Clearance of Vancomycin during High-Efficiency Hemodialysis in End Stage Renal Disease Patients

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ชื่อวิทยานิพนธ์	อัตราการกำจัด vancomycin ในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายขณะทำ hemodialysis แบบมีประสิทธิภาพสูง
ผู้เขียน	นางสาวณัฏฐา กลั่นสุวรรณ
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บทคัดย่อ

มีการใช้ยา Vancomycin อย่างแพร่หลายสำหรับรักษาการติดเชื้อแบคทีเรีย MRSA โดยเฉพาะในผู้ป่วยโรคไตที่ได้รับการล้างไตบ่อย ๆ เนื่องจากยามีการกำจัดทางไตเกือบทั้งหมด การกำจัดจึงลดลงอย่างมากในผู้ป่วยไตบกพร่องรุนแรง และมีรายงานว่า ในผู้ป่วยที่ได้รับการทำ high-flux หรือ high-efficiency hemodialysis มีการกำจัดยา vancomycin อย่างมีนัยสำคัญ การศึกษานี้จึงมีวัตถุประสงค์เพื่อหาอัตราการกำจัด (clearance) ของ vancomycin ในผู้ป่วยที่เข้ารับการทำ high-efficiency hemodialysis เพื่อกำหนดแนวทางการปรับขนาดยา vancomycin ให้เหมาะสมในผู้ป่วย โดยทำการศึกษาในผู้ป่วยโรคไตที่เข้ารับการทำ hemodialysis และใช้เมมเบรนชนิด cellulose triacetate ณ โรงพยาบาลสงขลานครินทร์ ระหว่าง มกราคม 2546 ถึง มีนาคม 2547 โดยผู้ป่วยติดเชื้อ MRSA และได้รับยา vancomycin ขนาด 1 กรัม ฉีดเข้าหลอดเลือดดำนาน 1 ชั่วโมง หลังเสร็จสิ้นการทำ hemodialysis ในแต่ละรอบมีการเจาะเลือดผู้ป่วยตามเวลาที่กำหนด จำนวน 6 ครั้ง ดังนี้ (1) ที่ 1 ชั่วโมงหลังได้รับยา vancomycin (2) ก่อนเริ่มทำ hemodialysis ครั้งที่ 2 (3) ระหว่างการทำ hemodialysis ครั้งที่ 2 (4) เมื่อเสร็จสิ้นการทำ hemodialysis ครั้งที่ 2 (5) ก่อนเริ่มทำ hemodialysis ครั้งที่ 3 และ (6) เมื่อเสร็จสิ้นการทำ hemodialysis ครั้งที่ 3 การศึกษานี้เก็บข้อมูลทั้งหมดจำนวน 24 ครั้ง (ผู้ป่วย 20 คน โดย 2 คนมีการเก็บข้อมูล 2 รอบและ 1 คน เก็บข้อมูล 3 รอบ) วิเคราะห์หาระดับยา vancomycin ในซีรั่มโดยวิธี HPLC และคำนวณค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของระบบ พบว่า ค่าพารามิเตอร์ (ค่าเฉลี่ย$\pm$ค่าเบี่ยงเบนมาตรฐาน) มีดังนี้ อัตราการกำจัดยา vancomycin 93.4$\pm$37.1 มิลลิลิตร/นาที และร้อยละการกำจัดยาหลัง hemodialysis ครั้งที่2 เป็น 37.1$\pm$13.1 มีระดับยาสูงสุด (การเจาะเลือดครั้งที่ 1 หลังได้รับยา) 25.3$\pm$8.1 มิลลิกรัม/ลิตร (พิสัย 12.0-48.8) และพบว่า ร้อยละ 66.7 (16/24) และ 91.6 (22/24) มีระดับยาต่ำกว่าช่วงการรักษาหลังการทำ hemodialysis ครั้งที่ 2 และ ครั้งที่ 3 ตามลำดับ จากการศึกษา สรุปได้ว่าปริมาณ vancomycin ถูกกำจัดออกอย่างมีนัยสำคัญ หลัง hemodialysis ผู้ป่วยควรได้รับ vancomycin ขนาดเริ่มต้น 1 กรัม และได้รับยา 500 มิลลิกรัม หลัง hemodialysis แต่ละครั้ง

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ABSTRACT

Vancomycin is commonly used for treatment of gram-positive (MRSA) infections in critically ill patients with end-stage renal disease. Vancomycin is mainly eliminated through kidney. Its excretion is therefore substantially reduced in severe renal impaired patients. Although several studies demonstrated that significant amounts of vancomycin are removed during high-flux/high-efficiency hemodialysis, more data are required to optimize clinical applications in our setting. We determined vancomycin clearance in 20 patients with end-stage renal diseases who were receiving high-efficiency hemodialysis with cellulose triacetate dialyzer at Songklanagarind Hospital during January 2003 and March 2004. The clearance would then be used to predict appropriate vancomycin dosage and dosing interval among these patients. In a prospective opened label design, 20 patients (two patients were included twice and one of them was included three times) received 1g vancomycin, 1 hour infusion, immediately after hemodialysis. Six scheduled blood samples were drawn as followed: (1) 60 minutes after vancomycin infusion (C_{peak}); (2) immediately before starting the second hemodialysis; (3) 2 hours after starting the second hemodialysis; (4) immediately after the second hemodialysis; (5) immediately before starting the third hemodialysis; and (6) immediately after the third hemodialysis (C_{min}). We measured vancomycin serum levels using HPLC technique. The serum concentrations were used to calculate all relevant pharmacokinetic parameters. The pharmacokinetic parameters (mean$\pm$SD) were: clearance 93.4$\pm$37.1 ml/min; %removal of vancomycin after the second hemodialysis 37.1$\pm$13.1: peak plasma concentration 25.3$\pm$8.1 mg/L (range 12.0-48.8); subtherapeutic levels were found in 66.7% (16/24) and 91.6% (22/24) after the second and the third hemodialysis, respectively. In conclusion, hemodialysis with cellulose triacetate

dialyzer under our dialysis condition removes significant amount of vancomycin, a loading dose of 1 g, and 500 mg after every subsequent hemodialysis is recommended.

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LIST OF ABBREVIATIONS AND SYMBOLS

ESRD = end stage renal disease

ARF = acute renal failure

CRF = chronic renal failure

BUN = blood urea nitrogen

MRSA = methicillin resistant *Staphylococcus aureus*

MIC = minimum inhibitory concentration

V_d = volume of distribution

HD = hemodialysis

MW = molecular weight

CrCL = creatinine clearance

CT = cellulose triacetate

AUC = area under the plasma concentration-time curve

CL = clearance

UFR = ultrafiltration rate

k_e = elimination constant

CrRR = creatinine reduction ratio

URR = urea reduction ratio

C_{peak} = peak concentration of vancomycin after 1 hour infusion of vancomycin

C_{min} = minimum concentration of vancomycin at the end of the third hemodialysis

$T_{1/2}$ = half-life

mg/L = milligram per litre

CHAPTER 1

INTRODUCTION

1. Introduction

End stage renal disease (ESRD) patients are commonly present with particular syndromes, such as azotemia, proteinuria, hypertension, edema, abnormal urine analysis, electrolyte disorder, and abnormal urine volume. The two kinds of renal diseases are acute renal failure (ARF) and chronic renal failure (CRF).

ARF is a syndrome characterized by rapid (hours to weeks) decline in glomerular filtration rate (GFR) and retention of nitrogenous waste products such as urea and creatinine. ARF contributes approximately 5% of hospital admissions and up to 30% of admissions to intensive care unit (Anderson, *et al.*, 1980). Approximately 10-18% of patients with ARF are older than 60 years of age. The dominant risk factors are age and concurrent multisystem involvement. The contributing factors to the vulnerability of elderly population developing ARF are hypertension, glucose intolerance, coronary heart disease and cerebral ischemia (Yap, *et al.*, 1996).

Initially, ARF is asymptomatic and diagnosed when patients reveal a recent increase in blood urea nitrogen (BUN) and creatinine (Cr) concentration. Oliguria (urine output less than 400 ml/day) presents about 50% of cases. The kidney is remarkably organ among the organs of the body in its ability to recover from almost complete loss of function, and most ARF is completely reversible (Danovitch, *et al.*, 1979).

The other type of renal failure, CRF, refers to the permanent loss of renal function, which eventuates in the signs and symptoms so-called uremia. The specific causes of the uremic syndrome are unknown. In addition to failure of renal excretion of solutes and metabolic products, CRF loses metabolic and endocrine functions of the healthy kidney. The likely retained toxins causing this syndrome are breakdown products of proteins and amino acids. CRF is persistently

azotemia caused either by gradual renal parenchymal damage or by tissue loss from short-lived process, such as a poststreptococcal glomerulonephritis. The common etiologies of CRF are diabetic nephropathy, nephrosclerosis due to hypertension and chronic glomerulonephritis, each of which accounts for 20-30% of cases (Abuelo, 1995; Isselbacher, *et al.*, 1994).

Uremia causes deleterious effects on cellular functions and metabolism and on volume and composition of body fluids. With progressive nephron losses, the ability of diseased kidney to concentrate urine is impaired, resulting in isosthenuria and may lead to polyuria and nocturia.

For the reasons above, ESRD, either ARF or CRF poses a serious threat to life. Body fluid compartments may be expanded by retention of salts and water and the accumulation of toxic waste products may give rise to the uremic syndrome. Correction of body fluid volume and composition toward normal, as well as removal of toxic waste products, can be effectively accomplished by dialysis. Indications for dialysis in a patient with renal failure are listed in Table1-1. On some occasions, the rise in BUN or creatinine concentration may be used as an indication for dialysis. Goal of dialysis are immediate, such as lowering an elevated serum potassium concentration or removing excess fluid or controlling uremia to preclude pericarditis or to improve platelet dysfunction. In fact, dialysis techniques are effective in controlling electrolyte and fluid imbalances and preventing uremia complications such as convulsion and pericarditis (Abuelo, 1995; Brenner, *et al.*, 1987).

Table 1-1 Indications for dialysis

Fluid overload
Severe hyperkalemia, non-responsive to conversative treatments
Severe metabolic acidosis
Uremia in association with pericarditis, encephalopathy, convulsion, bleeding

Since hemodialysis needs access to bloodstream, this vascular access may increase the risk of infection including MRSA *(Methicillin resistant Staphylococcus aureus)* or *Enterococci*. Antibiotic of choice is vancomycin, tricyclic glycopeptide which is effective for the treatment of infection caused by gram positive bacteria. Its antibacterial spectrum includes coagulase positive (e.g., *Staphylococcus aureus* including MRSA strains) and coagulase negative (e.g., *S. epidermidis*) bacteria. It is also active against *Streptococci*, *Clostridium species*, and *Enterococci*. Vancomycin exhibits concentration independent pharmacodynamic property. Bactericidal effects are increasing when the concentrations are increased to 3-5 times of its minimum inhibitory concentration (MIC), the higher concentrations beyond that, however, does not enhance its antibacterial effect.

Hemodialysis at Songklanagarind hospital uses cellulose triacetate membrane (sureflux® 150E). The characteristics of the membrane are as follows: membrane surface area 1.5 m^2, Kuf 20.5 ml/hr/mmHg, dialysate flow rate 500 ml/min, and blood flow rate 300-400 ml/min. Patients are hemodialyzed 2 or 3 occasions per week with duration of 4-5 hours. In patients who are infected during hemodialysis, vancomycin 1 g per week is given. As vancomycin is removed by 23-55% during high-flux hemodialysis (Quale, *et al.*, 1992; Scott,*et al.*, 1997; Touchette,*et al.*, 1995), post-hemodialysis blood level may be lower than therapeutic range (10-40 mg/L).

2. Objectives

This study aimed to

2.1 Determine the dialysis clearance of vancomycin in ESRD patients receiving high-efficiency hemodialysis.

2.2 Determine the dosage and the dosing interval of vancomycin used in ESRD patients undergoing high-efficiency hemodialysis.

CHAPTER 2

LITERATURE REVIEW

Literatures relevant to the study of vancomycin clearance during high-efficiency hemodialysis as outlined below were reviewed.

- Alterations of pharmacokinetics due to renal failure
- Hemodialysis process
- Review of vancomycin
- Vancomycin clearance in hemodialysis

1. Alterations of pharmacokinetics due to renal failure

Declining renal function is leading not only to disturbance in fluid and electrolytes, but also an alteration in the pharmacokinetics of the drug due to physiologic and metabolic changes. Physiological changes associated with uremia can induce changes in drug absorption, drug distribution (including both volume of distribution (V_d) and protein binding), and elimination (renal excretion) that may not be predictable. The physiological changes can alter drug concentrations within the plasma or blood and at targeted tissue site of activity; and can affect drug efficacy and toxicity.

The absorption of drugs in patients with renal disorders could be inhibited by gastrointestinal (GI) disturbances present in uremia (e.g., nausea, vomiting, and diarrhea). Edema of GI tract can occur in nephrotic syndrome and can impair absorption. Uremia also can increase gastric ammonia leading to increased gastric pH (Aweeka, *et al.*, 1995).

In patients with renal impairment, V_d of many drugs may be significantly increased or decreased (see Appendix 1-1). For vancomycin, the normal V_d of 0.64 L/kg may increase to 0.85 L/kg for ESRD patients. (Matzke, *et al.*,1993). Alterations in V_d may result from changes in protein binding and tissue binding, or pathophysiologic alterations in body composition. Drugs with a high degree of protein binding will have a small plasma concentration of unbound drug

available for dialysis. The mechanisms not completely understood, protein binding may decrease in uremic patients, such as furosemide. Analysis of the binding data of furosemide at its therapeutic concentration (6.6 mg/L) indicated that, among the four uremic toxin studied, 3-carboxy-4-methyl-5-propyl-2-furanpropionate showed the greatest inhibitory potency for the binding of furosemide to serum protein. Changes in binding may substantially increase in dialyzability of free drug. For example, the therapeutic range for phenytoin serum concentration in normal renal function patients is 10-20 mg/L. As the free fraction is approximately 10% in normal renal function, the free concentration range would then be 1-2 mg/L. However, in ESRD patients, the free fraction is increased to 15-26% (mean 20%), while the total concentration is lower as a result of the increased V_d. The total serum phenytoin concentration of 7 mg/L in ESRD patients might therefore be considered subtherapeutic, whereas the free fraction (20% of the total or 1.4 mg/L) is actually in the middle of therapeutic range (Matzke, *et al.*, 1993). So protein and tissue binding changes in patients with renal insufficiency is critically important in the serum drug concentrations.

The pharmacokinetic alterations described above are mostly affected drug distribution. The elimination half-life of drugs, especially those mainly excreted by renal, in patients with renal impairment are generally increased due to GFR reduction (Matzke, *et al.*, 1993). Vancomycin total body clearance declined from 74.6 to 158.6 ml/min in subjects with creatinine clearance (CrCL) greater than 80 ml/min to 4.0 to 6.8 ml/min in patients with ESRD (Matzke, *et al.*, 1984). The kidney eliminates drugs by filtration and tubular secretion. Characteristics of a drug that determine its filterability include its affinity for protein binding and molecular weight. Drugs with low protein binding are filtered more easily, but high molecular weight substance (drug) cannot be filtered due to their large sizes (Aweeka, *et al.*, 1995). Tubular secretion is a selective transfer of substances from blood into tubular fluid. The cells of the tubules remove certain molecules and ions from the blood and secrete them into the fluid within the tubules. For example, both hydrogen ions (H^+) and potassium ions (K^+) are secreted directly into the fluid within the distal and collecting tubules. In each case the secretion is coupled to the ion-for-ion uptake of sodium ions (Na^+).

2. Physiologic principles of hemodialysis

Hemodialysis comprises of blood perfusion and dialysate solution put on each side of membrane, which eventually equilibrates between water and solutes, such as urea and electrolytes. This option is the main therapy for ESRD patients.

2.1 Indications for hemodialysis

Besides indications for dialysis listed in Table 1-1, dialysis is initiated prophylactically in patients with ARF when the plasma urea nitrogen level reaches 100 mg/dl or when creatinine clearance decreases to less than 0.1 ml/min/kg. In CRF, dialysis should be initiated electively when CrCL falls to a certain lower limit, usually 0.1-0.5 ml/min/kg. The less common indications for dialysis therapy include drug intoxication, hypothermia, hypercalcemia, hyperuricemia and metabolic alkalosis (Daugirdas, *et al.*, 2000).

2.2 Hemodialysis apparatus

2.2.1 Dialyzer

The dialyzer shell is a box or tube with four ports. Two ports connect to a blood compartment and the remainders connect to a dialysate compartment. The semipermeable membrane separates the two compartments. The dialysate flows through the dialyzer usually in a direction opposite to that of blood flow (Brenner, 2000). In the hollow-fiber (also called capillary) dialyzer, the blood flows into a chamber at one end of the cylindrical shell (Fig. 2-1). From here, blood enters thousands of small capillaries tightly bound in a bundle. Once through the capillaries, the blood is collected in a chamber at the other end of the cylindrical shell and is then got back to the patient. (Brenner, 2000; Daugirdas, *et al.*, 2000).

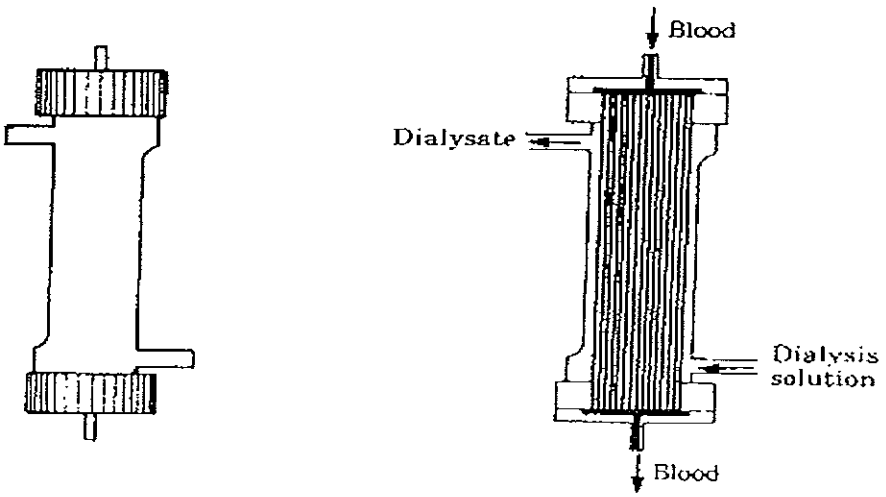


Fig. 2-1 Membrane structure, blood and dialysate flow pathway

2.2.2 Membranes

Membrane materials: There are four types of membranes currently used in dialyzer: cellulose; substituted cellulose; cellulosynthetic; and synthetic membranes (Daugirdas, *et al.*, 2000).

The cellulose is the first model of membrane that has low surface area resulting in poor permeability. It is obtained from processed cotton, such as regenerated cellulose, cuprammonium cellulose (Cuprophane), cuprammonium rayon, and saponified cellulose ester. Substituted cellulose, high-efficacy cellulose polymer, has a large number of free hydroxyl groups at its surface, such as cellulose acetate, cellulose diacetate, and cellulose triacetate membranes. These chemical membranes bonded to acetate group. However, this substituted cellulose has less surface area than cellulosynthetic. The cellulosynthetic is a tertiary amino compound added to liquefied cellulose during formation of the membrane. Cellulosynthetic is available commercially as Cellosyn or Hemophan. The synthetic membranes are high-flux membranes with no compound of cellulose-based. The materials used include polyacrilonitrile (PAN), polysulfone, polycarbonate, polyamide, and polymethylmethacrylate (PMMA). As a result, increasing of membrane surface area was also greatly increased biocompatibility.

2.2.3 Membrane permeability to solutes and water

The permeability to solutes and water of membranes can be altered markedly by adjusting the thickness of the membrane and the pore size (Daugirdas, *et al.*, 2001). The ability of a dialyzer to remove small molecular weight solutes, such as urea, is primarily a function of its membrane surface area (plus a minor component due to dialyzer and membrane design). A high-efficiency dialyzer is basically a big dialyzer with high surface area so that it has a high capability to remove urea and larger molecular weight solutes, such as β_2-microglobulin (MW 11,800).

2.2.4 Dialysis solution

Excess body acid is neutralized during dialysis by transfer of bicarbonate solution. A typical composition is shown in Table 2-1 and varied substantially in special clinical circumstances. High concentrations of calcium (Ca), magnesium (Mg), and bicarbonate cause the precipitation of calcium and magnesium carbonate. To prevent precipitation, Ca and Mg are not included directly in bicarbonate solution. Concentrate bicarbonate solution is prepared in two components, a bicarbonate and an acid component. The acid component contains a small amount of lactic, acetic, or citric acid plus Ca and Mg. Specially designed dialysis machines mix the two components and diluted with purified water. During mixing, the acids in acid component will react with equimolar amount of bicarbonate to generate carbon dioxide. The carbon dioxide will form carbonic acid which will lower pH approximately 7.0-7.4. In this pH range present in final mixture, calcium and magnesium remain in solution. However, the occurrence of certain amount of microprecipitation is reported (Daugirdas, *et al.*, 2000).

Table 2-1 Components of bicarbonate-containing dialysate

Component	Concentration (mEq/L)
Sodium	135-145
Potassium	0-4
Chloride	98-124
Acetate	2-4
Bicarbonate	30-40
Calcium	2.5-3.5
Magnesium	0.5-0.75
Dextrose	11
pCO_2	40-110
pH	7.1-7.3

2.3 Dialysis procedure

Renal replacement options for renal diseases can be divided into 2 main categories: intermittent and continuous therapies (Dipiro, *et al.*, 2002). The characteristics of most commonly used renal replacement therapies are shown in Table 2-2. Intermittent hemodialysis is primarily diffusion based. It is very efficient in removing low molecular weight solutes (< 500 Daltons) such as urea, creatinine, most electrolytes, and many drugs (Daugirdas, *et al.*, 2000).

Basically, dialysis involves separation of diffusible substances from less diffusible ones by the use of the semipermeable membrane with little or no net movement of fluid across the membrane (Daugirdas, *et al.*, 2001). Hemodialysis requires access to the blood vessels to allow the blood to flow to the dialysis machine and back to the body as shown in Fig 2-2 (Dipiro, *et al.*, 2002).

Table 2-2 Advantages and disadvantages of common renal replacement therapies

	Intermittent Hemodialysis	Intermittent Hemofiltration	Peritoneal dialysis	Slow Continuous Ultrafiltration (SCUF)	Continuous Arteriovenous Hemofiltration (CAVH)	Continuous Venovenous Hemofiltration (CVVH)	Continuous Arteriovenous Hemodiafiltration (CAVHDF)	Continuous Venovenous Hemodiafiltration (CVVHDF)
Solute control	Usually adequate	Inadequate	Inadequate	Inadequate	Inadequate	Adequate	Adequate	Adequate
Volume control	Variable	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Hemodynamic stability	Variable	Well tolerated	Well tolerated	Well tolerated	Well tolerated	Well tolerated	Well tolerated	Well tolerated
Access	Venous	Venous	Peritoneal	Arterial and Venous	Arterial and Venous	Venous	Arterial and Venous	Venous
Anticoagulation	Short duration	Short duration	None	Continuous	Continuous high dose	Continuous low dose	Continuous high dose	Continuous low dose

Table 2-2 (Continued)

	Intermittent Hemodialysis	Intermittent Hemofiltration	Peritoneal dialysis	Slow Continuous Ultrafiltration (SCUF)	Continuous Arteriovenous Hemofiltration (CAVH)	Continuous Venovenous Hemofiltration (CVVH)	Continuous Arteriovenous Hemodiafiltration (CAVHDF)	Continuous Venovenous Hemodiafiltration (CVVHDF)
Technical complexity	High	High	Low	Low	Low	Moderate	Moderate	High
Workload	Intermittent	Intermittent	Low	Low	Low	Moderate	Moderate	High
Drug dosing ease	Many published recommended	Difficult	Difficult	Negligible drug removal	Difficult	Many published recommended	Difficult	Difficult
Convective clearance (small and middle molecules)	Mixed	Minimal	Moderate	Moderate	Large	Large	Large	Large

Table 2-2 (Continued)

	Intermittent Hemodialysis	Intermittent Hemofiltration	Peritoneal dialysis	Slow Continuous Ultrafiltration (SCUF)	Continuous Arteriovenous Hemofiltration (CAVH)	Continuous Venovenous Hemofiltration (CVVH)	Continuous Arteriovenous Hemodiafiltration (CAVHDF)	Continuous Venovenous Hemodiafiltration (CVVHDF)
Dialytic clearance	Large	None	Large	None	None	None	Large	Large
Common complications	Hypotension	Hypotension	Hyperglycemia, atelectasis peritonitis	Arterial bleeding, hypotension	Arterial bleeding filter clotting	Hypotension	Arterial bleeding, increase serum lactate	serum lactate, hypotension

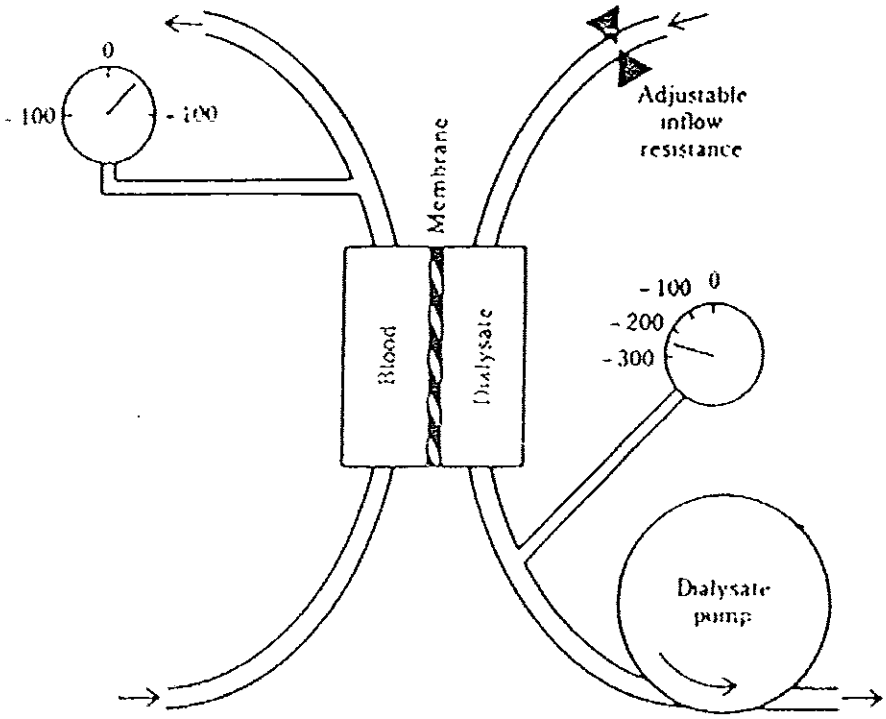


Fig. 2-2 **A dialyzer with blood flowing in one direction and dialysis solution flowing in an opposite direction**

2.4 Mechanism of solute transport

Solutes that can pass through the membrane pores are transported by two different mechanisms: diffusion and ultrafiltration (convection) (Brenner, 2000).

2.4.1 Diffusion

The mechanism is depending on concentration gradient. The relative rates of passage of a given solute from solution A to solution B and back again until equilibrium. The larger molecular weight of a solute gives a slower rate of transport across the membrane. The speed velocity of a molecule in solution is inversed to the weight of the molecule.

2.4.2 Ultrafiltration

Ultrafiltration occurs when water is pushed through the membrane by either a

hydrostatic or an osmotic force. The solutes that can pass easily through the membrane pores are swept along with water. The water being pushed through the membrane is accompanied by such solutes at close to their original concentrations. Larger solutes, especially those larger than the membrane pores, are held back.

2.5 Hemodialysis circuit

In clinical use, the box containing blood and dialysis solution (Fig.2-3) flowed directly opposite. The latter consists of highly purified water containing dissolved sodium, potassium, calcium, magnesium, chloride, bicarbonate, and dextrose. The low molecular weight waste products that accumulate in uremic blood are absent from the dialysis solution. For this reason, when uremic blood is exposed to dialysis solution, the flux rate of these solutes from blood to dialysate is initially much greater than the back flux from dialysate to blood. Eventually, if the blood and dialysate were left in static contact with each other *via* the membrane, the concentration of permeable waste products in the dialysate would become equal to that in the blood, and no further net removal of waste products would occur. Transport back and forth across the membrane would continue, but the rates of forth transport and back transport would be equal. In practice, during dialysis, concentration equilibrium is prevented, and the concentration gradient between blood and dialysate is maximized, by continuously refilling the dialysate compartment with fresh dialysis solution and by replacing dialyzed blood with undialyzed blood. Normally, the direction of dialysis solution flow is opposite to the direction of blood flow. The purpose of countercurrent flow is to maximize the concentration difference of waste products between blood and dialysate in all parts of the dialyzer (Daugirdas, *et al.*, 2000).

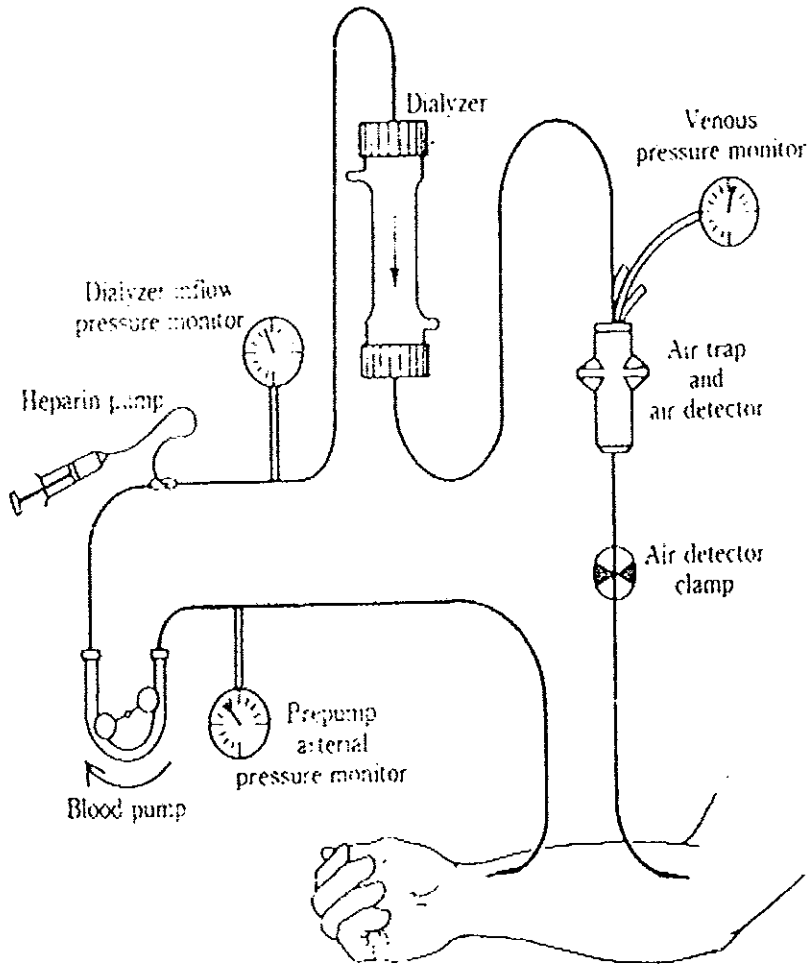


Fig. 2-3 The blood circuit in hemodialysis

2.6 Factors effecting blood clearance

2.6.1 Blood flow rate

The blood clearance increases in a direct proportional to the blood flow rate. As the blood flow rate increases, the dialyzer is able to remove urea with the higher degree of efficiency. As a result, the plasma urea nitrogen level at the dialyzer outlet decreases.

For dialysis of normal-size adults, the blood flow rate is usually set between 350 and 500 ml/min. (Daugirdas, *et al.*, 2000).

2.6.2 Dialysis solution flow rate

Clearance of urea depends on the dialysis solution flow rate as well. A faster dialysis

solution flow rate increases the efficiency of diffusion of urea from blood to dialysate the usual dialysis solution flow rate is 500 ml/min. In high-efficiency HD, a dialysis solution flow rate of 800 ml/min will increase urea clearance by about 12%, when compared with the blood flow rate of 350 ml/min (Daugirdas, *et al.*, 2000).

2.6.3 Dialyzer efficiency

A high-efficiency and high-flux dialyzer with a thin, large surface area membrane, wide pores, and a design that maximizes contact between blood and dialysate will remove a higher percentage of waste products than a low-efficiency dialyzer (Daugirdas, *et al.*, 2000).

2.6.4 Drug removal by dialysis

Pharmacokinetic characteristics including molecular size, V_d, protein binding, water solubility, and plasma clearance can affect drug dialyzability. For high molecular weight solutes, they move slowly through solution, and diffuse poorly through the membrane. As a result, while urea (MW 60) may be removed from blood with an efficiency of 75%, creatinine (MW 113) may be removed with an extraction efficiency of only 60%. For even larger solutes, such as vitamin B_{12} (MW 1355), the solute level at the blood outlet might be 75% of the level at the blood inlet. Thus, the percentage removed is 25%. With vitamin B_{12}, the dialyzer limits are reached early, and raising the blood flow rate above 200 ml/min has only a modest effect on increasing clearance of such larger molecules (Daugirdas, *et al.*, 2000). The movement of drugs or other solutes is largely determined by the size of the molecules in relation to the pore size of membrane.

Another important factor in determining drug dialyzability is the concentration gradient of unbound (free) drug across the dialysis membrane. A drug with a high degree of protein binding will have a small plasma concentration of unbound form. As mention earlier, uremia may decrease protein binding.

A drug with high water solubility will be dialyzed to a greater extent than those with high lipid solubility. In dialysis patients, renal clearance is largely replaced by dialysis clearance.

Appendix 1-2 showed effect of hemodialysis on clearance and half-life of some antimicrobial agents.

3. Review of vancomycin

3.1 Physicochemical properties

Vancomycin, a bactericidal glycopeptide antibiotic produced by *Streptomyces orientalis*, was introduced in 1956 for treatment of emerging strains of penicillinase-producing staphylococci (Matzke, 1986).

Vancomycin (MW 1448) is not well absorbed from the GI tract when administered orally. Intramuscular injection of vancomycin causes severe local pain; therefore, it is usually administered intravenously. Vancomycin hydrochloride is very soluble and stable in most parenteral solutions. It is a glycopeptide molecule consisting of a 7-membered peptide chain formed by parts of 3 phenylglycine system, 2 chlorinated tyrosine units, aspartic acid and *N*-methylleucine. 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 solvent such as acetone and ether. It is an extremely stable antibiotic, with the product packages insert labelling that reconstituted solutions are stable for 14 days at room temperature. Vancomycin admixed in either dextrose or saline solution retains its potency for at least 7 days at both 5 and 25°C. It is physically compatible with dextran, sodium bicarbonate and Ringer's lactate solution. It is incompatible with aminophylline, barbitone sodium, methicillin sodium, pentobarbitone, phenobarbitone, secobarbital sodium, and intravenous warfarin sodium. Unlike many other antimicrobial agents, the activity of vancomycin is not significantly influenced by the pH of biological fluid (Matzke, *et al.*, 1986).

3.2 Pharmacokinetics of vancomycin

The disposition of vancomycin following intravenous administration have characterised the serum concentration versus time profiles. A peak serum concentration reaches 1 to 2 hours after intravenous administration. The disposition of parenterally administered vancomycin was described by one-, two-, and three-compartment models in subjects with normal renal function. The half-life ($T_{1/2}$) of the initial phase is approximately 7 minutes, and that of the second phase is approximately 0.5-1 hour, while the terminal elimination $T_{1/2}$ ranges from 3-9 hours in subjects with normal renal function. Vancomycin distributes to a volume that

approximates or slightly exceed total body water. Serum protein binding is moderate about 55% (Evans, *et al.*, 1986; Matzke, *et al.*, 1986; Rodvold, *et al.*, 1995). No significant increase or decrease in vancomycin distribution volume was noted with age. V_d at steady state in adult and pedriatric subjects ranging from 0.39 to 0.92 and 0.45 to 0.97 L/kg, respectively.

In dog studies, Lee *et al.* (1957) documented that vancomycin concentrations was less than 3 mg/kg in liver tissue. Researchers concluded that vancomycin was not metabolised to any great extent. Kirby and Divelbiss (1957) reported that 86 to 100% of 1g and 2g intravenous doses were excreted unchanged in urine within 24 hours after administration, suggesting that vancomycin undergoes minimal metabolism in humans. The concentrations of vancomycin in liver tissue and bile were even below detection limits. Several studies suggested that non-renal clearance of vancomycin may occur in humans, approximately 5-20% of total body clearance. Marcias *et al.* (1991) suggested that nonrenal clearance appeared to decrease with the progression of renal failure.

The total body clearance of vancomycin is reduced in subjects with impaired renal function, it was also found to be significantly larger in the morbidly obese subjects (Evan, *et al.*, 1986). The clearance of vancomycin in pediatric patients appears to be related primarily to the degree of renal maturation, with no age-specific difference associated with the distribution or elimination of vancomycin when adjusted for renal function. Vancomycin clearance is decreased and the elimination half-life progressively prolonged in association with declining GFR, but the V_d at steady-state is not significantly correlated with declining renal function (Evan, *et al.*, 1986).

3.3 Analytical procedures

Methodologies available for quantitation of vancomycin in biological fluids include microbiology, radioimmunoassay (RIA), fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA) and high performance liquid chromatographic (HPLC) techniques. In general, these methods have equivalent sensitivity (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 (0.6-128 mg/L). RIA and FPIA may be superior due to the smaller

sample volume requirement, easier sample preparation and shorter turnaround time compared with HPLC, and their superior precision compared with FIA (Jusko, 1996; Matzke, *et al.*, 1986).

3.4 Vancomycin in patients with renal impairment

As vancomycin is primarily excreted unchanged *via* the kidneys, the progressive prolongation of $T_{1/2}$ and reduction of total body clearance of this drug was clearly noted in renal impaired patients. Vancomycin total body clearance declines from mean values of 74.6-158.6 ml/min in subjects with CrCL greater than 80 ml/min, to 4.0-6.8 ml/min in patients with ESRD receiving hemodialysis. V_d at steady-state does not decrease significantly, with mean values of 0.39-0.92 L/kg in subjects with CrCL greater than 80 ml/min and 0.8-0.9 L/kg in ESRD receiving hemodialysis. Dialysis procedures enhance drug clearance by providing additional route of vancomycin elimination (Matzke, *et al,* 1986).

3.5 Adverse effects of vancomycin: Incidence and serum concentrations relationship

Several reports have documented that vancomycin is an extremely safe drug. A review of the literature since 1956 to 1985 has revealed major and minor adverse effects (Matzke, *et al.*, 1986).

3.5.1 Nephrotoxicity

The incidence of nephrotoxicity varies between 0 and 5.7%. The relationship between nephrotoxicity and vancomycin serum concentrations is difficult to determine. Nephrotoxicity was reversible in the majority of cases when therapy was continued, or even after dosage reduction of this drug (Matzke, *et al.*, 1986). Some the adverse effects of this drug are as follows.

3.5.2 Ototoxicity

Vancomycin-associated ototoxicity is difficult to assess as most patients does not receive audiometric testing during the course of therapy. In addition, assessment of ototoxicity is neither sufficiently sensitive nor specific and thus hearing deficiencies is not reported unless they are substantial and at lower frequencies within the hearing range (2000 to 3000 Hz). The incidence of vancomycin-associated ototoxicity reported is 1.4 to 5.5% (Matzke, *et al.*, 1986).

3.5.3 Red-Neck syndrome

Rapid intravenous administration of vancomycin can result in a histamine-like reaction characterized by flushing, tingling, pruritus, tachycardia, and erythematous, macular rash involving the face, neck, upper trunk, back and arms with sparing of the rest of body. Systemic arterial hypotention or shock has also been noted (Matzke, *et al.*, 1986). The incidence of this reaction is 5.3 to 11.2%. The mechanism of this reaction appears to be a dose-dependent histamine mediated depression of myocardial contractility (Dajee, *et al.*, 1984). Maculopapular or erythematous skin rash has been observed in 6.5% of patients treated with vancomycin (Matzke, *et al.*, 1986).

3.6 Implications of pharmacokinetic properties for clinical use

Evidence of multicompartment pharmacokinetic characteristics, unpredictability of serum vancomycin concentrations, and possible non-renal elimination 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, altered drug distribution, altered renal function, and other factors such as age, and altered tissue binding (Jusko, 1996).

3.6.1 Dosing considerations

Adults with impaired renal function, elderly patients, morbidly obese patients, and paediatrics may have additional benefit from an individualized dosing approach based on serum concentrations.

3.6.2 Individualising the dosage

Matzke *et al.* (1984) studied the pharmacokinetics of vancomycin in 56 patients with different degrees of renal function after an intravenous dose of 18.4±4.7mg/kg (mean±standard deviation, SD). Seven subjects had a CrCL > 60 ml/min (group I), 13 had a CrCL of 10-60 ml/min (group II) and 36 had a CrCL < 10 ml/min (group III). Serial serum samples (range 3-8) were collected during the 168 hours after drug administration. The serum concentration-time profiles in all patients demonstrated monoexponential decay. The mean half-lives were 9.1, 32.3 and 146.7 hours in group I, II and III, respectively. A significant decline in vancomycin serum clearance (CL_S) was found i.e., 62.7, 28.3, and 4.87 ml/min in group I, II and III, respectively.

The steady state V_d (V_{dss}) varied between 0.72 and 0.90 L/kg. There was no significant relationship between V_{dss} and CrCL. The relationship between vancomycin clearance (CL_v) and CrCL was: $CL_v = 3.66 \pm 0.689 CrCL$; r = 0.8807), which might be used to devise dosage schedules for patients with any degree of renal impairment.

3.6.3 Therapeutic monitoring of vancomycin

The pharmacokinetic profile of vancomycin is described by a 1- , 2- or 3-compartment model. The fractional error in body clearance of vancomycin is less than 10% when assumed as 1-compartment model. Therefore, using a 1-compartment open model to describe the pharmacokinetics of vancomycin in the clinical setting should be adequate (Wagner, *et al.,* 1983). Peak vancomycin concentrations, for the purpose of clinical pharmacokinetic monitoring of efficacy and toxicity correlations, should be determined after the distribution phase is completed. Trough concentrations should be obtained just before or within 1 hour of the next scheduled dose. The V_{dss} can then be estimated either by model dependent techniques or by standard 1-compartment first order equation (Gibaldi&Perrier., 1982).

4. Clearance of high-flux or high-efficiency HD

Vancomycin removals on hemodialysis and appropriate dosages for hemodialysis patients were examined. All trials showed 23-55% removal of vancomycin (Foote, *et al.*, 1998; Mason, *et al.*, 2003; Quale, *et al.*, 1992; Scott, *et al.*, 1997; Welage, *et al.*, 1995). The recommendation of vancomycin 500 mg dosing supplement every subsequent dialysis was introduced by Zoer, *et al.* (1997).

Zoer *et al.* (1997) investigated vancomycin clearance by two highly permeable membranes and determining dosage adjustment in regular hemodialysis setting. The standard dosage of vancomycin in hemodialysis patients was 1 gram once a week. 12 patients receiving regular hemodialysis and treated with vancomycin either prophylactically or therapeutically were randomised to either dialysis with a polyacrylonitril parallel membrane (AN-69) or a cellulose acetate hollow fiber membrane. After administering vancomycin to the patients, the plasma vancomycin levels were measured. The vancomycin clearance by dialyzer was calculated from

blood sample taken 1 hour after starting dialysis. The CL_v (mean±SD) was 46±5 ml/min, and there were no difference between the two artificial kidneys. The average non renal clearance was 3.3 ml/min/1.73 m^2 while renal vancomycin clearance, as a fraction of CrCL (mean±SD) was found to be 0.83±0.2 ml/min. Therapeutic and non toxic vancomycin levels could be obtained by giving 1g of vancomycin intravenously as a loading dosage and 500 mg during every subsequent dialysis

Welage *et al.* (1995) evaluated the pharmacokinetics of vancomycin during hemodialysis with cellulose triacetate (CT110 and CT190) high-flux dialyzer and the effect of membrane surface area on intradialytic clearance using a randomized crossover design. 6 hemodialysis patients received 1 g of vancomycin immediately after the completion of dialysis session and subsequently, blood samples were obtained over a 5-day study period. On day 3, subjects were dialyzed with CT110 or CT190 membranes. The intradialytic clearances of vancomycin (mean±SD) were 56.7±7.5 and 100.7±10.7 ml/min with CT110 and CT190 membranes, respectively ($P < 0.05$). Significant rebound in vancomycin serum concentration occurred after dialysis. This rebound appeared to be completed 3 hours postdialysis. On the basis of post-rebound concentrations, the apparent percent removals of vancomycin (mean±SD) were 23.6±1.2 and 25.2±8.6% for CT110 and CT190 membranes, respectively (no statistically significantly difference). Vancomycin is significantly cleared during dialysis with cellulose triacetate membranes, and its clearance is dependent on membrane surface area. The determination of vancomycin removal can be used to estimate vancomycin serum concentrations as well as dosage requirements.

Keller *et al.* (1994) compared dosage of vancomycin for hemodialysis patients. Conventional dosage of vancomycin 1g once a week, which is usually recommended for hemodialysis patients, was compared with a modified dosing schedule consisting a loading dose of 1g and maintenance dose of 500 mg administered 3 times a week after hemodialysis. Different vancomycin regimens were retrospectively evaluated by therapeutic drug monitoring and

Bayesian parameter estimates in 39 dialysis patients. The trough levels (mean±SD) in 7 patients receiving only the conventional dosage regimen was significantly lower than 17 patients who treated by modified schedule (7±4 vs. 17±8 mg/L; p = 0.001). The corresponding peaks were low in both groups with no statistically significant difference (23±10 vs. 27±12 mg/L). The one-week average vancomycin clearance was significantly lower in the conventional dosage group compared with the modified dosage group (6±3 vs. 10±3 ml/min; p = 0.001). Vancomycin one-week average elimination half-life was 66 hours and the V_d was 50 L. Ototoxicity occurred in 1 patient, and vancomycin treatment was judged as ineffective against infection in 5 of the 39 patients, all patients had trough concentrations below 15 mg/L.

Mason *et al.* (2003) compared the pharmacokinetics of vancomycin when administered during the last 1-2 hours of dialysis to that administered after completion of dialysis. In a randomized, 3-way crossover trial, the pharmacokinetics of vancomycin were evaluated in 9 hemodialysis patients using cellulose triacetate membranes. These regimens were: vancomycin 15 mg/kg following dialysis (Phase I); vancomycin 15 mg/kg during the last hour of hemodialysis (Phase II); or vancomycin 30 mg/kg during the last 2 hours of hemodialysis (Phase III). Vancomycin was significantly removed (33.4 to 39.5%) during a 3- to 4- hour high-flux dialysis session occurring on day 3 after vancomycin administration. The immediate mean serum concentrations following vancomycin administration of 15 mg/kg over the last hour of dialysis and 30 mg/kg over the last 2 hours of dialysis were 77.7 and 95.5 μg/ml respectively, but fell to 25.9 and 40.5 μg/ml, respectively, by 4 hours postdialysis. Predialysis concentrations on day 3, 5 and 8 were similar for vancomycin 30 mg/kg administered over the last 2 hours of dialysis as compared with a 15 mg/kg dose given after dialysis. Vancomycin 15 mg/kg over the last hour of dialysis resulted in significantly lower subsequent predialysis concentrations than the other dosing schemes. So vancomycin administration of 30 mg/kg over the last 2 hours of dialysis achieves serum concentrations similar to conventional dosing of 15 mg/kg after dialysis and would allow dosing on a weekly basis.

Touchette *et al.* (1995) determined pharmacokinetics of vancomycin in 8 critically ill patients undergoing high-flux hemodialysis and using F-80 or F-60 polysulfone dialyzers. In patients dialyzed with F-80 dialyzers, interdialytic and intradialytic half-lives (mean±SD) for vancomycin were 162±69.8 hours and 4.7±1.3 hours, respectively. Intradialytic clearance was 108.5±16.3 ml/min, and vancomycin recovered in dialysate was 238±55 mg. In patients dialyzed with F-60 dialyzers, interdialytic and intradialytic half-lives for vancomycins were 211±166.8 hours and 4.6±0.4 hours, respectively. Intradialytic clearance was 100.6±18.3 ml/min, and vancomycin recovered in dialysate was 252±79 mg. Hemodialysis with high-flux polysulfone removes significant amount of vancomycin.

Scott *et al.* (1997) performed a mass transfer analysis of vancomycin removal by high-flux dialyser, and cellulose triacetate (CT). Cross-over study with 3-weeks washout between treatments. Eight subjects received (1) vancomycin 1 g during the last hour of dialysis, or (2) after dialysis. The (2) is control group. Dialysis removed 26.2% (range 16-44%) of the administered vancomycin dose. The AUC (mean±SD) among those using CT was significantly higher than the control group (677±103.7 *vs.* 950.2±287.3 mg/L/hour, respectively; $p < 0.05$).

Quale *et al.* (1992) investigated vancomycin concentration changes in patients on hemodialysis using permeable membrane by both in vivo and in vitro techniques. In vivo study with polyacrilonitrile dialyser, 5 patients received vancomycin prior to dialysis. Vancomycin concentration in serum (mean±SD) was 68±14% at the beginning. Postdialysis vancomycin concentrations were 63±11% of the predialysis concentrations ($p = 0.018$). The in vitro study compared vancomycin concentration obtained from hemodialysis using polyacrilonitrile and conventional cellulose. The corresponding values were 55.0±4.9% and 97.0±4.5%, respectively. At 90 minutes later, vancomycin concentrations were 41.0±0.2% and 91.0±6.8%, respectively.

Desoi *et al.* (1992) studied vancomycin clearance, measured in 5 patients during dialysis with cuprophane (CU), polysulfone (PS), cellulose triacetate (CT), and polyacrilonitrile

(PAN) dialyzers. Vancomycin was significantly cleared during high-flux hemodialysis with three membranes, but with CU.

Foote *et al.* (1998) evaluated the pharmacokinetics of relative high dose vancomycin administered during high-flux hemodialysis using polysulfone membrane (F-80). Five noninfected, anuric patients received a single dose of 25 mg/kg of vancomycin infused at a rate of 1g per hour over the last 1 hour of hemodialysis. Blood samples were drawn during the infusion, up to 6 hours after the end of dialysis and then prior to the next dialysis treatments. Dialysate was collected during infusion. Samples were analyzed using the EMIT assay. The percent of vancomycin lost during the first dialysis session ranged from 39.1-55.1% (mean$\pm$SD= 45.7$\pm$6.4). The concentration of vancomycin at 6 hours after hemodialysis ranged from 18.2-45.1 mg/l (mean$\pm$SD= 29.6$\pm$10.0 mg/L). Dialysis clearance ranged from 96.1-158.1 ml/min (mean$\pm$SD= 130.7$\pm$30.0 ml/min). One week after dosing, serum concentrations ranged from 8.1-10.1 mg/L (mean$\pm$SD= 9.0$\pm$1.0 mg/L). The study suggested that an initial dose of 25 mg/kg (1388 to 2375 mg) of vancomycin, giving during high flux dialysis, may provide adequate serum concentrations in anuric hemodialysis patients for up to 7 days.

Moellering *et al.* (1981) demonstrated the relation between vancomycin clearance and renal function studied in 22 patients with various degrees of renal function impairment. In 5 dialysis patients vancomycin clearance (mean$\pm$SEM) was 0.086$\pm$0.025 ml/min/kg. This relation enables to construct a nomogram for vancomycin dosage adjustment (based on a mean steady state serum vancomycin concentration of 15 mg/L) in patients with various degrees of renal function impairment (Fig. 2-4).

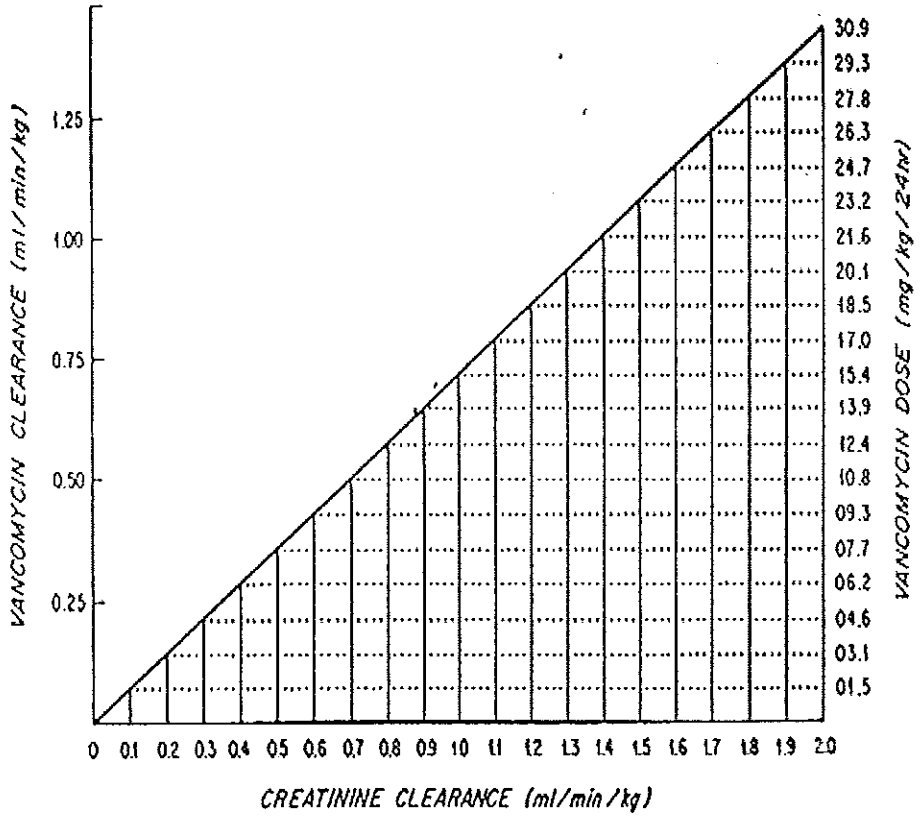


Fig. 2-4 Dosage nomogram for vancomycin in patients with impaired renal function

CHAPTER 3

MATERIALS AND METHODS

1. Setting

The study was carried out at the hemodialysis unit, Songklanagarind Hospital. Data were collected from January 2003 to March 2004.

2. Sample size

Sample size calculation was based on the relevant parameters published in literature and clinical judgement. The sample size required for estimating the mean of vancomycin hemodialysis clearance was:

$$n = \frac{(Z_{\alpha/2})^2 \sigma^2}{e^2}$$

Where n = sample size

$(Z_{\alpha/2})$ = standard normal deviate, for 95% confidence interval is 1.96

σ = standard deviation of clearance = 30 ml/min (Foote, *et al.*, 1998)

e = precision of the estimate, which is allowed to 10 ml/min

Thus

$$n = \frac{(1.96)^2(30)^2}{10^2}$$

$$= 40$$

Hence, this study required 40 episodes of hemodialysis in which vancomycin were given to the patients for treatment of MRSA infection.

3. Ethical consideration

The study protocol was approved by the Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University.

4. Subjects

Subjects who fulfilled the inclusion criteria, listed below were included in this study.

4.1 Inclusion criteria

In- and out-patients who were treated by hemodialysis and were prescribed vancomycin.

4.2 Exclusion criteria

Patients who developed or had a previous history of hypersensitivity to vancomycin were precluded from our study.

5. Methods of study

After recruitment, all individual patients were informed about the study protocol. Written informed consent (appendix 2) was obtained from all patients who participated in the study. Each patient was prescribed vancomycin 1 g infusion in 60 minutes starting at the end of hemodialysis and received another 1 g dose at 5-7 days later. The hemodialysis condition was: blood flow rate 300-350 ml/min and dialysate flow rate 500 ml/min. Each patient was hemodialyzed 2 or 3 times per week during which six blood samples, each containing 5 ml of blood, was drawn for determination of serum vancomycin levels. Data were collected in appendix 3 and appendix 4.

5.1 Vancomycin administration, hemodialysis schedule, and blood sampling schedule

To study the hemodialysis clearance of vancomycin, 6 blood samples were drawn throughout 3 consecutive hemodialysis sessions. The order of blood samples was specified in the bracket.

5.1.1 The first hemodialysis and blood sample

The initial dose of 1 g vancomycin was given *via* intravenous infusion for 60 minutes at the end of the first hemodialysis session.

(1) The first 5-ml blood sample was drawn at 60 minutes after the end of the infusion to quantify peak serum vancomycin concentration (C_{peak}).

5.1.2 The second hemodialysis and blood sample

During the second hemodialysis, blood samples were drawn consecutively as listed below:

(2) Immediately before hemodialysis

(3) 2 hours after starting hemodialysis

(4) At the end of hemodialysis

These three-point serum levels were required to determine the elimination rate (k_e) of the dialyzers.

5.1.3 The third hemodialysis and blood sample

(5) A sample of blood was drawn immediately before the third hemodialysis

(6) The last blood sample was collected at the end of the third hemodialysis to examine whether the lowest vancomycin level (C_{min}) fell within the therapeutic range.

5.2 Blood sample processing

Each blood sample was put in a screw-capped tube and centrifuged at 3000 g for 10 minutes. The serum portion was separated and stored at -20°C until assayed. Serum vancomycin concentrations were measured by using reverse phase HPLC (Punthananiwatkul and Palkachain, 2002 (unpublished); Schaedeli, *et al.*, 1998).

5.3 Calculation of pharmacokinetic parameters

Vancomycin clearance was determined using vancomycin concentration during hemodialysis and blood flow rates as the following equations (Hudson, *et al.*, 2004):

$$Q_{pa} = Q_a (1\text{-Hct})$$

$$Q_{pv} = Q_{pa} - UFR$$

$$CL_{HD} = [(Q_{pa} \times C_0) - (Q_{pv} \times C_p)] / C_0$$

C_p = Concentration of vancomycin at the time immediately complete the second hemodialysis (mg/L)

C_0 = Concentration of vancomycin at the time starting the second hemodialysis (mg/L)

CL_{HD} = Dialysis clearance (ml/min)

Hct = Hematocrit (%)

Q_a = Arterial blood flow rate

Q_{pa} = Arterial plasma flow rate

Q_{pv} = Venous plasma flow rate

UFR = Ultrafiltration rate

The vancomycin hemodialysis clearance was additionally predicted by using the urea reduction ratio (URR) and creatinine reduction ratio (CrRR), blood flow and hemodialysis time. We used URR and/or CrRR instead of Kt/V (it could show how well of hemodialysis was removing waste products from body), as they are used interchangeably in the regression model.

$$URR = \frac{\text{BUN before dialysis} - \text{BUN after dialysis} \times 100}{\text{BUN before dialysis}}$$

$$CrRR = \frac{\text{Cr before dialysis} - \text{Cr after dialysis} \times 100}{\text{Cr before dialysis}}$$

Drug removal during dialysis was calculated both from serum concentration obtained before and immediately after hemodialysis (the apparent percent of vancomycin removal)

$$\%removal = \left[(C_{preHD} - C_{postHD}) / C_{preHD} \right] \times 100$$

Vancomycin supplement dose ($D_{supplement}$) after complete hemodialysis was calculated from

$$D_{supplement} = \frac{(C_{desired})\,(CL_{HD}\ x60)(\text{HD time})}{1000}$$

6. Materials and Instruments

6.1 Materials

Hydrochlorothiazide (HCTZ), an internal standard and vancomycin standard (Lot 112K 1550) were purchased from Sigma (Germany). HPLC grade methanol and acetonitrile were purchased from LAB-SCAN Ltd. (Thailand). Water was deionized and distilled.

6.2 Preparation of reagents and solutions

Stock solutions of the internal standard (IS), HCTZ and vancomycin standard were prepared at concentrations of 1 mg/ml in methanol and 5 mg/ml in water, respectively. The solutions were diluted to 40 μg/ml in water for HCTZ and to 2, 5, 10, 15, 30 and 50 mg/L in plasma for vancomycin.

The mobile phase consisted of 10% acetonitrile (ACN) in a 0.025 mol/L phosphate buffer (0.025 M KH_2PO_4 (pH 7): ACN = 90:10).

6.3 Sample preparation for assay

100 μl of patients' serum was transferred to a 1.5 ml centrifuge tube. 50 μl of the standard HCTZ and 100 μl of methanol were added, mixed and centrifuged at 15,000 rpm, 23°C for 10 minutes. 20 μl of the supernatant was injected into the HPLC system.

6.4 Instrumentation

The HPLC system consisted of a Jasco PU-1580 intelligent HPLC pump (Japan), Rheodyne Injector (USA), and Jasco UV-975 intelligent UV visible detector (Japan). Separation was achieved on ThermoHypersil-Keystone BDS Hypersil C18 column (150 × 4.6 mm, 5 μm, USA) at a flow rate of 1.5 ml/min. The peaks were detected at 229 nm, integrated and recorded

by Waters 746 (USA). The quantification was based on the peak area ratio of vancomycin to the internal standard. The retention times of the internal standard and vancomycin were about 5 and 9 minutes, respectively.

7. Method validation

The assay method was validated for 1) selectivity 2) accuracy, precision, recovery 3) linearity 4) limit of quantitation and 5) stability as guided by U.S. Department of Health and Human Services Food and Drug Administration (USFDA) and International Conference on Harmonisation (ICH).

For selectivity, plasma peaks did not interfere with the peak of vancomycin and HCTZ as shown in the chromatogram figure 3-1. Also, possible concomitant medications were tested for interference as shown in table 3-1.

For accuracy 5 replications were performed at the concentrations 2, 15 and 50 mg/L which had percentages between 98.05 and 114.73 in accordance with USFDA & ICH criteria whose accuracy percentage is 80 –120 %.

Intra-day variability (coefficients of variation) for 5 replications at 2, 15 and 50 mg/L were 11.59%, 11.94% and 9.86%, respectively, whereas the corresponding inter-day variability was 17.95%, 5.11% and 7.91% (n=5), respectively. Ranges of recovery percentage of 5 replications at 2, 15 and 50 mg/L were 93.16 - 102.87%.

Linearity of vancomycin in serum performed 5 replications concentrations of 0, 2, 5, 10, 15, 30 and 50 mg/L showed the coefficient of determination of greater than 0.99 as guided by USFDA and ICH.

The lower limit of quantification was at 2 mg/L.

The stabilities of vancomycin in plasma were in triplications at concentrations of 25 and 50 mg/L was performed using 3 methods, short term, long term and freeze-thaw.

Freeze-thaw of serum vancomycin was performed in 3 cycles by freezing serum 24 hours and returning it to room temperature (25 $^{\circ}$C).

Short term stability was studied by keeping serum vancomycin at room temperature (25 °C) and sampling to analysis every 2 hours.

Long term stability was studied by keeping serum vancomycin at -20 °C and sampling to analyze every 3 days until 2 weeks.

From the stability studies, vancomycin in serum was stable.

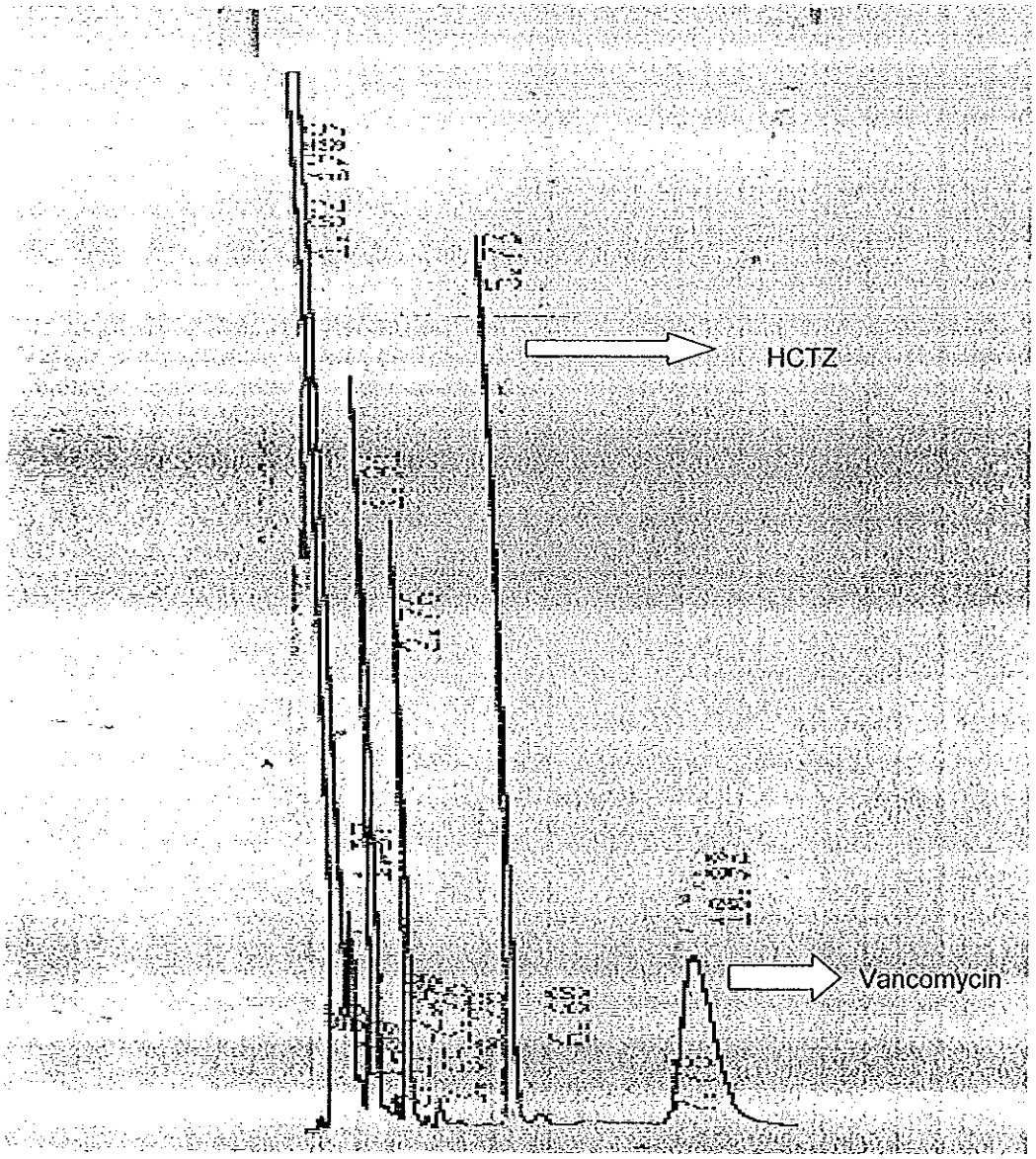


Fig. 3-1 Chromatogram of vancomycin and internal standard (HCTZ)

Table 3-1 Retention times of vancomycin, HCTZ and other concomitant medications

Drug	Retention time (minutes)
Vancomycin	12.33
HCTZ	5.73
Amphotericin	1.10
Sulperazone	1.43
Omeprazole	12.84
Paracetamol	2.33
Nifedipine	1.56
Domperidone	0.94
Imipenem	4.40
Metronidazole	3.01
Chlorpheniramine	0.94

8. Statistical analysis

The data were computerized using SPSS version 10.0. The descriptive statistics were analyzed. The vancomycin concentration-time profile was fitted in Excel program version 2003. The pharmacokinetics of vancomycin was analyzed by WinNonlin program. Regression analysis was performed to determine variable factors (%URR, %CrRR, UFR, blood flow rate, dialysis time, and %removal) affecting the dialysis clearance of vancomycin.

CHAPTER 4

RESULTS

24 samples of vancomycin serum concentration data were obtained from 20 patients (7 males and 13 females). Two patients were included twice and one of them was included three times because they were prescribed vancomycin for treatment of reinfections. 1 g of vancomycin was given to each patient over 1 hour for MRSA infection, and then, serum sample, C_{peak} was collected at 1 hour after the infusion completed. In most patients, blood sampling for measurement of C_{peak} levels were modified from that specified in our protocol as we previously designed to collect C_{peak} 1 hour after vancomycin infusion given after the first hemodialysis. These patients received vancomycin when they were treated in some other hospital wards outside the nephrology ward. The blood samples were collected at the wards before the patients arrived to the nephrology ward. Table 4-1 and appendix 1-3 present demographic data of the studied subjects recruited between January 2003 and March 2004. All patients received high-efficiency hemodialysis with cellulose triacetate dialyzer. 8 patients (2 males and 6 females) were ARF and 12 patients (5 males and 7 females) were CRF. Patients with CRF had been receiving hemodialysis twice weekly for 0.5 to 7 years. Individual UF goal and hemodialysis conditions were designed according to the patient's renal function or clinical signs and symptoms. The patients' characteristics reported as mean$\pm$SD were: age 52.3$\pm$15.8 years; the pre-dialysis mean weight 51.5$\pm$7.8 kg and calculated CrCL, using Cockcroft and Gault equation, 11.9$\pm$8.9 ml/min/1.73 m^2 (ranged 3.6 to 41.1 ml/min/1.73 m^2). The blood flow rates used ranged from 200 to 400 ml/min, i.e., 200 ml/min in 1 patient; 300 ml/min in 7 patients; 350 ml/min in 9 patients; and 400 ml/min in 7 patients. The hemodialysis times used were: 4 hours in 17 patients; 5 hours in 6 patients; and 4.5 hours in 1 patient.

Table 4-1 Demographic data of study subjects and hemodialysis conditions

Variables	Mean±SD (range)
Age (year)	52.5±15.8 (22-76)
Weight (kg)	51.5±7.8 (41-72)
Laboratory results	
BUN (mg/dl)	62.7±25.8 (30.9-135.0)
Cr (mg/dl)	6.7±3.7 (2.6-14.4)
CrCL (ml/min)	11.9±8.9 (1.6-10.4)
%URR	66.3±13.8 (32.2-86.1)
%CrRR	63.6±11.5 (35.5-80.6)
UF goal (L)	2.7±1.1 (1.0- 5.0)

Vancomycin serum concentrations of patients at the sampling times are shown in appendix 1-4 and their measured dialysis clearance of each patient is likewise shown in appendix 1-5. Pharmacokinetic parameters of vancomycin during high-efficiency hemodialysis are shown in Table 4-2. The peak vancomycin serum concentration (mean±SD) was 25.3±8.1 mg/L which declined rapidly, because of drug distribution and dialysis clearance, to 6.3±3.1 mg/L at the end of the third hemodialysis. Percent removal of vancomycin (mean±SD) was 37.1±13.1% and vancomycin dialysis clearance was 93.4±37.1 ml/min. The k_e was calculated by using graphing method of the first order pharmacokinetics. Calculation of $T_{1/2}$, and V_d (Table4-3) of vancomycin was done by WinNonlin program using 5 serum vancomycin concentration data.

Table 4-2 Pharmacokinetic parameters of vancomycin during high- efficiency HD

Mean±SD (range)				
CL (ml/min)	k_e (hr^{-1})	%Removal	C_{peak} (mg/L)	C_{min} (mg/L)
93.4±37.1 (30.8-167.5)	1.1±0.5 (0.5-2.6)	37.1±13.1 (12.7-58.1)	25.3±8.1 (12.0-47.8)	6.3±3.1 (2.6-20.1)

Table 4-3 Pharmacokinetic parameters of vancomycin in ESRD patients

Mean±SD (range)	
$T_{1/2}$ (hour)	V_d (L)
77.1±37.8 (42.6-171.9)	82.1±40.3 (30.2-162.5)

We performed regression analysis, using 2 different sets of predictors, to find appropriate models for prediction of vancomycin dialysis clearance. In the first method CrRR, URR, blood flow rate (Q), UFR, and dialysis time were used and the results were shown in Table 4-4. The regression model can substantially explain the variance of dialysis clearance (53%). Our final model was

$$\text{CL (ml/min)} = 2.61[\%\text{URR}] - 1.55[\%\text{CrRR}] + 0.30[\text{Q (ml/min)}] - 0.57[\text{time(hour)}] - 7.28[\text{UFR (L/ hour)}] - 75.42$$

Table 4-4 The output of regression analysis by using 5 predictors

R	R Square	Adjusted R Square	Standard Error of the Estimate
0.816	0.53	0.37	30.38

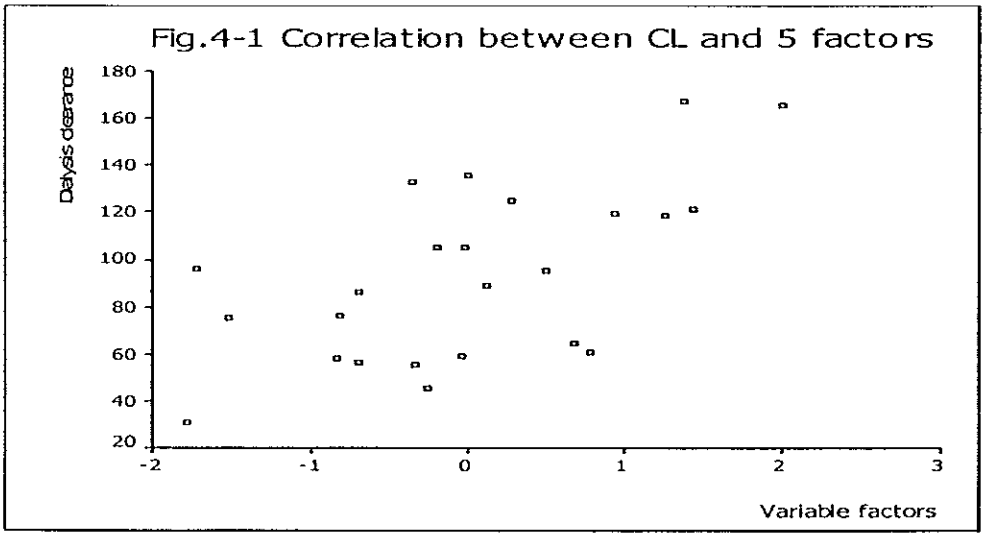
Predictors: (Constant), UFR, %URR, HD time, blood flow, %CrRR

Coefficients

Model	Unstandardized Coefficients		t	P-value
	Coefficients	Standard Error		
blood flow	0.30	0.217	1.39	0.18
%URR	2.61	1.036	2.52	0.03
%CrRR	-1.55	1.346	-1.15	0.26
HD time	-0.57	18.96	0.03	0.97
UFR	-7.28	35.38	-0.21	0.84
Constant	-75.42	155.52	-0.48	0.64

Dependent Variable: clearance

Where HD time = hemodialysis time



The results from the other regression model, using only %removal of vancomycin as a predictor, are shown in Table 4-5. This model can explain 83% of the dialysis clearance variance and the %removal was found to be a significant predictor. The model was

$$CL\ (ml/min) = 2.57[\%removal] - 1.81$$

Table 4-5 The output of regression analysis by using %removal

Model Summary

R	R Square	Adjusted R Square	Standard error of the Estimate
.909	.827	.819	15.7927

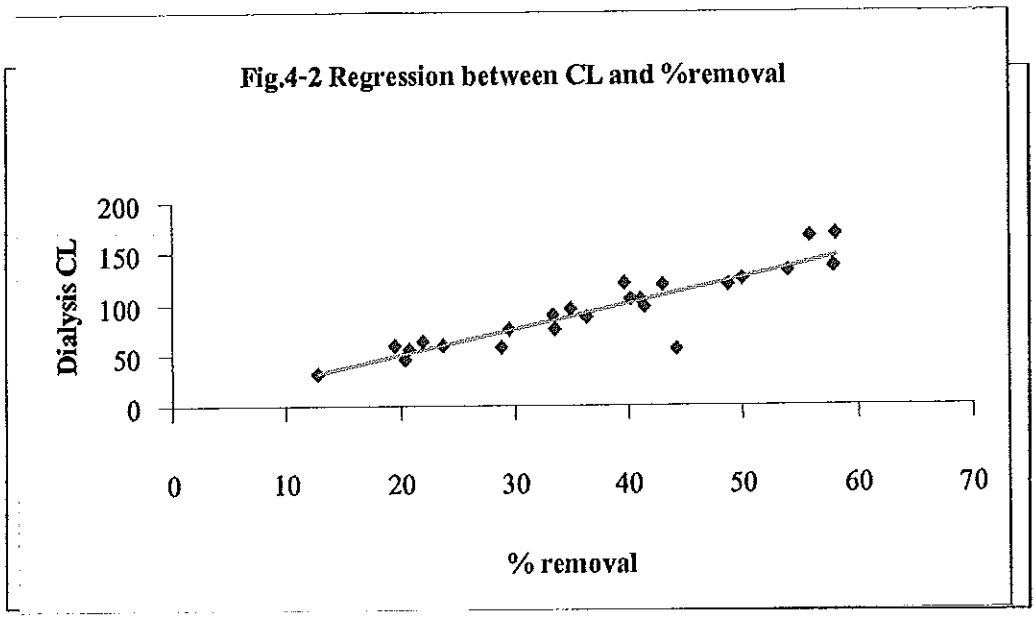
a Predictors: (Constant), %removal

b Dependent Variable: clearance

Coefficients

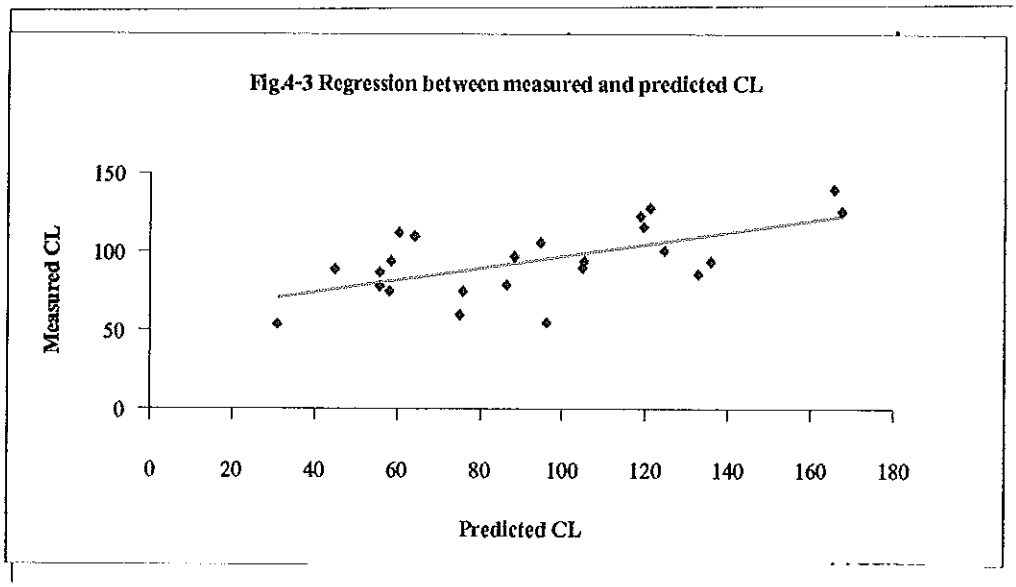
	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	Standard Error	Beta		
%removal	2.568	.251	.909	10.238	.000
Constant	-1.807	9.840		-.184	.856

a Dependent Variable: clearance



We found that the dialysis clearances predicted by these two models did not differ (paired t-test, p=0.46). We, however, suggest that the first model might be more practical for prediction of vancomycin dialysis clearance, especially when blood sampling must be avoided.

Correlation (Fig. 4-3) of the measured and the predicted vancomycin hemodialysis clearances were tested (paired t-test, p=0.849). The data are shown in Appendix 1-5.



Although all peak serum vancomycin concentrations did not reach the toxic level, the vancomycin concentrations (5.1-17.6 mg/L) were below therapeutic level in 66.7% (16/24) of patients after the second hemodialysis. At the end of the third hemodialysis, only 2 patients had the vancomycin concentrations in the therapeutic levels. We used the first regression model to

calculate the supplement dose of each patient to achieve appropriate vancomycin levels in the patients. Table 4-6 shows the supplement dose of vancomycin for each patient.

Table 4-6 Doses of vancomycin supplement predicted by using the first regression model and the predicted Cpss after 500 mg supplement dose

Predicted CL (ml/min)	Target Cpss (mg/L)	Calculated Dose (mg)	Predicted Cpss (mg/L) after 500 mg supplement dose
74.96	25	449.76	27.793
78.56	25	589.20	21.215
100.82	25	604.92	20.664
53.74	25	322.44	38.767
90.39	25	542.34	23.048
59.79	25	358.74	34.844
94.04	25	564.24	22.1537
112.18	25	673.08	18.571
55.04	25	412.80	30.281
94.04	25	564.24	22.1537
123.3	25	739.80	16.896
126.17	25	757.02	16.512
85.99	25	515.94	24.228
86.55	25	519.30	24.071

Table 4-6 (Continue)

Predicted CL (ml/min)	Target Cpss (mg/L)	Calculated Dose (mg)	Predicted Cpss (mg/L) after 500 mg supplement dose
75.44	25	452.64	27.616
110.36	25	662.16	18.878
105.8	25	634.80	19.691
88.52	25	663.90	18.828
127.56	25	956.70	13.066
140.39	25	947.63	13.191
97.09	25	582.54	21.458
94.11	25	564.66	22.137
77.7	25	582.75	21.450
115.95	25	869.63	14.374

Thus we recommend a supplement dose of 500 mg vancomycin after every subsequent hemodialysis.

CHAPTER 5

DISCUSSION

From our study, 1 g vancomycin administered every 5-7 days in hemodialysis patients, plasma vancomycin removal was about 37.1%. This may be dependent on hemodialyzer, blood flow rate, UFR, and dialysis treatment time. C_{peak} ranged from 12.0-47.8 mg/L, and no toxicity occurred. But C_{min} ranged from 2.5-16.6 mg/L (therapeutic level of vancomycin was 10-50 mg/L), subtherapeutic levels were found in 66.7% (16/24) and 91.6% (22/24) after the second and the third hemodialysis, respectively. The vancomycin dialysis clearance (mean$\pm$SD) was 93.4$\pm$37.1 ml/min.

Vancomycin is an effective antibiotic for MRSA therapy. In patients with severely impaired renal function vancomycin is an important drug because *Staphylococcus aureus* infection is frequent and its long $T_{1/2}$ allows prolonged dosing intervals. Therefore, we suggest that patients whose creatinine clearance is close to 10 ml/min should be monitored every 3-4 days. In our study we observed a decrease of vancomycin concentration during high-efficiency hemodialysis using cellulose triacetate dialyzers.

Several studies have demonstrated pharmacokinetics of vancomycin during high-efficiency to high-flux hemodialysis. The studied shown that vancomycin was removed during hemodialysis (Quale, *et al.*, 1992; Scott,*et al.*, 1997; Touchette,*et al.*, 1995).

In our study, we found that the serum vancomycin concentrations immediately before the third hemodialysis were higher than those after completing the second hemodialysis in 9 observations. This may be due to redistribution of vancomycin in the body. This phenomenon was not observed in the remainders. Because in patients with renal failure the protein-binding increased to 18% (the usual protein-binding was normally 50-60%) (Abuelo, 1995). Therefore the drug's V_d was altered. In patients with low protein-binding, their vancomycin free forms were increasing which then removed mostly by hemodialysis.

Vancomycin was mainly (90-95%) excreted unchanged by the kidney. Although it is clear that renal clearance of vancomycin decreases in patients with renal failure. It has also been suggested that nonrenal clearance of vancomycin, which usually accounts for approximately 30% (40 ml/min) of total clearance in normal renal function, is reduced to as low as 5-6 ml/min in chronic ESRD patients. The mechanism of this decline in nonrenal clearance was unknown (Vacher, *et al.*, 2002, Macias, *et al.*, 1991). So that nonrenal clearance appears to decrease with the duration of renal failure (Macias, *et al.*, 1991).

Diffusive solute removal is a function of transmembrane concentration gradient. Dialysis parameters that tend to enhance these gradients are high dialysate and blood flow rate, and low membrane thickness. On the other hand, solute molecular size, time during hemodialysis, ultrafiltration rate, and dialyser surface area also determine solute removal.

Vancomycin has been reported that, in ESRD patients, the average vancomycin elimination $T_{1/2}$ is 7.5 days (about 180 hours), whereas it is about 6-7 hours in patients with normal renal function (Vacher, *et al.*, 2002). Our study shows that elimination $T_{1/2}$ was about 77.1 ± 37.8 hours. The elimination $T_{1/2}$ was even decreasing in patients on hemodialysis, because of drug removal. Our dialyser and hemodialysis condition might be different from those previously reported.

According to our data, they clearly show that many factors affecting dialysis clearance. These factors varied between individual patients. Our findings exhibited a relationship between dialysis clearance with URR, CrRR, blood flow rate, UFR, and times during dialysis. Even though some factors did not significantly predict the clearance (except blood flow rate), but this model might be useful in clinical practice since all the model variables were usually obtained from routine laboratories. Using this model as a rough estimation of vancomycin clearance can avoid additional blood sample collection. It is suggested that we may predict vancomycin dialysis clearance by using the regression model and assess its predictability.

When we did a subgroup analysis according to the disease types, CRF and ARF patients, and chose a model for each group of patients. We could not find a good model for each group because the sample size became smaller, and all selected variables could explain not as

much the variance of dialysis clearance as that of the whole group. Moreover, comparing vancomycin dialysis clearances predicted by disease type-specific regression models with those predicted by the common model, the difference from the measured clearance of the previous one was larger.

There are some limitations in our study. The small number of patients recruited in the study period, and the condition of the dialyser (new/reused). Some participated patients were excluded because of death, discontinue vancomycin therapy and/or referral. Differences in dialyzer conditions were, however, minimized as dialyzers with priming volumes not less than 80% were used in this study.

Based on our findings, a loading dose of 1 g vancomycin intravenously infused post hemodialysis and a 500 mg infusion every subsequent dialysis should be recommended for patients undergoing high-efficiency hemodialysis with cellulose triacetate dialyzer. However, close monitoring of serum vancomycin concentrations would be warranted. 91.6% of our patients had subtherapeutic levels after the third hemodialysis because of drug removal. It should be noted that our experience is limited to our hemodialysis conditions with cellulose triacetate membranes, and dialysis prescription. This data should be generalised with caution to other settings with different hemodialysis conditions.

CHAPTER 6

CONCLUSION

Vancomycin therapy is widely used in ESRD patients with MRSA infection, and serum levels of this agent must be closely monitored in such patients in order to avoid toxicity and subtherapeutic levels.

In ESRD patients receiving a 1 g dose of vancomycin after high-efficiency hemodialysis, the drug is largely removed by subsequent high-efficiency hemodialysis. Following a single dose of 1 g vancomycin infusion, peak values of 12-47 mg/L decline rapidly to 10 to 20 mg/L after the next hemodialysis; the concentrations then slowly decline to 3 to 7 mg/L over the next 5 to 7 days of hemodialysis. We found that vancomycin levels decreased to 37.1% by using cellulose triacetate membranes. Vancomycin dialysis clearance was 93.4±37.1 ml/min. A (500 mg) maintenance doses should be administered according to the plasma trough levels.

Finally, to ensure efficacy during long-term treatments, measurements of serum vancomycin concentrations are recommended, especially in patients with residual renal function. The regression model allows predictions of vancomycin dialysis clearance and then used their clearances to calculate additional dosing required. However serum vancomycin concentration monitoring may be helpful in aiding the clinician in maintaining therapeutic vancomycin concentrations in patients being dialyzed with high-efficiency membrane.

BIBLIOGRAPHY

Abuelo JG. Renal failure. Netherland, Kluwer Acadamic. 1995; 49-63.

Anderson D.M. and Kothmann M.M.. Relationship of distance traveled with diet and weather for Hereford Heifers. J range management. 1980; 33(3): 202-208.

Aweeka FT. Young LY and Koda-Kimmble MA. Applied therapeutic: The clinical use of drug. (ed 6). New York, Applied Therapeutic,Inc. 1995; 19-32.

Brenner BM. Coe FL, Rector FC. Clinical nephrology. Philadelphia, W.B. Saunders company. 1987; 315-328.

Brenner BM. The kidney. (ed 6). United State of America. W.B. Saunders Company. 2000; 1201-1246.

Dajee H, Laks H, Miller J, Oran R. Profound hypotension from rapid vancomycin administration during cardiac operation. J.Thorac.Cardiovasc. 1984;87(1):145-6.

Danovitch G, Carvounis C, Weinstein E, Levenson S., Nonoliguria acute renal failure. Isr J med Sci. 1979; 15(1): 5-8.

Daugirdas JT, Blake PG, Ing TS. Handbook of dialysis. (ed 3).Philadelphia, Lippincott Williams and Wilkins. 2000; 15-147.

Desoi CA. Sahm DF, Umans JG. Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes. Am.J.Kidney Dis. 1992;354-360.

Dipiro JT, Chisholm MA, Mulloy LL, Jagadeesan M, Martin BC. Effect of clinical pharmacy services on the blood pressure of African-American renal transplant patients. Ethn.Dis. 2002;12(3):392-397.

Evans WE, Schentag JS, Jusko WJ. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. (ed 2). Philadelphia, Lippincott Williams and Wilkins. 1986; 400-434.

Foote EF, Dreitlein WB, Steward CA, Kapoian T, Walker JA, Sherman RA. Pharmacokinetics of vancomycin when administered during high flux hemodialysis. Clin.Nephrol. 1998;50:51-55.

Gibaldi M, and Perrier JD. Pharmacokinetics (ed 2). New York, Marcel Dekker, Inc. 1982; 411-414.

Hudson JQ, Comstock TJ, Feldman GM. Evalulation of an in vitro dialysis system to predict drug removal. Nephrol Dial Transplant. 2004; 19: 400-405

Kirby WMM and Divelbiss CL. A critical evalulation of vancomycin for treatment of bacterial meningitis. J Pediatric Infectious Dis. 1997; 16(9): 895-903.

Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL. Harrison's principles of internal medicine. New York, McGraw-Hill Companies Inc. 1994; (13):447-460.

Jusko WJ. Applied pharmacokinetics. (ed 2). Philadelphia, Lippincott Williams and Wilkins. 1996; 10-50.

Keller F, Horstensmeyer C, Looby M, Borner K, Pommer W, Erdmann K, Giehl M. Vancomycin dosing in haemodialysis patients and Bayesian estimate of individual pharmacokinetic parameter. Int.J.Artif.Organs 1994;17:19-26.

Lee CC, Andersen RC and Chen K.K. Vancomycin, a new antibiotic V. distribution, excretion, and renal clearance. Antibiotics annual 1956-1957. Medical Encyclopedia, Inc. New York, N.Y. 1957; 82-89.

Macias WL, Mueller BA, and Scarim SK. Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. Clin.Pharmacol.Ther. 1991;50(6):688-694.

Mason NA, Neudeck BL, Welage LS, Patel JA, Swartz RD. Comparison of 3 vancomycin dosage regimen during hemodialysis with cellulose triacetate dialyzers: post-dialysis versus intradialytic administration. Clin.Nephrol. 2003; 60(2): 96-104.

Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin.Pharmacokinet. 1986; 11(4): 257-282.

McEvoy G. McEvoy G, editor.AHFS Drug Information. 2001 ed. Wisconsin: American Soceity of Health-System Pharmacists, Inc. 2001; 471.

Mollering RC, Krogstad DJ, Greenblatt DJ. Vancomycin therapy in patients with impaired renal function: a nomogram for dosage. Ann.of Internal Med. 1981;94(3):343-6.

Punthananiwatkul B; Palkachain A. Determination of vancomycin in human plasma for therapeutic drug monitoring by HPLC technique. (unpublished) 2002.

Quale JM, Halloran JJ, Vincenzo ND, Barth RH. Removal of vancomycin by high-flux hemodialysis membranes. Antimicrob.Agent.Chemother. 1992;36:1424-1426.

Rodvold KA; Erdman SM; Pryka RD. Therapeutic Drug Monitoring. Philadelphia, Lippincott Williams and Wilkins. 1995; 587-625.

Schaedeli F, Uehlinger DE, Dominik E. Urea kinetics and dialysis treatment time predict vancomycin elimination during high flux hemodialysis. Clin.Pharmacol.Ther. 1998;63:26-37.

Scott MK, Mueller BA, Clark WR. Vancomycin mass transfer characteristics of high-flux cellulosic dialysers. Nephrol.Dial.Transplant. 1997;12:2647-2653.

Touchette MA, Patel RV, Anandan JV, Dumler F, Zarowitz BJ. Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. Am.J.Kidney Dis. 1995;26(3):469-474.

Vacher VL, Izzedine H, Mercadal L, Deray G. Clinical review:use of vancomycin in haemodialysis patients. Critical.Care. 2002; 6:313.-316.

Wagner JG. Modified Wagner-Nelson absorption equations for multiple-dose regimens. J Pharm Sci. 1983;72(5):578-579.

Welage LS, Mason NA, Hoffman EF, Odeh RM, Dombrouski J, Patel A, Swartz RD. Influence of cellulose triacetate hemodialyzers on vancomycin pharmacokinetics. J.Am.Soc.Nephrol. 1995;6:1284-1290.

Yap HK; Tan CC; Woo KT. Optimising renal therapy: the challenge for the twenty-first century. Singapore society of nephrology; 1996; 100-101.

Zoer J, Schrander-van der Meer AM, Dorp WT. Dosage recommendation of vancomycin during during haemodialysis with highly permeable membranes. Pharm.World Sci. 1997;19:191-196.

APPENDIX

Appendix 1-1 Effect of Renal Failure on Volume of Distribution

Drug	Volume of distribution (L/kg)	
	Normal	ESRD[a]
Increased		
Amikacin	0.20	0.29
Cefazolin	0.13	0.16
Cefoxitin	0.16	0.26
Cefuroxime	0.20	0.26
Clofibrate	0.14±0.02*	0.24±0.04
Cloxacillin	0.14	0.26
Dicloxacillin	0.08	0.18
Erythromycin	0.57	1.09
Furosemide	0.11±0.01*	0.18±0.03
Gentamicin	0.20	0.29
Isoniazid	0.60	0.80
Naproxen	8.30	11.90
Phenyltoin	0.64	1.40
Trimethoprim	1.36	1.83
Vancomycin	0.64	0.85

Appendix 1-1 (Continued)

Drug	Volume of distribution (L/kg)	
	Normal	ESRD[a]
Decreased		
Chloramphenicol	0.87	0.60
Digoxin	513±104	280±87
Ethambutol	3.70	1.60
Methicillin	0.45	0.30

[a] ESRD, End-stage renal disease, * Mean±SE

Appendix 1-2 Effect of hemodialysis on clearance and half-life of antimicrobial agent

Drug	Half-life (hr)		Effect of Hemodialysis	
	Normal	ESRD	CL (ml/min)	$T_{1/2}$ (hr)
Amikacin	1.6	39.0	70.6	3.5
Ampicillin	1.3	10-20	30-154	2.9-5.0
Aztreonam	2.0	7.0	43.0	2.7
Cefazolin	2.2	28.0	NR	2.6-5.0
Cefotaxime	0.9	2.5	91.2	2.1
Ceftazidime	1.8	26.0	50-155	1.2-3.2
Cefuroxium	1.3	15-22	103.0	1.6-3.5
Ciprofloxacin	4.4	8.4-12.0	48.6	5.3
Gentamicin	2.2	53.0	24-116	3.0-11.3
Imipenem	0.9	2.9	73.5	1.6
Penicillin G	0.7	4.1	37.5	2.3
Piperacillin	1.2	3.9	92.4	1.3
Ticarcillin	1.2	14.8	46.6	2.7
Tobramycin	2.5	58.0	31-120	4.3-6.7
Trimethoprim	14	26-40	29-66	5-9.4
Vancomycin	6.9	161	16.1-150	4.5-24

NR = Not report

Appendix 1-3. Demographics of patients

Pt No.	sex	Age (y)	wt. (kg)	BUN (mg/dl)	Cr (mg/dl)	CrCL (ml/min)	Blood flow rate (ml/min)	UFR (ml/min)	UF goal (L)	HD time (hour)
1	F	61	42.0	110	5.3	7.4	300	0.31	2.0	4.0
2	F	61	41.0	36.4	2.1	18.2	300	0.30	1.0	5.0
3	F	75	65.8	79	4.4	11.5	350	0.56	2.0	4.0
4	M	46	48.0	74	5.8	10.8	300	0.45	1.5	4.0
5	M	66	72.0	17.4	1.8	41.1	400	0.87	3.7	4.0
6	F	32	45.4	65	11.0	5.2	350	0.92	2.8	4.0
7	F	32	45.0	42.1	7.4	7.6	400	0.90	2.0	4.0
8	F	27	46.0	70.4	7.5	8.2	350	0.60	2.5	4.0
9	F	60	47.5	71.8	5.8	7.7	300	0.70	3.0	5.0
10	M	59	49.2	72.1	13.2	4.2	350	0.92	2.0	4.0
11	F	57	51.6	76.4	11.7	4.3	400	0.67	1.8	4.0
12	F	57	50.5	78.5	13.7	3.6	400	0.72	2.8	4.0
13	F	57	51.5	27.8	6.0	8.4	300	1.01	4.5	4.0
14	M	62	57.0	33.8	14.2	4.4	350	0.50	2.0	4.0
15	F	54	59.0	40.7	6.9	8.7	300	0.82	3.0	4.0
16	F	42	66.2	52	6.0	12.8	400	1.28	5.0	4.0
17	M	70	57.0	76.9	8.9	6.2	350	0.70	3.5	4.0
18	F	29	52.0	21.6	2.6	26.2	300	0.68	2.5	5.0
19	F	31	47.5	102	3.4	17.9	400	1.00	5.0	5.0
20	F	22	44.5	76.8	2.4	26.1	400	0.53	1.5	4.5
21	F	60	47.8	32.6	4.2	10.9	350	0.97	3.0	4.0
22	M	76	48.2	66.9	7.3	5.8	300	0.82	3.0	4.0
23	F	55	52.0	87.1	5.3	9.9	200	0.39	1.2	5.0
24	M	65	48.0	95.2	2.9	17.4	350	0.21	3.5	5.0
mean		52.5	51.5	62.7	6.7	11.9	341.7	0.70	2.7	4.3
SD±		15.8	7.8	25.8	3.7	8.9	50.4	0.30	1.1	0.4

Appendix 1-4. Pharmacokinetics parameters of patients

Pt No.	C_{peak} (mg/L)	$C_{mid\ 0h}$ (mg/L)	$C_{mid\ 2h}$ (mg/L)	C_{mid4h} (mg/L)	C_5 (mg/L)	C_{min} (mg/L)
1	15.32	9.15	8.08	6.52	6.21	6.03
2	29.79	15.73	13.48	10.01	10.22	9.65
3	20.94	10.15	7.61	5.08	4.17	3.68
4	26.29	15.95	15.23	13.93	10.58	5.29
5	32.74	15.28	9.62	9.15	8.87	6.79
6	27.13	10.11	7.67	7.12	6.08	2.45
7	47.80	20.14	18.60	16.20	14.50	7.70
8	28.82	9.64	8.63	7.35	4.39	3.63
9	31.69	10.47	8.25	6.13	3.92	3.73
10	23.98	18.49	11.07	10.90	7.81	5.42
11	19.48	9.01	5.66	5.14	4.56	4.19
12	24.21	7.32	4.29	3.07	5.88	5.42
13	18.25	6.78	5.21	3.12	5.13	3.07
14	34.53	22.28	18.82	17.65	17.60	10.15

Appendix 1-4. (Continued)

Pt No.	C_{peak} (mg/L)	$C_{mid\ 0h}$ (mg/L)	$C_{mid\ 2h}$ (mg/L)	$C_{mid\ 4h}$ (mg/L)	C_5 (mg/L)	C_{min} (mg/L)
15	30.68	24.11	22.71	16.04	15.59	8.92
16	18.65	12.90	11.32	10.07	10.51	7.78
17	21.54	14.23	11.91	9.26	8.32	6.40
18	18.53	11.21	9.91	8.93	7.7	6.80
19	39.11	33.22	29.64	20.05	18.43	16.58
20	16.93	5.85	2.92	2.58	4.48	4.04
21	23.74	15.38	11.54	10.24	12.17	9.22
22	23.93	12.19	7.93	5.13	6.72	4.82
23	21.78	10.54	7.83	5.89	6.06	5.12
24	12.04	6.22	4.75	3.19	4.65	3.12
Mean	25.33	13.60	10.96	8.86	8.53	6.25
SD±	8.12	6.47	6.28	4.88	4.35	3.12

Appendix 1-5. Compared measured and predicted clearance

Pt. No.	Measured CL (ml/min)	Predicted CL (ml/min)
1	57.99	74.96
2	86.37	78.56
3	124.41	100.82
4	30.79	53.74
5	104.82	90.39
6	75.18	59.79
7	58.63	94.04
8	60.32	112.18
9	96.16	55.04
10	105.42	94.04
11	118.93	123.30
12	167.52	126.17
13	132.72	85.99
14	55.67	86.55
15	75.86	75.44
16	64.18	110.36
17	94.58	105.80
18	45.08	88.52
19	121.12	127.56
20	165.69	140.39
21	88.37	97.09
22	135.86	94.11
23	55.81	77.70
24	119.45	115.95
Mean±SD	93.45±37.1	94.5±22.9

Paired Samples Statistics measured and predicted clearance

CL (ml/min)	Mean	N	Standard Deviation	Standard Error
measured	93.37	24	37.08	7.56
predicted	94.52	24	22.95	4.68

Paired Samples Correlations

N	Correlation coefficient	P-value
24	0.616	0.001

Paired Samples Test

Paired Differences					t	df	P-value (2-tailed test)
Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval of the Difference				
			Lower	Upper			
-1.15	29.2	5.96	-13.48	11.18	-0.193	23	0.849

Appendix 2

ใบยินยอมเข้าร่วมโครงการศึกษา

ชื่อโครงการ "อัตราการกำจัดแวนโคไมซินในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายขณะทำ hemodialysis แบบมีประสิทธิภาพสูง"

ข้าพเจ้า (นาย, นาง, นางสาว).....นามสกุล.....ยินยอมเข้ารับการศึกษาดังวิธีที่เภสัชกรหญิงณัฏฐา กลั่นสุวรรณ ได้อธิบายให้ข้าพเจ้าทราบ หากข้าพเจ้ามีข้อสงสัยเกี่ยวกับการศึกษาข้าพเจ้ามีสิทธิ์ซักถามได้ หากการกระทำและการชี้แจงของนักวิจัยยังไม่เป็นที่พอใจ ข้าพเจ้ามีสิทธิแจ้งต่อประธานกรรมการจริยธรรม(คณบดีคณะแพทยศาสตร์ โทร 074-451100 หรือผู้อำนวยการโรงพยาบาลสงขลานครินทร์ โทร 074-451010) และหากข้าพเจ้าไม่พอใจข้าพเจ้ามีสิทธิปฏิเสธการศึกษาได้ทันทีโดยไม่เสียสิทธิในการรับการรักษาในโรงพยาบาลสงขลานครินทร์ต่อไป ข้าพเจ้าได้อ่านและเข้าใจเกี่ยวกับ การศึกษาทั้งหมดข้างต้นแล้ว ข้าพเจ้ายินยอมรับการศึกษาตามวิธีดังกล่าว

.....	.....
ลายมือชื่อผู้ป่วย	วัน/เดือน/ปี
.....	.....
ลายมือชื่อพยาน	วัน/เดือน/ปี
.....	.....
ลายมือชื่อนักวิจัย	วัน/เดือน/ปี
.....	.....
ลายมือชื่อแพทย์	วัน/เดือน/ปี

Appendix 3

Drug Therapy Monitoring Worksheet

Name.....H.N.....Age.....Gender.....

Ht.....WL.....Admit.....D/C.....

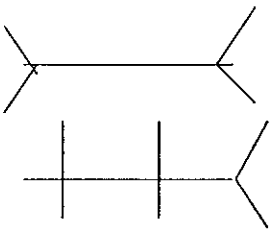
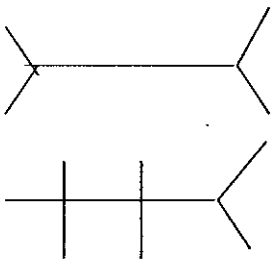
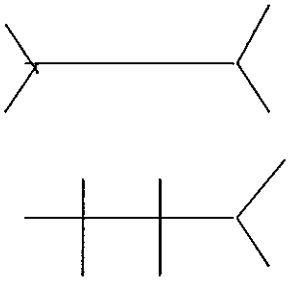
Address.....Bed/Ward.....

CC:.....	MedsPTA:.....
.....	.....
PMH:.....	.....
.....	.....
.....	.....
Allergies:.....	Smorking/Drinking:.....
Fx:.....	PE:.....
Dx:.....	.....
.....	.....
Chemotherapy	.....
Plan:.....	.....
.....	.....

Note: .....

.....

.....

Date	Daily note	List	MEDS	Start	Stop
	T..... BP.....RR.....PR..... CrCL..... 				
	T..... BP.....RR.....PR..... CrCL..... 				
	T..... BP.....RR.....PR..... CrCL..... 				

Note .....

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Appendix 4

Hemodialysis monitoring

Hemodialysis HN..... Age..... Sex..... Date..... Dx..... Dialyzer..... No. reused..... Machine.....				BW (kg)	Hct	BUN/Cr	Na,K,Cl,CO_2
			Pre HD				
			Post HD				
			Dry				
			UF Goal (L)				
time	UFR (ml/min)	Blood flow (ml/min)	Hep (iu)	PR (ครั้ง/ นาที)	BP (mmHg)	RR (ครั้ง/ นาที)	BT ($^{\circ}C$)

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