv	6-8[b]	1.1-1.4	NR	
Patients without meningitis								
Odio et al. (1984)	Infants	8	15 mg/kg	IV	1-2	0.2-1.0	NR	
Spears & Koch (1960)	Children	7	13.3-20 mg/kg	IV	1-12	< 0.8	NR	
Kirby & Divelbiss (1957)	Adults	2	2000mg	IV	NR	0-10	50-100	0-10
Geraci et al. (1957)	Adults	9	500mg	IV	1.9 ± 0.4	0.0	6.3 ± 1.6	0

a Values expressed as means (± SD or SEM, if available) or ranges.

b Time expressed as days.

Abbreviations: IV = intravenous; Inv = intraventricular; NR = not reported.

lowing intravenous administration in normal subjects. Vancomycin renal excretion occurs primarily via glomerular filtration. The relationship of vancomycin renal clearance (CL_R) and inulin clearance has not been reported. Significant relationships between vancomycin CL_R and creatinine clearance (CL_{CR}) or ^{125}I-iothalamate clearance ($CL_{iothalamate}$) have been reported. Nielsen et al. (1975) reported the ratio of vancomycin CL_R to ^{125}I-iothalamate and creatinine clearances to be 0.79 ± 0.11 and 0.53 ± 0.11, respectively (mean ± SD). Krogstad et al. (1980) reported a mean (± SEM) vancomycin CL_R : CL_{CR} ratio of 0.68 ± 0.07. These significant differences between vancomycin CL_R and CL_{CR} suggest that either renal tubular reabsorption of the drug or significant protein binding is occurring. No direct evidence of renal tubular secretion or reabsorption of vancomycin in human subjects has been reported.

Although the difference between vancomycin CL_R and CL_{CR} is probably related to protein binding and/or some degree of renal tubular reabsorption, further studies to confirm these hypotheses are necessary.

4. Influence of Age and Various Pathophysiological States on Vancomycin Pharmacokinetics

4.1 Age

Vancomycin pharmacokinetics have been evaluated at the two ends of the age spectrum, i.e. in paediatric and geriatric patients (Cutler et al. 1984; Gross et al. 1985; Schaad et al. 1980; Schaible et al. 1984).

4.1.1 Infants and Children

Gross et al. (1985) characterised vancomycin disposition in 9 premature infants of similar gestational age (29 to 35 weeks) after single intravenous doses of 6.7 to 17.5 mg/kg administered every 8 or 12 hours. Infants weighing less than 1kg had similar total body clearances, but significantly larger volumes of distribution and lower $t_{½\beta}$ values than infants weighing greater than 1kg (CL = 1.099 ± 0.293 ml/min/kg, mean ± SD; Vd_{area} = 0.970 ± 0.426 L/kg; $t_{½\beta}$ = 9.920 ± 2.594 hours *versus* CL = 1.030 ± 0.208 ml/min/kg; Vd_{area} = 0.453 ± 0.116 L/kg; $t_{½\beta}$ = 5.348 ± 0.773 hours, respectively). These data suggest that vancomycin clearance is not directly related to conceptual age and hence renal maturity.

In contrast, Schaad et al. (1980) reported that total body clearance increased from 15 to 30 ml/min/1.73m^2, $t_{½\beta}$ decreased and no significant change in Vd_{area} occurred with an increase in gestational age (table I). These data are comparable to the observations made when aminoglycoside antibiotics are administered to premature infants and thus contradict the findings of Gross et al. (1985).

Schaad et al. (1980) also evaluated vancomycin disposition in older infants and in children up to 7.8 years of age (table I). These investigators reported a progressive increase in vancomycin total body clearance as a function of increasing age, with a peak in the 3.9-year age group. Vancomycin clearance was 25 and 30% lower in the 5.8- and 7.8-year age groups, respectively, while the elimination half-lives were similar and no significant alterations in Vd_{area} were observed.

Hence, the clearance of vancomycin in paediatric patients appears to be related primarily to the degree of renal function. No apparent age-dependent changes in vancomycin disposition when adjusted for renal function have been observed. However, caution should be exercised when calculating vancomycin doses for premature infants. With the significant interpatient variability seen in the small numbers of patients studied to date, dosing recommendations in this age group are imprecise. Serum vancomycin concentrations should be closely monitored for optimisation of therapy.

4.1.2 Elderly Patients

Only one study has dealt with the pharmacokinetics of vancomycin in the geriatric population. Cutler et al. (1984) evaluated vancomycin pharmacokinetics in 6 geriatric (age range 61 to 77 years) and 6 young (age range 20 to 26 years) healthy males with normal renal function (table I). Elderly males were noted to have significantly increased

Table V. Summary of the effects of various disease states on vancomycin pharmacokinetics[a]

References	Disease state	No. of subjects	Pharmaco-kinetic model[b]	CL_{CR} (ml/min)	CL (ml/min)	CL (ml/min/kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Vc (L)	Vc (L/kg)	Vd_{ss} (L)	Vd_{ss} (L/kg)
Dunn et al. (1984)	End-stage renal disease	10	Two	HD[c]	4.0 ± 1.2	0.055 ± 0.017		0.55 ± 0.30	188.6 ±57.4	15.8 ± 6.0	0.218 ± 0.085	64.9 ± 14.7	0.86 ± 0.28
Lam et al. (1981)	End-stage renal disease	7	Two	HD[c]	5.6 ± 2.3	NR		NR	129 ± 38.0	NR	NR	NR	0.80 ± 0.11
Cunha et al. (1981)	End-stage renal disease	5	Two	HD[c]	6.9	NR		NR	180.0	24.5	NR	67.6	NR
Matzke et al. (1984)	End-stage renal disease	36[d]	One	HD[c]	4.9 ± 2.6	0.083 ± 0.038			146.7 ± 65.5			NR	0.90 ± 0.21
Brown et al. (1983)	Impaired hepatic function	9	Two	108[e] ± 46.3	48.0 ± 48.0	NR		NR	37.0 ± 74.3	8.0 ± 4.0	NR	22.0 ± 12.0	NR
Blouin et al. (1982)	Morbid obesity	6	Three	180 ± 43.9	187.5 ± 64.7	1.11 ± 0.16	4.7 ± 3.2	0.69 ± 0.27	3.3 ± 0.6	6.4 ± 3.2	0.040 ± 0.019	43.0 ± 9.9	0.26 ± 0.03

a Values expressed as means (± SD where available).
b Number of exponentials which best describe the data.
c Patients all undergoing long term haemodialysis.
d 47 observations.
e Calculated values.

Abbreviations: See table I.

Vd_{ss} and $t_{1/2\beta}$ and reduced CL values compared with younger males (0.93 ± 0.06 L/kg, 12.14 ± 0.77h, 3.6 ± 0.2 L/h *versus* 0.64 ± 0.04 L/kg, 7.24 ± 0.39h, and 4.7 ± 0.3 L/h, mean ± SEM, respectively). These pharmacokinetic changes did not correlate with creatinine clearance. However, the CL_{CR} range was narrow in both groups, thus potentially masking any true correlations which may have been present. In addition, no significant differences in serum protein binding were observed between the two groups. These investigators hypothesised that the differences in the pharmacokinetic parameters of vancomycin in the geriatric population may be the result of altered tissue binding and/or tissue distribution volume. Further investigations are required in this area.

The potential for vancomycin accumulation in the geriatric age group due to reduced clearance may be a problem, even in patients with 'normal renal function'. Careful dosing based on creatinine clearance and serum vancomycin concentration determinations appear warranted to avoid the potential adverse effects associated with elevated vancomycin serum concentrations.

4.2 Obesity

Blouin et al. (1982) studied the pharmacokinetics of vancomycin in 4 normal [total bodyweight (TBW) 65.9 to 89.1kg] and 6 morbidly obese (TBW 111.4 to 226.4kg) subjects with CL_{CR} greater than 90 ml/min/1.73m^2 (table V). The serum concentration *versus* time data were best described by a triexponential function in all subjects. These investigators reported no significant difference between the two groups in Vc [0.04 ± 0.02 L/kg (TBW) or 0.11 ± 0.06 L/kg (ideal bodyweight; IBW) *versus* 0.11 ± 0.03 L/kg in the morbidly obese and normal groups (mean ± SD), respectively]. However, the morbidly obese subjects were noted to have a significantly smaller Vd_{ss} than the normal subjects [0.26 ± 0.03 L/kg (TBW) or 0.68 ± 0.07 L/kg (IBW) *versus* 0.39 ± 0.06 L/kg, respectively]. Elimination half-lives were also significantly shorter in the morbidly obese subjects when compared with normal subjects (3.2 ± 0.6 and 4.7 ± 0.4 hours, respectively). Although morbidly obese subjects were observed to have a significantly greater absolute actual vancomycin total body clearance than the normal subjects, this difference was nonexistent when CL was normalised per kg of total bodyweight [1.112 ± 0.160 ml/min/kg (TBW) for morbidly obese subjects and 1.085 ± 0.071 ml/min/kg for normal subjects]. Significant correlations were reported between TBW and both Vd_{ss} and CL. Furthermore, the total body clearance of vancomycin in morbidly obese patients correlated well with creatinine clearance.

These data suggest that morbidly obese patients requiring vancomycin therapy should be dosed on a mg/kg basis using TBW as in usual clinical practice. However, due to the altered $t_{1/2\beta}$ and Vd_{ss} in the morbidly obese population, this group of subjects will require smaller maintenance doses (in terms of mg/kg actual bodyweight) administered at more frequent intervals in order to achieve and maintain the desired vancomycin serum concentration *versus* time profile.

4.3 Renal Impairment

As vancomycin is primarily excreted unchanged by the kidneys, the progressive prolongation of $t_{1/2\beta}$ and reduction of total body clearance noted as renal function declines is not unexpected (table V) [Cunha et al. 1981; Dunn et al. 1984; Lam et al. 1981; Matzke et al. 1984; Moellering et al. 1981a; Nielsen et al. 1975]. Vancomycin total body clearance declined from mean values of 74.6 to 158.6 ml/min in subjects with CL_{CR} greater than 80 ml/min, to 4.0 to 6.8 ml/min in patients with end-stage renal disease undergoing haemodialysis (Cunha et al. 1981; Dunn et al. 1984; Lam et al. 1981; Matzke et al. 1984). Volume of distribution at steady-state did not change significantly with declining renal function, with mean values of 0.39 to 0.92 L/kg in subjects with CL_{CR} greater than 80 ml/min and 0.80 to 0.90 L/kg in patients with end-stage renal disease undergoing haemodialysis.

Although marked variability in vancomycin total body clearance within a defined range of renal function has been observed, highly significant re-

lationships of vancomycin clearance and creatinine clearance have been reported by Nielsen et al. (1975), Moellering et al. (1981a), and Matzke et al. (1984). The degree of decline in vancomycin clearance (ml/min = 3.66 + 0.689 × CL_{CR}) and elimination rate constant (h^{-1} = 0.0044 + 0.00083 × CL_{CR}) associated with various degrees of renal impairment have been characterised by Matzke et al. (1984). In addition, 77 to 85% of the variability in vancomycin clearance has been ascribed to changes in CL_{CR} (Matzke et al. 1984; Moellering et al. 1981a). These relationships have been utilised to calculate dosing regimens for vancomycin use in patients with renal impairment (Matzke et al. 1984; Moellering et al. 1981a; Nielsen et al. 1975) [see section 6.1].

4.4 Dialysis

Numerous factors affect the removal of a drug by dialysis, including physicochemical properties of the drug, mechanical properties of the dialysis system, blood flow and/or dialysate flow rates during the dialysis procedure, and pharmacokinetic characteristics of the drug. The primary impact of dialysis procedures appears to be enhancement of drug clearance by providing an additional route of vancomycin elimination. Although patients on long term haemodialysis have been noted to have altered disposition of several compounds, apparently by other mechanisms such as altered protein or red blood cell binding, tissue uptake, volume of distribution, or metabolism, no data are available to confirm the presence or absence of dialysis-associated changes in these aspects of vancomycin pharmacokinetics.

The effect of dialysis on vancomycin elimination can be quantitated in several ways. Although measurements of changes in $t_{1/2\beta}$ or total body clearance between and during dialytic periods and calculation of dialysis clearance values are useful, calculation of the fraction of drug in the body which is removed by the dialysis procedure provides an independent index of the relative efficiency of various dialysis procedures.

4.4.1 Haemodialysis

Lindholm and Murray (1966) concluded that vancomycin was dialysable, but so slowly that the dosage schedule need not be modified for persons undergoing haemodialysis. These conclusions were drawn from *in vitro* studies based on a two-pool dialysis experimental technique. However, this method of assessment did not simulate the blood flow or dialysate flow rates that are used during clinical dialysis procedures. Although reports of vancomycin therapy in patients on long term haemodialysis appeared in the 1970s, these studies did not evaluate the effect of the dialysis procedure on vancomycin serum concentrations (Barcenas et al. 1976; Eykyn et al. 1970; Morris & Bilinsky 1971).

Based on their clinical observations of 13 hospitalised, critically ill, anephric patients undergoing haemodialysis every 48 hours, Wilson and Van Scoy (1978) suggested that some anephric patients may require vancomycin dosing as infrequently as every 2 days. This suggestion led to further evaluation of the effects of haemodialysis on vancomycin elimination. The variability of results derived from these studies may be the result of use of multiple different dialysers.

Bierman et al. (1980) measured pre- and post-haemodialysis vancomycin serum concentrations in a single subject undergoing treatment for a serious staphylococcal infection. A minimal decline in vancomycin serum concentration during haemodialysis was reported (24.5 ± 2.0 to 21.5 ± 2.0 mg/L). Schaad et al. (1981) obtained serum specimens immediately before and after 4-hour haemodialysis periods on 6 occasions and reported reductions in vancomycin serum concentration over the dialysis period of 0.8 to 3.0 mg/L (mean 2.0 mg/L). Salem et al. (1984) recently evaluated the haemodialysis clearance of vancomycin in 6 subjects with end-stage renal disease. The dialysis clearance, calculated by quantitating the amount of vancomycin removed in the dialysate, exceeded the patients' total body clearance of vancomycin by a factor of 5 (table VI). However, only 7.6% (approximately 45mg) of the vancomycin dose was removed during the dialysis procedure. These studies suggest that minimal removal occurs during

Table VI. Effects of dialysis on vancomycin pharmacokinetics

References	Dialysis method	No. of subjects	Route of admin.	Half-life ($t_{½\beta}$) during dialysis (h)	Half-life ($t_{½\beta}$) off dialysis (h)	Vd_{ss} (L/kg)	CL_{PT} (ml/min)	CL_T (ml/min)	CL_D (ml/min)	C_{pre} (mg/L)	C_{post} (mg/L)	ΔC (mg/L)	C_D (mg/L)	Serum/C_D (%)
Salem et al. (1984)	HD	6	IV				3.4		16.1					
Ahmad et al. (1982)	HP	1	IV						23.6[a]	37.0	21.5	15.5		
									85.2[b]	29.0	9.0	20.0		
Nielsen et al. (1979)	IPD	11	IV	18					6.1			. . .[c]	0-10	
Ayus et al. (1979)	IPD	1[d]	IV	43.4	184.8	37.2[e]	2.3		9.8	11-23				1.27
	IPD	1[d]			262	58.7[e]	2.1						1-9	1.26
Glew et al. (1982)	IPD	1[d]	IV	30					14.2	15	11	4	4.4	3.7
	IPD	1[d]	IP							3-7			0-22.5	
Magera et al. (1983)	IPD	4[d]	IV		205.2	1.07			2.34	6.3	5.8		4-33.0	1.22
Pancorbo & Comty (1982)	CAPD	4	IP	66.9		0.43			2.40					
Bunke et al. (1983)	CAPD	6	IP	65.8		1.29[f]		15.1	2.50				1.6-9.4	
	CAPD	6	IV	81.5		0.88[f]		9.4	1.48				1.3-4.1	
Blevins et al. (1984)	CAPD	4	IV	90.2		0.73		6.4	1.35				1.0-5.0	4.0
Talbert et al. (1983)	CAPD	1[d]	IV	61.5		0.48		3.0	1.13					
Harford et al. (1984)	CAPD	5/7[d]	IV	93.5		49[e]		4.9	3.82					

a Gambro charcoal cartridge.
b Amberlite XAD-4 resin cartridge.
c Serum concentration decreased by 39.7% in 15 hours.
d Peritonitis patients.
e Total volume (L).
f Vd_{area}.

Abbreviations: CL_{PT} = total body clearance (CL) off dialysis; CL_T = CL during dialysis; CL_D = dialysis clearance; C_{pre} and C_{post} = serum concentration pre- and post-dialysis; ΔC = change in serum concentration during dialysis; C_D = dialysate concentration; HD = haemodialysis; HP = haemoperfusion; IPD = intermittent peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; IV = intravenous; IP = intraperitoneal.

haemodialysis and thus no dosage supplementation is required after the procedure.

4.4.2 Haemoperfusion

Haemoperfusion through activated charcoal or exchange resin cartridges may be useful in the treatment of drug intoxications, especially overdose situations (Blye et al. 1984). One recent case report has suggested that prompt reductions in vancomycin serum concentration and increases in vancomycin clearance may be obtainable with this form of therapy. Ahmad et al. (1982), utilising haemoperfusion with charcoal and XAD-4 resin cartridges, reported vancomycin clearance values of 23.6 and 85.2 ml/min, respectively, and prompt, sharp declines in vancomycin serum concentrations in the 1 subject evaluated (table VI). These clearance values were substantially greater than those expected on the basis of the patient's renal function (less than 10 ml/min).

Based on these extremely limited data, haemoperfusion would appear to be the method of choice for extracorporeal removal of vancomycin. Active measures to remove vancomycin would seldom be indicated; usually only in the inadvertent overdose situation.

4.4.3 Intermittent Peritoneal Dialysis

The pharmacokinetics of vancomycin have been evaluated in 21 patients undergoing intermittent peritoneal dialysis (IPD) [table VI; Ayus et al. 1979; Glew et al. 1982; Magera et al. 1983; Nielsen et al. 1979]. Nielsen et al. (1979) reported a mean peritoneal dialysis clearance of 6.1 ml/min and observed an approximate 40% decline in serum vancomycin concentration during the 15 hours after dosing in uninfected IPD patients. These authors concluded that vancomycin was significantly cleared by peritoneal dialysis and that supplemental dosing upon completion of dialysis was necessary to maintain effective drug concentrations. Unfortunately, they did not determine vancomycin total body clearance and only measured serum concentrations for 15 hours after drug administration. In addition, the vancomycin serum concentration *versus* time profile between dialyses was not assessed. Thus, the contribution of the dialysis procedure to total body clearance and the incremental decrease in serum concentration is really unknown.

The three studies examining vancomycin pharmacokinetics during IPD in patients suffering from peritonitis have yielded variable results. While the 2 patients studied by Ayus et al. (1979) and Glew et al. (1982) had dialysis clearance values of 9.8 and 14.2 ml/min, respectively, the 2 patients of Magera et al. (1983) had dialysis clearances of only 1.0 and 3.6 ml/min. No appreciable differences (6.3 ± 1.2 mg/L *versus* 5.8 ± 1.1 mg/L, mean ± SD) in pre- and post-dialysis serum vancomycin concentrations, respectively, were noted. These investigators calculated that only 60mg of a single 1g intravenous vancomycin dose would be cleared during a week of IPD at 14 hours per day. These data thus suggest minimal clearance of vancomycin by IPD.

Since the IPD clearance of vancomycin is quite variable (1.0 to 19.8 ml/min), it is possible that IPD may have a significant impact on vancomycin total body clearance. The use of IPD for continuous periods in excess of 24 to 48 hours may require dosage supplementation following the procedure (Ayus et al. 1979; Glew et al. 1982). Monitoring of serum concentrations is recommended in this situation with subsequent individualisation of the dosage regimen (Sawchuk et al. 1976).

4.4.4 Continuous Ambulatory Peritoneal Dialysis

Continuous ambulatory peritoneal dialysis (CAPD) utilises the constant presence of dialysate solution in the abdominal cavity for removal of waste products and maintenance of fluid and electrolyte homeostasis. The pharmacokinetics of vancomycin during CAPD have been extensively and rigorously evaluated following both intravenous and intraperitoneal drug administration and provide sound pharmacokinetic data in this population (Blevins et al. 1984; Bunke et al. 1983; Harford et al. 1984; Pancorbo & Comty 1982; Talbert et al. 1983) [table VI].

Intravenous vancomycin therapy has resulted

in the attainment of dialysate concentrations in excess of the minimal inhibitory concentration (MIC) for most susceptible Gram-positive organisms (Blevins et al. 1984; Harford et al. 1984). All 5 published studies have documented similar $t_{1/2\beta}$ and CAPD clearance values. The $t_{1/2\beta}$, however, is markedly shorter (range 61 to 90 hours) in this patient population than in subjects undergoing IPD or haemodialysis. Furthermore, although peritoneal penetration of vancomycin may be increased in the presence of peritonitis, no significant difference in vancomycin pharmacokinetic parameters has been demonstrated in patients with peritonitis. Various dosage recommendations for intravenous vancomycin have been proposed to maintain either a peak and trough concentration profile (23 mg/kg IV followed by 17 mg/kg IV every 7 days) or a relatively constant serum concentration profile (30 mg/kg IP followed by 1.5 mg/kg IP every 6 hours) [Blevins et al. 1984; Bunke et al. 1983].

The pharmacokinetics of vancomycin following intraperitoneal administration (Bunke et al. 1983; Pancorbo & Comty 1982) suggest that there is no significant difference in the elimination half-life of vancomycin relative to that observed after intravenous administration. Approximately 54 to 65% of the intraperitoneally instilled dose is absorbed systemically. The CAPD clearance is approximately 1 ml/min greater than that reported following intravenous administration; however, the ratio of CAPD clearance to total body clearance is similar with both administration routes. The intraperitoneal route of administration is not associated with any significant alterations in the pharmacokinetic parameters of vancomycin and may therefore be an alternative route for administration of vancomycin to CAPD patients.

5. Adverse Effects of Vancomycin: Incidence and Relationship to Serum Concentrations

Although early reports suggested that vancomycin therapy was frequently associated with the appearance of adverse events, the actual number of patients who have experienced adverse reactions while receiving vancomycin is small and incidence data are extremely difficult to ascertain. Recently, several reports have documented that vancomycin is an extremely safe drug. A review of the literature from 1956 to 1985 has revealed only 2 major and 6 minor or rare adverse effects (Matzke 1986).

5.1 Nephrotoxicity

Although vancomycin-associated nephrotoxicity has been reported by many investigators during the past 30 years (Matzke 1986), the incidence of nephrotoxicity (0 to 5.7%, depending on the series) has not changed significantly. The incidence of vancomycin-associated nephrotoxicity during the 1950s and 1960s is difficult to document because many of the subjects had received concomitant aminoglycoside therapy, had pre-existing renal disease, and/or had life-threatening staphylococcal infections with accompanying failure of one or more major organ systems.

The relationship of nephrotoxicity to vancomycin serum concentrations is difficult to determine, as most investigators either did not perform serum concentration monitoring or did not specify the timing of blood sampling in relation to drug administration. The sparse data available suggest that patients developing nephrotoxicity tend to have vancomycin trough concentrations of 30 mg/L or greater and that a return of the serum creatinine concentration to baseline may be associated with dosage reduction (Farber & Moellering 1983).

Recent studies suggest that the earlier, less purified preparations of vancomycin may have had more nephrotoxic potential than the preparation in use today. Over 50% of the reported cases of vancomycin nephrotoxicity appeared in the literature during the first 6 years of its clinical use (Dangerfield et al. 1960; Waisbren et al. 1960; Woodley & Hall 1961). It was not until the 1970s that the more purified product came into clinical use. Farber and Moellering (1983) recently completed a retrospective study of 98 patients receiving a total of 100 courses of vancomycin between the years 1974 and 1981. These researchers reported a 5% incidence of nephrotoxicity in subjects treated with vancomy-

cin alone. Nephrotoxicity was reversible in the majority of cases even when therapy was continued, usually after dosage reduction.

Vancomycin nephrotoxicity in subjects receiving concurrent aminoglycoside therapy has been reported to be additive and the incidence to be as high as 35% (Farber & Moellering 1983; Odio et al. 1984). Aronoff et al. (1981) demonstrated that doses of vancomycin in rats of up to 400 mg/kg/day did not alter renal function. Wold and Turnipseed (1981) documented a similar lack of vancomycin nephrotoxicity in rats. However, concomitant administration of vancomycin and tobramycin resulted in a significant decline in renal function compared with the lack of functional change noted with either agent alone. Further studies will be required to delineate the risk, incidence, and serum concentration dependence of combination vancomycin/aminoglycoside nephrotoxicity.

5.2 Ototoxicity

Vancomycin-associated ototoxicity has been difficult to assess as most patients have not received audiometric testing during the course of therapy. As a result, assessment of ototoxicity was neither sufficiently sensitive nor specific and thus hearing deficiencies were not reported unless they were substantial and at lower frequencies within the hearing range (2000 to 3000Hz). Although the incidence of vancomycin-associated ototoxicity (1.4 to 5.5%, depending on the series) has not changed significantly over the past 30 years (Matzke 1986), it is difficult to draw conclusions from early reports because many patients had risk factors previously mentioned predisposing them to ototoxicity.

The precise relationship between serum vancomycin concentrations and ototoxicity is unknown since most investigators either did not perform serum concentration monitoring or did not specify the timing of blood sampling in relation to drug administration. Despite this lack of precision, it appears that vancomycin ototoxicity is most frequently associated with serum concentrations in the range of 80 to 100 mg/L or greater (Dutton & Elmes 1959; Geraci et al. 1958; Kirby et al. 1960).

During the 1970s and 1980s, data were reported that suggested a causal relationship between vancomycin administration, vancomycin serum concentration (peak concentrations of 25 to 50 mg/L and trough concentrations of 13 to 32 mg/L), and auditory toxicity (Ahmad et al. 1982; Hook & Johnson 1978; Morris & Bilinsky 1971; Sorrell et al. 1982; Traber & Levine 1981). These data also suggested that ototoxicity may be reversed, if not prevented, by close monitoring of vancomycin serum concentrations. However, whether excessive peak or excessive trough vancomycin concentrations are primarily related to the development of ototoxicity is unknown. Recently, Farber and Moellering (1983) reported no clinically apparent cases of auditory toxicity in 98 patients treated with 100 courses of vancomycin.

In summary, although ototoxicity has been associated with vancomycin therapy, the incidence in general is less than 2%.

5.3 'Red-Neck Syndrome'

Rapid intravenous administration of vancomycin has resulted in a histamine-like reaction characterised by flushing, tingling, pruritus, tachycardia, and an erythematous, macular rash involving the face, neck, upper trunk, back and arms with sparing of the rest of the body. Systemic arterial hypotension or shock has also been noted (Ackerman & Bradsher 1985; Garrelis & Peterie 1985; Holliman 1985; Matzke 1986). The incidence of this reaction (5.3 to 11.2%, depending on the series) has not changed appreciably over the 30 years of clinical use of the drug. The mechanism of this reaction appears to be a dose-dependent histamine-mediated depression of myocardial contractility (Dajee et al. 1984; Miller & Tausk 1977). Recent data suggest that this syndrome can be avoided by infusing vancomycin at a rate no greater than 15 mg/min (Newfield & Roizen 1979).

5.4 Miscellaneous Adverse Reactions

5.4.1 Skin Rashes

Maculopapular or erythematous skin rashes have been observed in 2 to 6.5% of patients treated with

vancomycin (Matzke 1986). The incidence of rash was highest in the 1950s but declined in the 1960s, and has stabilised at approximately 2 to 3%. Farber and Moellering (1983) recently reported 3 cases of rash during 100 courses of vancomycin. In all 3 instances, the rash resolved with discontinuation of the drug.

5.4.2 Thrombophlebitis, Chills and Fever

Early preparations of vancomycin were associated with a greater than 50% incidence of chemical thrombophlebitis. The incidence has declined to approximately 6% during the 1970s and 1980s with the advent of the purer preparation (Matzke 1986).

Similar incidence data have also been reported for vancomycin-associated chills and fever (Matzke 1986). Farber and Moellering (1983) recently documented significantly lower incidences of thrombophlebitis, chills, and fever over the period from 1974 to 1981 compared to the 1950s and 1960s, suggesting that these adverse reactions were probably related to impurities in the early preparations which have been eliminated by current manufacturing techniques.

5.4.3 Neutropenia

Case reports of vancomycin-associated neutropenia have increased significantly in the 1970s and 1980s, probably secondary to the increased use of the drug in the long term therapy of endocarditis and osteomyelitis (Mackett & Guay 1985; Matzke 1986). The aetiology of this reaction is unclear, and no relationship between this adverse effect and vancomycin dose or serum concentration has been reported. Farber and Moellering (1983) reported 2 cases of neutropenia in 100 courses of vancomycin (2%). Both patients received greater than 3 weeks of therapy and the leucocyte count promptly returned to normal after discontinuation of the drug. As the leucocyte count was not monitored prospectively in all patients in this study, this incidence figure is probably an underestimate. Periodic monitoring of the leucocyte count is recommended in patients receiving long term (greater than 2 weeks) vancomycin therapy.

6. Implications of Pharmacokinetic Properties for Clinical Use

Evidence of multicompartment pharmacokinetic characteristics (table I), unpredictability of serum vancomycin concentrations (Alpert et al. 1984), and possible non-renal elimination (Brown et al. 1983; Rotschafer et al. 1982) suggest that the disposition of vancomycin may be quite complex. The unpredictability of peak and trough serum vancomycin concentrations may be related to the use of variable infusion times (Banner & Ray 1984), altered drug distribution (Blouin et al. 1982), altered renal function (Matzke et al. 1984; Moellering et al. 1981a), and other factors such as age (Cutler et al. 1984; Gross et al. 1985; Schaad et al. 1980) and altered tissue binding (Cutler et al. 1984).

In addition to these pharmacokinetic factors, the specific infectious and clinical status of the patient must be considered when an initial dosing regimen is being designed. The site and severity of infection, the suspected pathogen, concomitant disease states, and concomitant antimicrobial therapy are variables that should be considered when designing and modifying vancomycin dosing regimens.

6.1 Dosing Considerations

Initial assessment of the patient's renal function, the type and site of infection and other risk factors should result in an improved approach to initial dosing of vancomycin. At present, adults with impaired renal function, elderly patients, morbidly obese patients, and paediatric patients may derive additional benefit from an individualised dosing approach based on serum concentration determinations.

Four dosing methods which have been proposed to achieve and maintain desired vancomycin serum concentrations (Matzke et al. 1984; Moellering et al. 1981a; Nielsen et al. 1975; Rotschafer et al. 1982) have recently been compared by Matzke et al. (1985). These investigators performed a retrospective assessment of these 4 methods in 24 subjects with various degrees of renal function (CL_{CR} range 10 to 130 ml/min). The mean

percentage error in the calculated *versus* actual maintenance dose required to maintain mean steady-state serum concentrations of 15 mg/L was 10.9 and 8.1% for the Moellering et al. (1981a) and Matzke et al. (1984) methods, respectively (see figs 4 and 5). The predicted doses did not differ significantly from the actual doses. Although the mean difference in maintenance dose determined from the Nielsen et al. (1975) formula was similar to that of the other two methods (−9.3%), it was statistically different from the actual dose and the doses predicted by the Moellering et al. (1981a) and Matzke et al. (1984) methods. The Rotschafer et al. (1982) method was the least precise; it substantially overpredicted maintenance doses.

These data suggest that, depending upon the desired serum concentration *versus* time profile, the Moellering et al. (1981a) and Matzke et al. (1984) methods would have the greatest likelihood of producing the desired serum concentration *versus* time profile. However, significant variability was observed with both methods (range of error, −40% to +242%). Further individualisation of vancomycin dosing using serum concentration determinations is recommended, particularly when the severity of the infection justifies the added cost.

6.1.1 Individualising the Dosage

The following procedure is recommended for individualisation of vancomycin therapy. A loading dose of vancomycin should be calculated on

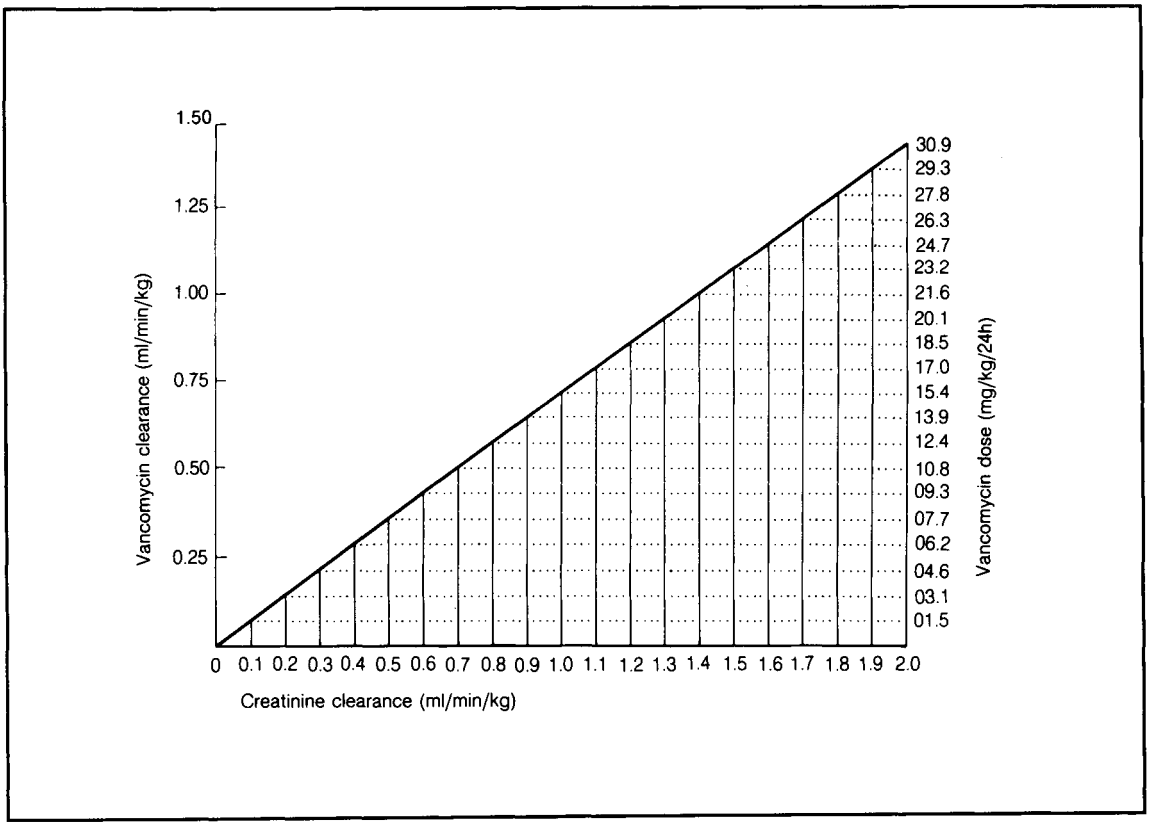

Fig. 4. Dosage nomogram for vancomycin in patients with impaired renal function. The nomogram is not valid for functionally anephric patients on dialysis; for such patients, the dose is 1.9 mg/kg/day. The therapeutic goal is an average steady-state concentration of 15 mg/L (reproduced with permission from Moellering et al. 1981a).

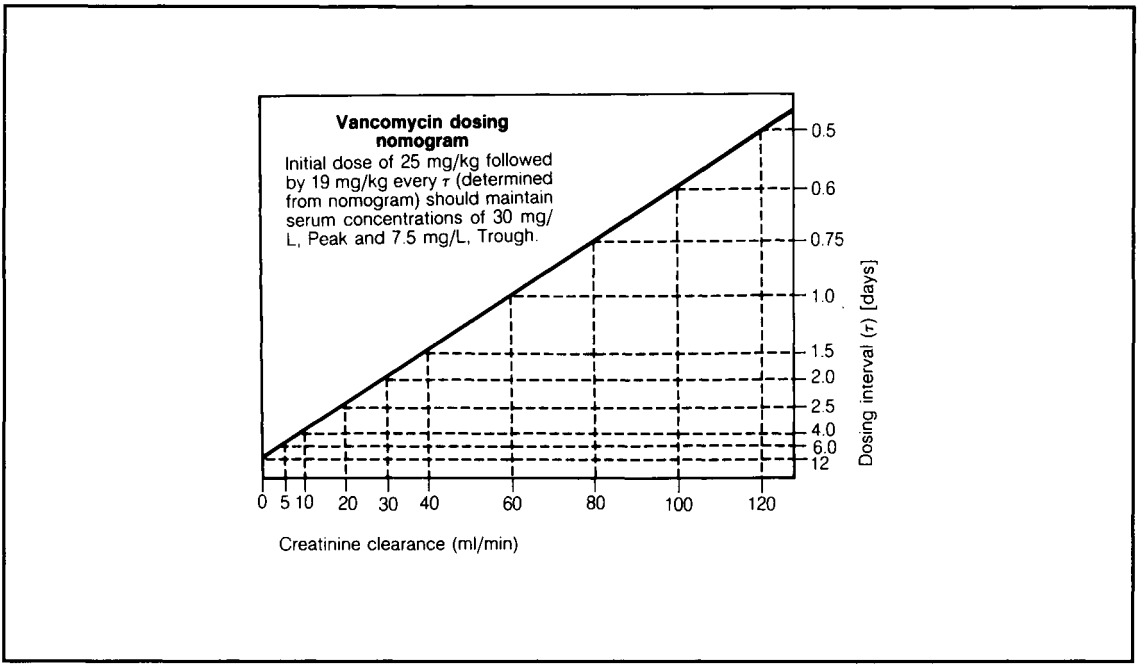

Fig. 5. Dosage nomogram for vancomycin in patients with various degrees of renal dysfunction. The nomogram is not valid for peritoneal dialysis patients. The therapeutic goal is peak and trough serum concentrations of 30 and 7.5 mg/L (reproduced with permission from Matzke et al. 1984).

the basis of: (a) the patient's total bodyweight (kg); (b) the appropriate volume of distribution estimate from population data (L/kg); and (c) the desired peak serum concentration (mg/L). Initial maintenance dose and dosing interval can then be calculated on the basis of estimated terminal elimination rate, desired peak and trough serum concentrations or serum concentration *versus* time profile, and use of 1 of the 4 dosing methods mentioned previously.

Although peak and trough serum concentrations for the individual patient will depend on previously mentioned factors, in general, peak and trough serum concentrations should be about 8 times and 1 to 2 times the minimum inhibitory concentration of the pathogen, respectively. The elimination rate constant of vancomycin in adults can be estimated from the relationship between CL_{CR} and terminal elimination rate (Matzke et al. 1984). In some subjects with serum creatinine concentrations of less than 1 mg/dl, the calculated CL_{CR} may be exceedingly high. In these subjects, use of 120 ml/min as a conservative estimate of CL_{CR} is recommended as the basis of initial dosing until vancomycin clearance can be measured. The terminal elimination rate constant can be approximated in paediatric patients from the relationship between age and elimination rate (Schaad et al. 1980).

6.1.2 Paediatric Dose Guidelines

Dosing recommendations for the initiation of vancomycin therapy in paediatric patients have been defined by Schaad et al. (1980). With use of their age-specific guidelines, Schaad et al. (1980, 1981) reported excellent agreement between desired and actual serum concentrations. However, Alpert et al. (1984), using the same dosing guidelines, found that 30 to 70% of peak vancomycin

concentrations and 25 to 53% of trough vancomycin concentrations exceeded the desired maximum values of 30 mg/L and 12 mg/L, respectively. Further investigation will be required to determine the reason for these disparate results in therapy of paediatric patients.

6.1.3 Dose Guidelines in Dialysis Patients

Haemodialysis (Salem et al. 1984) and intermittent peritoneal dialysis (Ayus et al. 1979; Glew et al. 1982; Magera et al. 1983; Nielsen et al. 1979) procedures have resulted in minimal alterations in the pharmacokinetics of vancomycin. Although vancomycin total body clearance is enhanced during the time of the dialysis procedure, the amount of vancomycin removed during usual periods of haemodialysis and intermittent peritoneal dialysis is minimal and thus no dosage supplementation is required. However, the effect of continuous ambulatory peritoneal dialysis on the pharmacokinetics of vancomycin may be significant (Blevins et al. 1984; Bunke et al. 1983; Harford et al. 1984; Pancorbo & Comty 1982; Talbert et al. 1983). The fractional addition of continuous ambulatory peritoneal dialysis to vancomycin clearance is similar to that observed with intermittent peritoneal dialysis. The application of this dialysis mode on a 24-hour daily basis does result in a significant impact on the elimination rate constant and total body clearance of vancomycin.

Guidelines for the initiation of vancomycin therapy in CAPD patients have been proposed and may be used for initial dosing recommendations (Blevins et al. 1984; Bunke et al. 1983). However, since significant variability has been reported in the $t_{1/2\beta}$ and Vd_{ss} of vancomycin, individualisation of dosing based on serum concentration measurements is recommended.

6.2 Therapeutic Drug Monitoring of Vancomycin Serum Concentrations

Although the pharmacokinetic profile of vancomycin is best described by a 2- or 3-compartment model, the collection of a sufficient number of serum concentrations to perform these characterisations in individual patients is not practical or cost-justified in routine clinical practice. Therefore an approach similar to that used for the aminoglycoside antibiotics appears to be most practical. The fractional error in vancomycin total body clearance that will be present if one assumes a 1-compartment rather than a 2- or 3-compartment model for disposition of vancomycin, and the degree of multicompartmental character of the data, can be ascertained by determining the ratios of the distribution volumes calculated from the 2- or 3-compartment data (Wagner 1983). Furthermore, it is possible to assess how well the 1-compartment model predicts the average amounts of drug in the body when a multicompartment model is actually operative (Wagner 1983). When the criteria of Wagner (1983) are applied to the vancomycin pharmacokinetic data in the literature, the error in vancomycin clearance prediction is less than 10%. Therefore, the use of a 1-compartment open model to describe the pharmacokinetics of vancomycin in the clinical setting should be adequate for most patients.

Blood samples for measuring vancomycin serum concentrations after an intravenous infusion should be designed to encompass one elimination half-life, whenever possible. To determine the blood sampling times, one may use an estimate of the patient's CL_{CR}, a measured CL_{CR} or population-averaged kinetic parameters to obtain a projection of the patient's elimination half-life.

Banner and Ray (1984) have recently raised the question of what constitutes a 'peak' vancomycin concentration, and its relationship to efficacy and toxicity. The true peak concentration for this multicompartment drug would be expected to occur immediately at the end of the infusion period. Data on efficacy and toxicity of vancomycin, however, have been based primarily on 'peak' concentrations determined during the initial hour after a bolus injection or 1 to 2 hours after an intravenous infusion. This variability in the times at which 'peak' concentrations have been obtained and the expected alteration in peak concentrations when the

same dose is administered over different time intervals make interpretation of the relationship between toxicity and/or efficacy and peak serum concentration extremely difficult.

Clinically, it seems most appropriate to monitor vancomycin in a manner similar to that used for aminoglycosides. Peak vancomycin concentrations, for the purpose of clinical pharmacokinetic monitoring and for the establishment of efficacy and toxicity correlations, should be determined after the distribution phase is completed. Using the criteria of 5 times the distribution half-life to define the end of the distribution phase, the measurement of peak concentrations at least 3 hours after the end of an intravenous infusion should be adequate in most situations. Trough concentrations should be obtained just before or within 1 hour of the next scheduled dose.

For patients with stable renal function, peak and trough vancomycin serum concentrations should be determined when the patient has reached steady-state on the dosing schedule. If the actual peak and trough values are within 20% of the desired peak and trough concentrations, the patient may remain on the current dosage regimen. If the vancomycin serum concentrations are inconsistent with the desired values, a new dosing regimen should be designed.

For patients with fluctuating renal function, a predose serum concentration and a series of postdose serum concentrations should be obtained early during the course of therapy. Assessment of serum concentration *versus* time data should include determination of the patient's $t_{1/2\beta}$ and elimination rate constant based on linear or non-linear regression analysis of the log serum concentration *versus* time data.

The Vd_{ss} can then be estimated either by model-independent techniques (Gibaldi & Perrier 1982) or by standard 1-compartment first-order equations (Sawchuk & Zaske 1976). Once the patient's pharmacokinetic parameters have been calculated, the most appropriate dose and dosage interval to achieve the desired serum concentrations can be determined using the equations of Sawchuk and Zaske (1976).

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