เภสัชจลนศาสตร์ของยาอะมิกาซินที่ให้ทางการฉีดเข้ากล้ามเนื้อในผู้ป่วยที่ติดเชื้อจากการล้างไตทางช่องท้องอย่างต่อเนื่อง

นางสาวภัทรินทร์ กิตติบุญญาคุณ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชกรรม ภาควิชาเภสัชกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2543

ISBN 974-346-924-9

PHARMACOKINETIC OF AMIKACIN GIVEN INTRAMUSCULARLY IN INFECTED-CAPD PATIENTS

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Pharmaceutical Sciences

Department of Pharmacy

Faculty of Pharmaceutical Sciences

Chulalongkorn University

Academic Year 2000

ISBN 974-346-924-9

Thesis Title	Pharmacokinetic of Amikacin Given Intramuscularly in Infected-CAPD patients
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ภัทรินทร์ กิตติบุญญาคุณ : เภสัชจลนศาสตร์ของยาอะมิกาซินที่ให้ทางการฉีดเข้ากล้ามเนื้อในผู้ป่วยที่ติดเชื้อจากการล้างไตทางช่องท้องอย่างต่อเนื่อง (Pharmacokinetic of amikacin given intramuscularly in infected-CAPD patients) อ.ที่ปรึกษา : รศ.ดร.ดวงจิต พนมวัน ณ อยุธยา , อ.ที่ปรึกษาร่วม : พลตรีหญิง อุษณา ลุวีระ : ...110... หน้า.
ISBN 974-346-924-9

การศึกษาครั้งนี้มีวัตถุประสงค์ เพื่อศึกษาเภสัชจลนศาสตร์ของการให้ยา amikacin โดยทางการฉีดเข้ากล้ามเนื้อในผู้ป่วยที่ติดเชื้อจากการรักษาด้วยวิธีการล้างไตทางช่องท้องอย่างต่อเนื่อง และต้องการประเมินว่าการให้ยา amikacin ทางการฉีดเข้ากล้ามเนื้อจะให้ระดับยาในน้ำยาล้างช่องท้องสูงเพียงพอสำหรับรักษาการติดเชื้อในช่องท้องหรือไม่ และระดับยาต่ำสุดในเลือดก่อนให้ยาขนาดต่อไปอยู่ในระดับที่เป็นพิษต่อหูหรือไม่ รวมทั้งเพื่อศึกษาว่ามีความสัมพันธ์ระหว่างระดับยา amikacin ในเลือดและในน้ำยาล้างช่องท้องหรือไม่ โดยมีผู้ป่วยติดเชื้อที่ทำการศึกษาทั้งหมด 12 ราย มีกลุ่มผู้ป่วยที่เกิดการติดเชื้อในช่องท้องจำนวน 7 ราย และกลุ่มที่เกิดการติดเชื้อแทรกซ้อนจากสายล้างช่องท้องจำนวน 5 ราย ผู้ป่วยทุกรายจะทำการล้างไตทางช่องท้องอย่างต่อเนื่องวันละ 4 ครั้ง โดยมีระยะเวลาค้างน้ำยาล้างช่องท้องในแต่ละครั้งเท่ากับ 6 ชั่วโมง ผู้ป่วยได้รับยา amikacin ขนาด 7.5 มิลลิกรัม/กิโลกรัม ร่วมกับการให้ยา cefazolin อย่างต่อเนื่องทางช่องท้องเพื่อเป็นการรักษาก่อนทราบผลการเพาะเชื้อ และเก็บตัวอย่างเลือดและน้ำยาล้างช่องท้องภายในเวลา 48 ชั่วโมง

ผลการศึกษาพบว่าระดับยา amikacin สูงสุดในเลือดมีค่าเฉลี่ย 25.3 มิลลิกรัมต่อลิตร ที่เวลาประมาณ 2.6 ชั่วโมง โดยที่ระดับยาสูงสุดอยู่ในช่วงของการรักษา(15-30 มิลลิกรัม/ลิตร) และระดับยาต่ำสุดในเลือดที่เวลา 48 ชั่วโมง มีค่าเฉลี่ย 10.3 มิลลิกรัมต่อลิตร ซึ่งสูงกว่าระดับยาที่ปลอดภัย (ควรน้อยกว่า 5 มิลลิกรัมต่อลิตร) ทำให้ผู้ป่วยมีความเสี่ยงต่อการเกิดพิษที่หู ปริมาตรการกระจายของ amikacin ในร่างกายมีค่าเฉลี่ย 35.99 ลิตร (0.56 ลิตรต่อน้ำหนักตัว 1 กิโลกรัม) การขจัดยาออกจากร่างกายมีค่าเฉลี่ย 0.64 ลิตรต่อชั่วโมง (10.73 มิลลิลิตรต่อนาที) และมีค่าครึ่งชีวิตของ amikacin เฉลี่ยประมาณ 38 ชั่วโมง amikacin มีค่าการขจัดยาผ่านทางวิธีการล้างไตทางช่องท้องอย่างต่อเนื่องโดยเฉลี่ย 0.23 ลิตรต่อชั่วโมง (3.9 มิลลิลิตรต่อนาที) และปริมาณยา amikacin ที่ถูกขจัดออกโดยเส้นทางนี้มีค่าประมาณ 54 เปอร์เซ็นต์ของขนาดยาที่ได้รับ การฉีดยา amikacin เข้าทางกล้ามเนื้อจะให้ระดับยาสูงสุดในน้ำยาล้างช่องท้องที่เวลาสุดท้ายของการค้างน้ำยาไว้ในช่องท้องแต่ละถุง และพบระดับยาสูงสุดในน้ำยาล้างช่องท้องถุงแรก มีค่ามากที่สุด โดยมีระดับยาเฉลี่ย 17.6 มิลลิกรัม/ลิตร ซึ่งสูงกว่าเกณฑ์ที่กำหนดโดย The United States' National Committee for Clinical Laboratory Standards (NCCLS ; ซึ่งกำหนดในระดับที่สามารถฆ่าเชื้อได้ดี คือ $\geq$ 16 มิลลิกรัม/ลิตร) เพียงเล็กน้อย และพบว่ามีความสัมพันธ์ระหว่างระดับยา amikacin ในเลือดและในช่องท้อง

โดยสรุปพบว่าการใช้ยา amikacin ขนาด 7.5 มิลลิกรัม/กิโลกรัม ทุก 48 ชั่วโมง โดยการฉีดเข้ากล้ามเนื้อ ไม่เหมาะสมในการนำมาใช้รักษาการติดเชื้อในช่องท้องของผู้ป่วยที่รักษาด้วยวิธีการล้างไตทางช่องท้องอย่างต่อเนื่อง เพราะนอกจากระดับยาที่เวลาส่วนใหญ่ จะต่ำกว่าระดับที่ให้ผลการรักษาแล้ว ระดับยาต่ำสุดในเลือดก่อนให้ยาในขนาดต่อไปยังสูงกว่าระดับที่ปลอดภัยซึ่งอาจทำให้เกิดพิษต่อหูได้ อย่างไรก็ตาม การศึกษาครั้งนี้แสดงให้เห็นว่าสามารถใช้ข้อมูลระดับยา amikacin ในน้ำยาล้างช่องท้อง มาคำนวณค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ เพื่อทำนายระดับยา amikacin ในเลือด หรือสามารถทำนายในทางกลับกันได้ ควรมีการศึกษาในเรื่องนี้ต่อไป

ภาควิชา.....เภสัชกรรม.....**ลายมือชื่อนิสิต**.....

สาขาวิชา.....เภสัชกรรม.....**ลายมือชื่ออาจารย์ที่ปรึกษา**.....

ปีการศึกษา.....2543.....**ลายมือชื่ออาจารย์ที่ปรึกษาร่วม**.....

##4176573033 :MAJOR HOSPITAL AND CLINICAL PHARMACY
KEY WORD: PHARMACOKINETIC / AMIKACIN/INFECTED-CAPD PATIENTS /INTRAMUSCULAR . PATTARIN KITTIBOONYAKUN: PHARMACOKINETICS OF AMIKACIN GIVEN INTRAMUSCULARLY IN INFECTED-CAPD PATIENTS. THESIS ADVISOR : ASSOCIATE PROFESSOR DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D. THESIS CO-ADVISOR: MAJ.GEN USANA LUVIRA, M.D.110 PP.ISBN 974-346-924-9

The objective of this study was to determine pharmacokinetic parameters of amikacin administered by intramuscular route (IM) in infected – CAPD patients, to evaluate whether or not the amikacin concentration in plasma and dialysate within 48 hours following the drug administration could achieve the therapeutic level and whether or not its trough plasma concentration was in the range that claimed to be safe for ototoxicity and to determine the relationship between plasma and dialysate of amikacin concentrations following IM route of administration. Twelve patients who participated in this study performed CAPD four exchange per day with six hours dwell period. Of the 12 infected-CAPD patients, seven patients had peritonitis (58.3%) and five patients had catheter-related infection with no peritonitis (41.7%).The patients received only one dose of IM amikacin 7.5 mg/kg along with continuous IP cefazolin as an empirical treatment. Both plasma and dialysate samples from the patients were collected within 48 hours.

The results showed that all patients had peak plasma concentration of amikacin in the therapeutic range (15-30 mg/L) with the mean peak concentration equaled to 25.3 mg/L and the mean time to peak was at 2.6 hour. The trough plasma concentration of amikacin at 48 hours in all patients were higher than 5 mg/L with the mean concentration equaled to 10.3 mg/L which may cause ototoxicity if this dosage would be given every 48 hours. The mean volume of distribution was 35.99 L (0.56 L/kg), the mean total body clearance was 0.64 L/hr (10.73 ml/min) with the mean half-life approximately 38 hours. The mean peritoneal amikacin clearance was 0.23 L/hr (3.90 ml/min). Approximately 54% of the dose of amikacin administered was removed by CAPD. Amikacin concentration in dialysate showed the peak concentration every six hours at the end of each dialysate exchange and the maximum peak dialysate was found at the end of the first dialysate bag with the mean equaled to 17.6 mg/L which was slightly higher than therapeutic concentration (≥ 16 mg/L) recommended by the United States' National Committee for Clinical Laboratory Standards (NCCLS) .There was relationship between amikacin concentration in the plasma and in the dialysate.

In conclusion, intramuscular administration of amikacin with the single dose of 7.5 mg/kg every 48 hours for the treatment of peritonitis in CAPD patients might not be an appropriate dosage regimen since the dialysate concentrations were mostly too low to be effective while the trough concentration in plasma was too high resulting in high risk of ototoxicity. However, the amikacin concentrations in dialysate could be used to derive the pharmacokinetic parameters which could then be used to predict the amikacin concentrations in plasma or vice versa. Further study should be continued.

Department…...……Pharmacy…… Student's signature……
Field of study……Pharmacy……Advisor's signature ……..…….
Academic Year…… 2000…….……Co-advisor's signature ……..

ACKNOWLEDGEMENT

For successful completion of this work, I would like to take this opportunity to thank for contributions.

I would like to express my sincere gratitude to my thesis advisor, Associate Professor Duangchit Panomvana Na Ayudhya of the Department of Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, for the invaluable advice, continual guidance, suggestion, enthusiastic encouragement, kindness and understanding throughout the course of this study.

To my thesis co-advisor, Maj. Gen. Usana Luvira, M.D., Nephrology Division, Department of Medicine, Phramongkutkloa's Hospital. I wish to express my deeply appreciation for her constructive guidance, interest, and the time she devoted to helpful discussion and valuable contributions entire the course of study.

My honest thanks are extended to Col. Associate Professor Panbubpa Choovichian , Maj. Aschara Boonyagarn, Sub. Lt. Vanna Prakongkaew, and all docters and personels in Nephrology Division, Department of Medicine , Maj. Sudaluck Chantaratchada head of Microbiology Division, Department of Clinical Pathology, Maj. Songsak Srijinda head of Blood Bank Division, Col. Saichit Wongyai head of Biochemistry Division at Phramongkutkloa's Hospital and Ltc. Boontham Khoprasert head of Toxicological Section Army Institute of Pathology, Phramongkutkloa's Medical Center for their helpful cooperation and supporting in providing many facillities. And also all patients participated in my study for their generous cooperation.

Thanks are also due to Chulalongkorn University for providing partial financial support to fulfill this study.

Above of all, I appreciatively have to say thank you to my parents and my friends for their encouragement, understanding and supporting throughout my graduate study.

Pattarin Kittiboonyakun

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ABBREVIATIONS

ESRD	=	end-stage renal disease
CAPD	=	continuous ambulatory peritoneal dialysis
PD	=	peritoneal dialysis
SEP	=	sclerosing encapsulated peritonitis
ESI	=	exit site infection
TI	=	tunnel infection
IP	=	intraperitoneal
IV	=	intravenous
IM	=	intramuscular
C/S	=	specimen culture and antimicrobial susceptibility test
Pt.	=	patient
HTN	=	hypertension
DM	=	diabetic mellitus
IHD	=	ischemic heart disease
CHF	=	congestive heart failure
CTIN	=	chronic tubulointerstitial nephritis
CGN	=	chronic glomerulonephritis
CV	=	coefficient of variance
Cpeak	=	peak plasma concentration
Ctrough	=	trough plasma concentration just before the next dose
Ctargetd	=	target concentration of amikacin in dialysate for treatment of peritonitis
AUC	=	area under plasma concentration versus time curve mg/L hr

Ka	=	absorption rate constant (hr^{-1})
α	=	distribution rate constant (hr^{-1})
β	=	elimination rate constant (hr^{-1})
Vd	=	volume of distribution (L)
TBCl	=	total body clearance (L/hr or ml/min)
$T_{1/2}$	=	half-life (hr)
kd	=	dialysate excretion rate constant (hr^{-1})
βd	=	elimination rate constant calculated from data of dialysate sample (hr^{-1})
%kd/βd	=	fraction of drug dose eliminated by CAPD (%)
Clpd	=	peritoneal amikacin clearance (L/hr or ml/min)
Cpmeasured	=	measured plasma concentration (mg/L)
Cpcalculated	=	calculated plasma concentration (mg/L)

CHAPTER I

INTRODUCTION

Peritoneal dialysis (PD) has been used to treat uremic patients since the mid-1940s (1).Although the overall management of the patients undergoing continuous ambulatory peritoneal dialysis and the new technology in bags, catheters, connection devices and exchange procedures have been developed, peritonitis remains the major complication of CAPD today (2). Frequency recurrence of peritonitis can cause sclerosing encapsulating peritonitis (SEP) and peritoneal sclerosis that leads to reducing in efficiency of peritoneum as semipermeable membrane in eliminating waste products from end-stage renal disease patients as a result to the failure of solute transport and ultrafiltration (3). Moreover, peritonitis has influence on the development of malnutrition, especially in malnourished patient. Because during peritonitis, patients lose more protein in effluent dialysate than normal condition (4).

Almost CAPD patients usually exchange two liters of dialysate bag into and out of peritoneal cavity four exchanges per day by strictly sterile technique for preventing peritonitis. However, peritonitis remains the leading cause of morbidity, CAPD failure, transferring to hemodialysis and reducing the chance for renal transplantation (5-6).Furthermore, two recent studies have found that there are association between peritonitis and mortality (7-8). Peritonitis is reported to cause death about 1-6% of CAPD patients, especially gram negative peritonitis is associated with higher mortality than gram-positive peritonitis (2,7).

Other infected complication related to patients undergoing CAPD is catheter-related infection such as exit-site infection (ESI) and tunnel infection (TI). These types of infection are important complications of long-term peritoneal dialysis. They are also a major source of peritonitis and may lead to catheter loss especially peritonitis associated with tunnel infection (9).

Although the double-cuff catheters have two dacron cuffs compositing of outer cuff and inner cuff which are placed immediately above peritoneal membrane and subcutaneous about a centimeter from the exit-site to prevent infection tracking along the tunnel. However both the exit and tunnel still get infected which cause subsequently peritonitis (10). Several organisms originating from the patient's skin may cause ESI, but most significantly, *Staphylococcus aureus* is an important organism leading to peritonitis with many complications and high mortality (11).

Most of the episodes of peritonitis are related to accidental contamination secondary to break in sterile technique in the exchange of the bags or the transfer set. In addition, the contamination may well be related to fluid leaks from the lines, connecting set cracks, faulty bags or from the exit site of the catheter (10).The incidence of peritonitis is about 1.1-1.3 episodes per year (12). Previous studies have found that gram positive bacteria causes 50-60% of episodes of peritonitis. *Staphylococcus epidermis* is the most common pathogen followed by *Staphylococcus aureus*, *Streptococcus spp.* Gram negative causes 30-40% of episodes with predominant in *Escherichia coli* followed by *Klebsiella spp.*, *Enterobacter spp.*, *Proteus spp.* and *Pseudomonas spp.* Fungi, anaerobic bacteria, mixed infection and culture negative cause between 5-15% of episodes (1,10, 12).

Retrospective study from CAPD unit of Phramongkutklao's hospital, the data about infection in CAPD patients was collected between 1986-1999 (13). In this study, there were 54 patients who had infection during CAPD and 24 patients who had no infection. Among these there were 50 patients who developed peritonitis. The incidence of peritonitis was about 1.2 episodes per year. Culture negative was found 47% of episodes. A gram-positive bacteria was the most common pathogen accounted for 31% of episodes. *Staphylococcus aureus* was the most causative organism followed by *Staphylococcus coagulase negative* and *Streptococcus spp.* Gram negative bacteria caused 20% of episodes which *Escherichia coli* was the most causative organism followed by *Acinetobacter iwoffii* and *Klebsiella pneumoniae.* Fungal peritonitis was found 1.5% of episodes caused by *Candida albican* and *Trichophyton rulsum* . There were 25 patients who had exit-site infection and 4 patients who had tunnel infection *Staphylococcus aureus* was the most common pathogen causing both exit-site and tunnel infection. Peritonitis associated with exit-site infection was found in 10 patients and it is caused by *Staphylococcus aureus* and *Pseudomonas aeurginosa.* Peritonitis associated with tunnel infection was found in 5 patients and caused by *Staphylococcus aureus* (13).

When patients was first diagnosed having peritonitis, the physicians can not diagnose the type of causing pathogen from clinical symptom within 72 hours. So, initial empirical treatment within 72 hours requires a broad spectrum regimen to cover eradicating both gram positive and gram negative bacteria until dialysate culture and antimicrobial susceptibility test were available and then treatment can be revised. In 1993, the Advisory Committee on Peritonitis Management of the International Society of Peritoneal Dialysis (ISPD) suggested the use of once-weekly vancomycin by intraperitoneal (IP) or intravenous (IV) route with continuous aminoglycoside by IP route for empirical treatment (14). However, reports of infection with vancomycin-resistant enterococcus were identified (15-16). There were concerns that vancomycin resistance would develop in other organisms such as *Staphylococcus spp.* Vancomycin resistance can be transferred in vitro from enterococci to *Staphylococcus aureus* (2). So in 1996, the Advisory Committee on Peritonitis Management refined its recommendation and suggested the use of continuous IP of cefazolin with continuous or intermittent IP of aminoglycosides for empirical treatment (12).

This ISPD treatment guideline for peritonitis is useful for initial therapeutic approach. However, it should not be a tool for introducing therapeutic paralysis-the fear of changing from guidelines in individual cases when conditions make it necessary. Although IP route is advantage for local eradicating causative organism in peritoneal cavity, for disadvantage, this route may irritate peritoneum to cause chemical peritonitis (17-19) and increase risk of infection by contaminating if added antibiotics into dialysate bag is performed by inexperience nurse. Since duration of peritonitis therapy takes about 14 days and stability of most antibiotics added into dialysis solution is only stable for 24 hours ,therefore, CAPD patients who develop peritonitis or their cousins must waste the working time to take the bags for adding antibiotics by dialysis-nurse at the CAPD centers every day and they must pay more expenses in transportation besides the antibiotic cost.

Almost the CAPD patients of Phramongkutklao's Hospital live in remote areas and they have the inconvenient problem and inadequate budget to pay the cost of transportation to get the emergency treatment for CAPD-associated with peritonitis at the center in Bangkok. Besides that, the nurses working in hospitals in remote or provincial areas of Thailand who have skill and experience in adding antibiotics into dialysate bag with sterile technique are still inadequate. Therefore parenteral treatment by intramuscular or intravenous route may be more appropriate than intraperitoneal route administered by inexperience nurses.

The benefits of administering the drug by intramuscular route (IM) for treatment of peritonitis are known,i.e, patients can receive the service of treatment near their home in outpatient clinic in remote area which can decrease the risk of contamination from the process of adding antibiotic into dialysate bag by inexperience nurses and can be early therapeutic intervention. Also, there were many studies investigated the efficacy of once-daily IP and oral administration of antibiotic for peritonitis treatment to improve disadvantage or reduce difficulties of continuous IP administration (20-26).

There have been many studies about pharmacokinetic of aminoglycoside (amikacin, gentamicin, tobramycin) administered by IP and IV route in patients undergoing CAPD with no peritonitis (27-30). Smeltzer BD and et al (27) investigated pharmacokinetic of amikacin in five stable patients undergoing CAPD. Each patient was studied after the administration of 7.5 mg of amikacin per kg by both the IV and IP route, allowing a 1-month washout period between doses. No differences in amikacin half-life, volume of distribution, total body clearance or peritoneal clearance was noted between the two routes of administration. Amikacin pharmacokinetic was consistent with those of other aminoglycosides in CAPD patients when the drug was administered either IV or IP.

However, there is no study about pharmacokinetic of amikacin administered by IM route in CAPD-patients with peritonitis and no study that consider the efficacy of amikacin in treating peritonitis from dialysate level and the ototoxicity from its trough level in serum. So the purpose of this study were to determine pharmacokinetic parameters of amikacin administered by IM route in infected CAPD-patients and to evaluate whether or not the drug concentration from IM route can achieve therapeutic level both in serum and in dialysate as well as the safety from ototoxicity by evaluating the amikacin trough level in serum concentration before the next dose.

The purpose of this study

1. To determine pharmacokinetic parameters of amikacin administered by IM route in infected-CAPD patients.

2. To evaluate whether or not the amikacin concentrations in plasma and dialysate within 48 hours following the drug administration could achieve the therapeutic level and whether or not its trough plasma concentration was in the range that claim to be safe for ototoxicity.

3. To determine the relationship between plasma and dialysate amikacin concentrations following IM route of administration.

CHAPTER II

REVIEW OF LITERATURES

Definition of End-Stage Renal Disease

Uremia is a clinical syndrome that develops insidiously as renal function declines and as a result of uremic toxin accumulation. The search for these uremic toxins has led to the identification of nitrogenous compounds in the serum and has given rise to the "uremic toxin" theory of uremia (32). A major hormonal imbalance present in uremia is the elevated blood concentration of parathyroid hormone (PTH) (32). PTH may have adverse effects on many organ systems and may act as a catabolic agent, thus enhancing uremic toxicity (32). Uremia begins with nonspecific syndromes , which become progressively worse as the creatinine clearance drops below 10 ml/min (31-32). At this stage, the patient requiring chronic dialysis or renal transplantation for relief of uremic symptoms is said to have ESRD(31-32). ESRD and the resulting uremic syndrome have multiple metabolic effects on the patient ; these are outlined in table 1.

Treatment Modalities for ESRD Patients

Several modalities are available for the treatment of end-stage renal disease (ESRD),including as main categories renal transplantation , hemodialysis (HD) and peritoneal dialysis (33). During the course of renal replacement therapy , patients may move from one treatment modality to another, for example from CAPD to transplantation and after transplant failure , to the hemodialysis and perhaps a second transplant (33).

Table 1 : Metabolic effects of uremia (32)

Metabolic Effects of Uremia	
Fluid, Electrolyte, and Acid-Base Effects	**Gastrointestinal (GI)**
Fluid retention	Anorexia
Hyperkalemia	Nausea, Vomiting
Hypermagnesemia	Delayed gastric emptying
Hyperphosphatemia	GI bleeding
Hypocalcemia	Ulcers
Metabolic acidosis	**Neurological**
Hematological	Lethargy
Anemia	Depressed sensorium
Hemostatic abnormalities	Tremor
Immune suppression	Asterixis
Cardiovascular	Muscular irritability and cramps
Hypertension	Seizures
Congestive heart failure	Motor weakness
Pericarditis	Peripheral neuropathy
Atherosclerosis	Coma
Endocrine	**Dermatological**
Calcium phosphorus imbalance	Altered pigmentation
Hyperparathyroidism	Pruritus
Metabolic bone disease	**Psychological**
Altered thyroid function	Depression
Altered carbohydrate metabolism	Anxiety
Hypophyseal-gonadal dysfunction	Psychosis
	Miscellaneous
	Reduced exercise tolerance

Epidemiology of End –Stage Renal Disease

Many diseases of the kidney , either idiopathic or secondary to systemic illness can ultimately result in ESRD. Over 257,200 Americans were treated for ESRD in 1995 (35). Black individuals have approximately a four–fold greater rate of renal failure than white individuals (31). The incidence of ESRD has increased an average of 8.8% annually for the last several years,with the largest increase in the 65- to 79-year-old population (31). Diabetes , hypertension , and primary glomerulonephritis are the three most common cause of ESRD in the United States (31-32). It accounts for 41% of new ESRD patients with a primary diagnosis of diabetes. Hypertension is the cause of ESRD in 26% of newly diagnosed ESRD patients (31).

Although hemodialysis (HD) , kidney transplantation (KT) and continuous ambulatory peritoneal dialysis (CAPD) had been established in Thailand for 38, 28 and 17 years respectively , we still have no data about the renal replacement therapy in Thailand . In 1997 , the Nephrology Society of Thailand commenced the first national registry for renal replacement therapy (34). Sixty – six centers returned the three registration forms (TRT) registry forms , 52% were government centers ; 46% private center ; 3% non – profit organizations. Fifty – eight percent of the centers were in Bangkok.There were a total of 235 hemodialysis machine.Twenty and fifteen centers were able to perform CAPD and KT repectively (34).

A total of 1802 patients received renal replacement therapy in 1997 which indicated for 30 per million population. 616 new cases entering treatments during the year 1997.HD was the most popular modality accounted for 61% of all patients. CAPD and KT were 33% and 6% respectively. Diabetes mellitus , hypertension and chronic glomerulonephritis were the three most common causes of ESRD in the registry (28% , 17% and 17% of the patients respectively) (34).

Continuous Ambulatory Peritoneal Dialysis (CAPD)

The first patients treated with Continuous Ambulatory Peritoneal Dialysis (CAPD) were described in 1975 (31). In 1976, Popovich and colleagues described a new method of peritoneal dialysis : they used bottled dialysate and four exchanges per day, thus making the method affordable and suitable for home programs (1). In 1978, Oreopoulus and colleagues modified the technique by using plastic bags for dialysis fluid, thereby reducing considerably the number of connections between dialysate bag and peritoneal catheter and making the method feasible for home dialysis in large number of patients (1). Mechanical and clinical improvements to the delivery system, such as improved catheters and dialysate bags, led to rapid increase in the use of CAPD as a viable alternative to hemodialysis for the treatment of ESRD in the past decade. In Thailand, CAPD was used first in 1982 at Siriraj Hospital by Professor Dr.Sumalee Nimmannit.

Principles of Peritoneal Dialysis

The three basic components of dialysis, namely, a blood-filled compartment separated from a dialysate-filled compartment by a semipermeable membrane, are also used for peritoneal dialysis. In peritoneal dialysis, the dialysate-filled compartment is the peritoneal cavity, into which dialysate is instilled via a permanent peritoneal catheter that transverse the abdominal wall. The peritoneal cavity is surrounded by the contiguous peritoneal membrane. The cavity, which normally contain about 100 ml of lipid-rich lubricating fluid. has the ability to expand to capacity of several liters. The peritoneal membrane that lines the cavity functions as the semipermeable membrane, across which dialysis occur. The membrane is classically described as a monocellular layer of mesothelial cells. However, in reality, the dialyzing membrane is also comprised of the basement membrane and underlying connective and interstitial tissue. The peritoneal membrane is termed parietal (that part which underlines the abdominal wall) or visceral (which overlies the abdominal organs) and its total area approximates body surface area (about 1.73 m^2) Blood vessels supplying and draining the abdominal viscera, musculature, and mesentery constitute the blood-filled compartment (35).

Solutes and water to be removed from blood during PD are not in intimate contact with the dialysis membrane as they are in hemodialysis and must therefore travel a considerable distance to the dialysate-filled compartment. There are several resistances to the movement of solutes and water by diffusion, represented by the basement membrane and endothelium of the blood vessels, the thickness of the interstitial tissue surrounding the vessels, the peritoneal mesothelial cells, the peritoneal basement membrane and a stagnant layer of dialysate fluid in contact with the peritoneal membrane. Unlike hemodialysis, there is no easy method to regulate blood flow to the surface of blood and dialysate to increase diffusion and convection via changes in hydrostatic pressure. For these reasons, PD is a much less efficient process per unit time compared with hemodialysis and must therefore be a virtually continuous procedure to achieve acceptable goals for solute and water removal (35-36).

Since CAPD is essentially continuous, conditions similar to steady state occur, and solute profiles are more level over time. CAPD, therefore, may represent a more physiologic process that is similar to endogenous renal function. Furthermore, the massive swings in body water content are less than optimal. CAPD may therefore be more beneficial for patients with cardiovascular instability (35-36).

The relative advantages of CAPD include steady-state hemostasis, hemodynamic tolerance, peptide and middle molecule removal, simplicity, relative independence, and no systemic heparinization. Potential disadvantages of CAPD compared to hemodialysis include the requirement of continuous aseptic technique, possible injury to the peritoneum, infectious complications, excessive systemic glucose loading, protein loss, and body image issues (35).

CAPD is usually performed by the instillation of 2 L of sterile dialysate solutions into the peritoneal cavity through a surgically placed resident catheter. The solutions dwells within the peritoneal cavity for a period of four to six hours during the day and up to eight to ten hours overnight, and then is drained and replaced with a fresh dialysis solutions. Approximately 10-15 minutes are required for instillation and 30-40 minutes are required for drainage of dialysate. This process of fill, dwell, and drain is performed three to four times during the day with an overnight dwell by the patient in their normal home or work environment. Conceptually, the process is similar to hemodialysis such that uremic toxins are removed by diffusion down a concentration gradient into the dialysate solution. Fluid removal occurs by ultrafiltration through adjustment of the hydrostatic pressure in hemodialysis. Since hydrostatic pressure is not easily adjusted in peritoneal dialysis, fluid is removed by altering the osmotic pressure within the dialysate. This is accomplished by the addition of dextrose monohydrate (90% d-glucose) to the dialysate in varying concentrations, depending upon the degree of fluid removal necessary in the patient.Concentrations include 1.5 %, 2.5 %, and 4.25 % dextrose with net fluid losses during a four-hour dwell period of 200 and 400ml for the 1.5 % and 2.5 % solutions, respectively, and approximately 700 ml for the 4.25 % solution following the overnight dwell (35-37).

The composition of the dialysate differs primarily in the dextrose concentration that is traditionally offer in 1.5%, 2.5% and 4.25%. Typical solute concentrations are sodium 132 – 141 mEq / L, lactate 35 – 40 mEq / L, chloride 96-102 mEq. /L , magnesium 0.5 1.5 mEq. / L and calcium 2.5 – 3.5 mEq. /L. Standard dialysate is potassium free. The pH of these solutions varies between 5.2 to 5.5 (37).

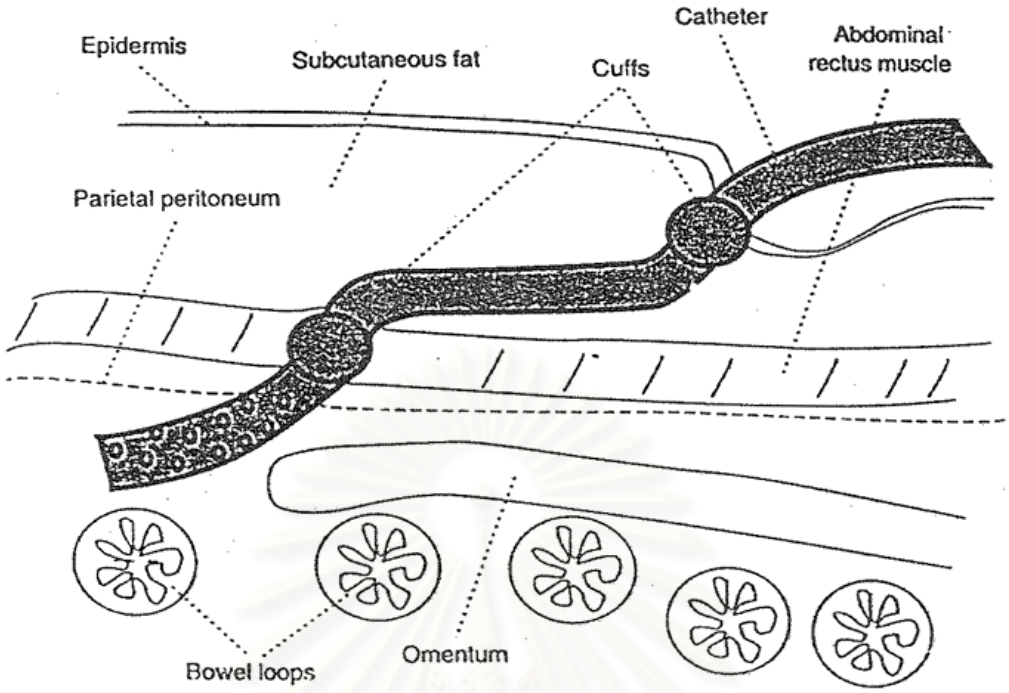


Figure 1. Schematic diagram of the placement of a peritoneal dialysis catheter through the abdominal wall into the peritoneal cavity

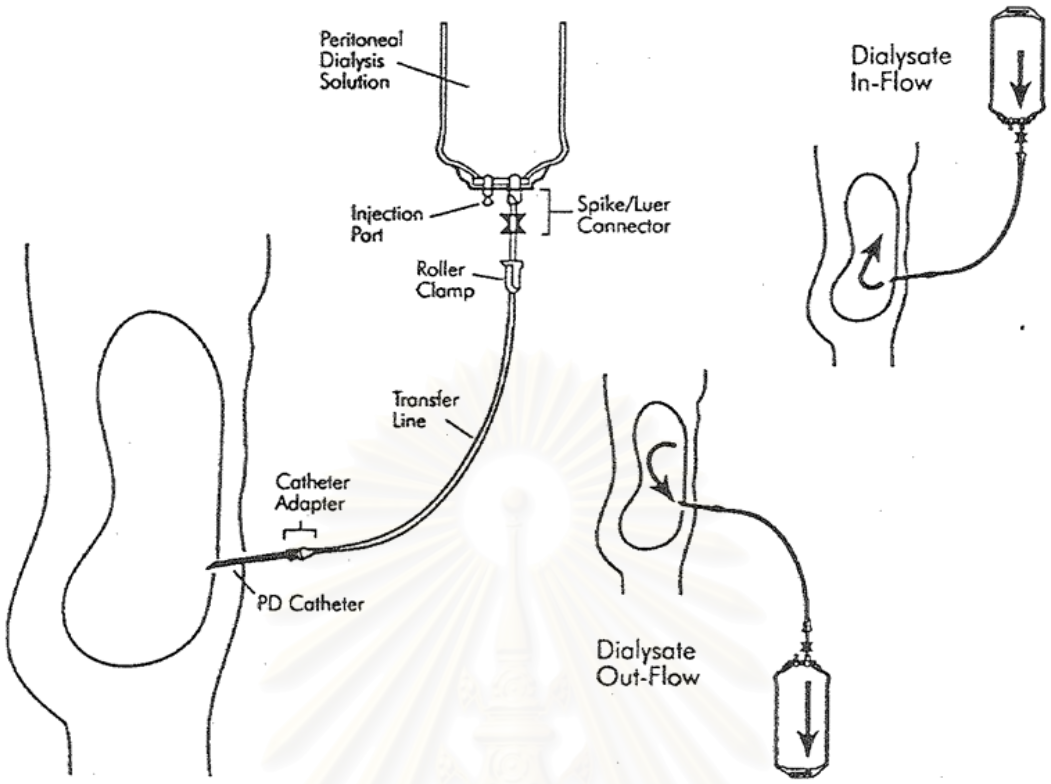


Figure 2. Schematic representation of CAPD and techniques of inflow and outflow

Complications of CAPD

The numerous medical complications are shown in Table 2. An average PD patient absorbs up to 60% of the dextrose in each exchange. This continuous supply of calories leads to increased adipose tissue disposition, decreased appetite, malnutrition, and altered requirements for insulin in diabetic patients (35).

Infectious complications of CAPD are major cause of morbidity and mortality and are the leading cause of technique failure and transfer from CAPD to hemodialysis. The two predominant infectious complications are peritonitis and catheter-related infections which include both exit-site and tunnel infections. Some 40% to 60% of patients develop their first episode of peritonitis within 1 year of starting CAPD. Peritonitis is a major cause of catheter loss in CAPD patients. In one series, peritonitis was responsible for the loss of 17% of all catheters in patients older than 60 years of age. Together, catheter-related infections plus peritonitis are the most common cause of catheter loss in this population, responsible for 61% and 60% of catheters lost in the <50 and >60 year age groups, respectively (35).

Table 2. Medical complications of peritoneal dialysis (35)

Cause	Complication	Treatment
		Increase
Glucose load	Exacerbation of diabetes mellitus	IP insulin
Fluid overload	Exacerbation of CHF Edema Pulmonary congestion	Ultrafiltration
Electrolyte abnormalities	Hyper- and hypocalcemia	Alter dialysate content
PD additives	Chemical peritonitis	Discontinue PD additives
Malnutrition	Albumin loss Loss of amino acids Muscle wasting Increased adipose tissue	Dietary changes Parenteral nutrition Discontinue PD
Unknown	Fibrin formation in dialysate	IP heparin

CHF = Chronic Heart Failure

Peritonitis

The typical signs and symptoms of peritonitis are shown in table 3. Peritonitis has several imprecise definition, but most recent guidelines suggest that an elevated dialysate white blood cells count > 100/mm^3, of which at least 50% are polymorphonuclear neutrophils, is necessary to confirm the diagnosis of peritonitis (12,35).

Table 3. Signs and symptoms of peritonitis (35)

	% Patients
Symptoms	
Cloudy effluent	98
Abdominal pain	78
Fever	38
Nausea, vomitting	25-30
Chills	18
Signs	
Abdominal tenderness	76
Fever >37^{O}C	28

The majority of infections (40% to 50%) are caused by gram-positive bacteria, of which *Stappylococcus epidermidis* is the predominant organism as shown in table 4. There is no single predominant gram-negative and gram-negative organisms account for 25% to 35% of all episodes of peritonitis and constitute the spectrum against which initial empiric treatment is directed (35).

Table 4. Organism causing peritonitis (35)

Organisms	% Episodes
Gram positive	**40-50**
Staphylococcus epidermidis	30-45
Staphylococcus aureus	10-20
Streptococci	10-15
Enterococci	3-5
Diphteroids	< 5
Gram negative	**25-35**
Escherichia coli	5-12
Pseudomonas aeruginosa	5-8
Enterobacter	2-3
Acinetobacter	2-3
Klebsiella	2-3
Proteus	2-3
Mixed gram positive and negative	**10-15**
Fungi	**5-20**
Sterile culture	**5**

Treatment of Peritonitis

The Ad Hoc Advisory Committee on Peritonitis Management of International Society of Peritoneal Dialysis evaluates the diagnostic and therapeutic data every 3 to 4 years . Their most recent report includes a series of algorithms that provide excellent guidelines for diagnostic or pharmacotherapy of peritoneal dialysis associated infections. It should be emphasized that these guidelines are arbitrary, being based on modeling rather than upon much published clinical experience (12-35).

The concept behind once-daily IP gentamicin was to employ the ideal antimicrobial characteristics of aminoglycosides, namely concentration-dependent killing, the post antibiotics effect, and saturable uptake by renal and cochlear tissue. Thus, for peritonitis, once-daily IP dosing should minimize the sustained, elevated serum aminoglycoside concentrations that predispose patients to ototoxicity or nephrotoxicity (an important consideration for those CAPD patients who have residual renal function) (35).

Table 5. Empiric pharmacotherapy selection for peritoneal dialysis patients with suspected peritonitis (12).

Agent	Continuous dose	Intermittent dose (in one exchange/day)	
		Residual urine output (ml/day)	
		Anuria(<500)	Nonauria (>500)
Cefazolin Cephalothin	500 mg/L load, then 125 mg/L in each exchange	500 mg/L or 1.5 mg/kg	625 mg or 19 mg/kg
Gentamicin Netilmicin Tobramycin	8 mg/L load, then 4 mg/L in each exchange	0.6 mg/kg body weight	Initial loading dose-1.5 mg/kg Maintenance dose-0.6 mg/kg body weight Dosing frequency should be individualized based on serum/dialysate levels
Amikacin	25 mg/L load, then 12 mg/L in each exchange	2 mg/kg body weight	Initial loading dose-5 mg/kg Maintenance dose-2 mg/kg body weight Dosing frequency should be individualized based on serum/dialysate levels

The Ad Hoc Advisory Committee's recommendation for treatment of dialysate culture-positive, gram-positive infection are detailed in Figure3. The presence of *Enterococcus* would indicate the possible continuation of the aminoglycoside, depending on sensitivities. The presence of *Staphylococcus aureus* (methicillin sensitive) would warrant the discontinuation of the aminoglycoside. Oral rifampicin might be added if there was an inadequate clinical response defined as continued cloudy dialysate, abdominal pain, and elevated dialysate white blood cells. If the organism is methicillin-resistant *Staphylococcus aureus*, then the entire regimen should be changed to one of oral rifampicin and IP vancomycin or clindamycin. *S.aureus* infections should be treated for 21 days. The presence of any other gram-positive species can usually be treated by the continuation of IP cephalosporins alone (12,35).

If a single gram-negative species is cultured, it is unnecessary to continue aminoglycosides, because monotherpy with IP cephalosporins may be sufficient.
Therapy must be chosen based on organism sensitivities. However, isolation of *Pseudomonas* or *Xanthomonas* should dictate the use of two concurrent agents with activity against these organisms. In addition, in the face of limited data, but with the concerns about intermittent therapy discussed previously,the Initial Ad Hoc Advisory Committee recommends switching patients who were on intermittent aminoglycoside to continuous therapy, together with an additional agent (Fig. 4) (12,35).

Fungal peritonitis is associated with a poor prognosis and high morbidity and mortality. One problem with prospective assessment of antifungal regimens is the infrequency with which these infections occur. This makes it difficult to design and implement comparative studies. Most literatures about antifungal treatment are therefore retrospective or limited to reports of local experience. There is controversy as to whether the PD catheter should be removed immediately upon the isolation of fungal organisms, or whether to observe the patient's response. The Ad Hoc Advisory Committee recommendations are to treat with oral flucytosine (2-g loading dose then 1 g daily) plus fluconazole 100 to 200 mg orally or IP daily. Treatment should be continued for 4 to 6 weeks if the patient is responding, but the catheter should be moved within 4 to 7 days if there is inadequate clinical response (12,35).

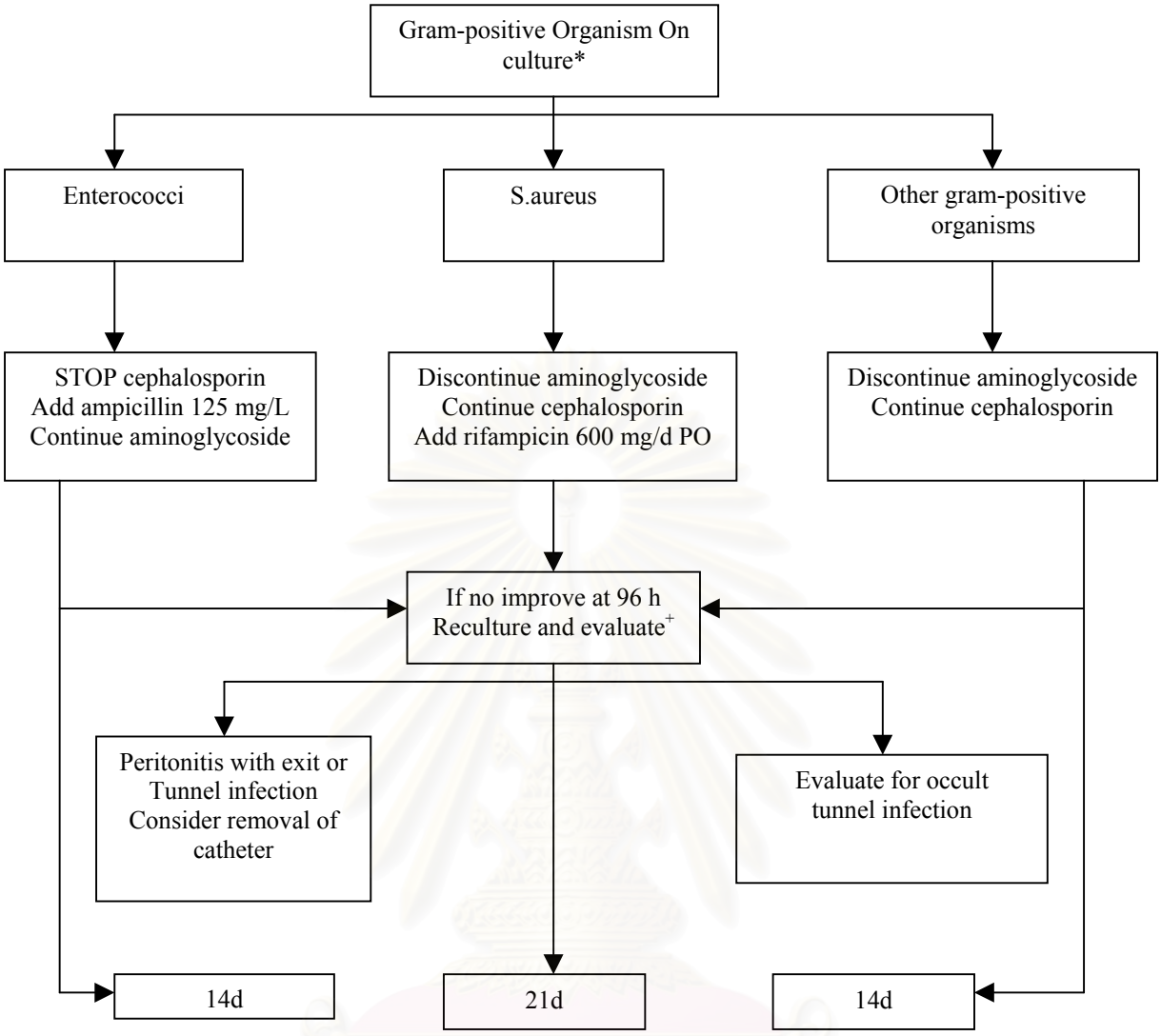
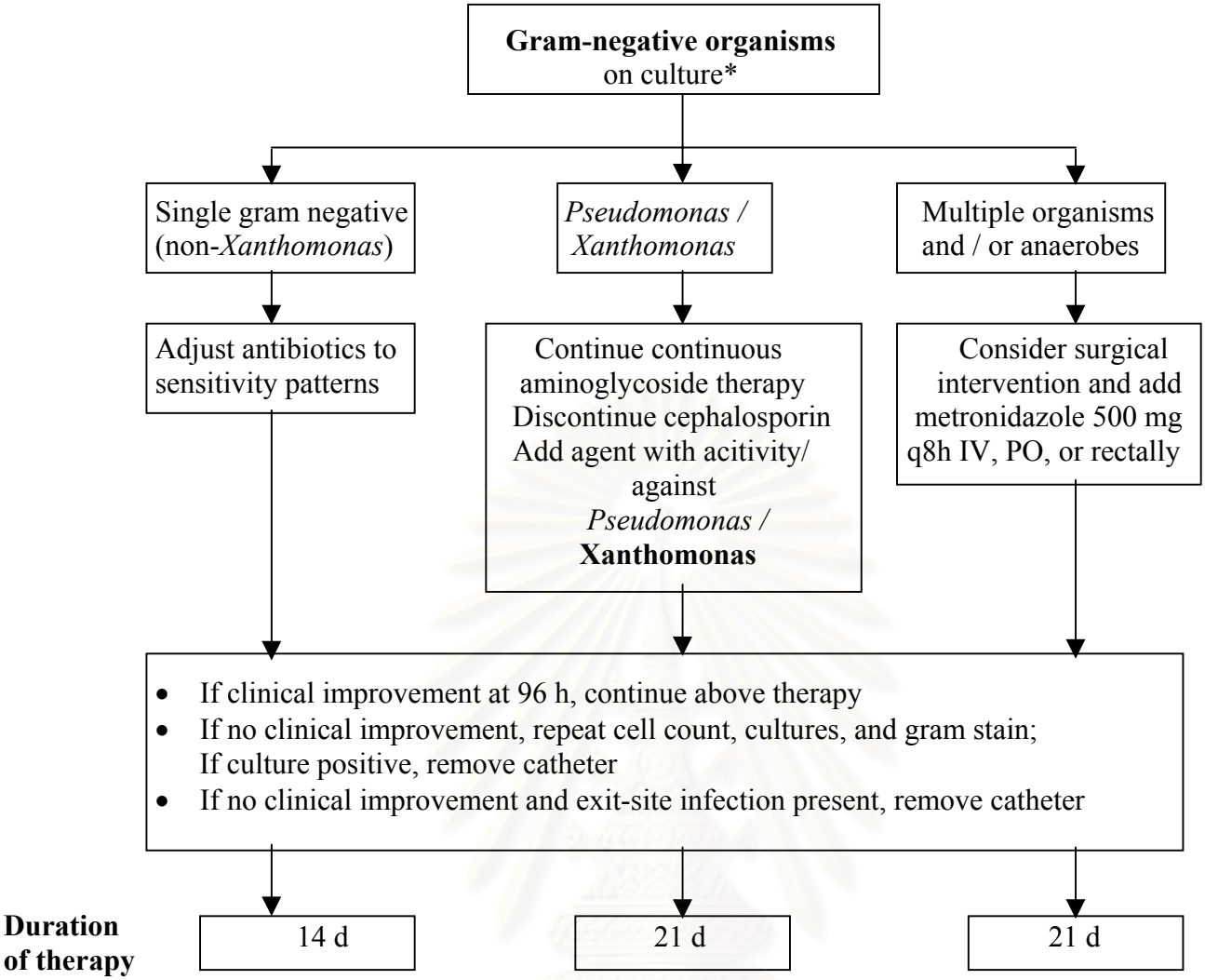


Figure 3 Pharmacotherapy recommendations for the treatment of documented gram-positive peritonitis (35)
***Choice of therapy should always be guided by sensitivity pattern.**
+If as MSRA is cultured and the patient is not clinically responding, clindamycin or vancomycin should be used.



Agents with anti-*Pseudomonas* or anti-*Xanthomonas* activity

Agent	**Dosage**
Ceftazidime	125 mg/L IP
Piperacillin	4 g q 12 h IV (adults) 150 mg/kg q 12 h (children)
Ciprofloxacin	500 mg BID PO (avoid in chlildren)
Aztreonam	LOAD : 1000 mg/L MAINT : 250 mg/L IP
Imipenem	LOAD : 500 mg/L MAINT : 200 mg/L IP
Sulfamethoxazole / trimethoprim	LOAD : 1600/320 PO q 1-2 d. MAINT : 1600/320 q 1-2 d PO
Aminoglycosides	Increase dose to 6-8 mg/L IP n each exchange

Figure 4. Pharmacotherapy recommendation for the treatment of documented gram-negative peritonitis (35)
***Choice of treatment should always be guided by sensitivity patterns.**

Table 6 . Dosages for some of the more frequently used antibiotics (35)

Drug	Intermittent dosing (1 bag/day unless otherwise specified)	Continuous dosing (mg/L unless otherwise specified)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin	15 mg/kg	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Cephalexin	500 mg PO q.i.d.	NA
Cefamandole	1000 mg	LD 500, MD 250
Cefmenoxime	1000 mg	LD 100, MD 50
Cefoxitin	ND	LD 200, MD 100
Cefuroxime	400 mg PO/IV q.d.	LD 200, MD 100-200
Cefixime	400 mg PO q.d.	NA
Cefoperazone	ND	LD 500, MD 250
Cefotaxime	2000 mg	LD 500, MD 250
Cefsulodin	500 mg	LD 50, MD 25
Ceftazidime	1000 mg	LD 250, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Ceftriaxone	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Mezlocillin	3000 mg IV b.i.d.	LD 3 g IV, MD 250
Piperacillin	4000 mg IV b.i.d.	LD 4 g IV, MD 250
Ticarcillin	2000 mg IV b.i.d.	LD 1-2 g IV, MD 125
Ampicillin	ND	MD 125; or 250-500 mg PO b.i.d., 250-500 mg PO q.i.d.
Dicloxacillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	250-500 mg PO q. 12 h
Amoxycillin	ND	
Quinolones		
Ciprofloxacin	500 mg PO b.i.d.	Not recommended
Fleroxacin	800 mg PO, then 400 mg PO q.d.	Not recommended
Ofloxacin	400 mg PO, then 200 mg PO q.d.	Not recommended
Others		
Vancomycin	15-30 mg/kg q. 5-7 days	LD 1000, MD 25
Teicoplanin	400 mg IP b.i.d.	LD 400, MD 40*
Aztreonam	1000 mg	LD 1000, MD 250
Clindamycin	ND	LD 300, MD 150
Erythromycin	500 mg PO q.i.d.	LD ND, MD 150
Metronidazole	500 mg PO/IV t.i.d.	ND

Table 6. Continued…..

Drug	Intermittent dosing (1 bag/day unless otherwise specified)	Continuous dosing (mg/L unless otherwise specified)
Other (cont.)		
Minocycline	100 mg PO b.i.d.	NA
Rifampin	450-600 mg PO q.d. or 150 IP t.i.d.-q.i.d.	NA
Antifungals		
Amphotericin	NA	1.5
Flucytosine	1 g q.d. PO or 100 mg/L IP each exch x 3 days, then 50 mg/L/exch 200-800 mg PO q.d.	50 q.d.
Fluconazole	ND	ND
Ketoconazole		NA
Miconazole		LD 200, MD 100-200
Combinations		
Ampicillin/sulbactam	2 g q. 12 h	LD 1000, MD 100
Imipenem/cilistat	1 g b.i.d.	LD 500, MD 200
Trimethoprim/sulfamethoxazole	320/1600 q. 1-2 days PO	LD 320/1600, MD 80/400

The route of administration is intraperitoneal unless otherwise specified. The pharmacokinetic data and proposed dosage regimens presented here are based on published literature reviewed through January, 1996. There is no evidence that mixing different antibiotics in dialysis fluid (except for aminoglycosides and penicillins) is deleterious for the drugs or patients. Do not use the same syringe to mix antibiotics.

*This is in each bag x 7 days, then in 2 bags/day x 7 days, and then in 1 bag/day x 7 days.

LD = loading dose; MD = maintenance dose; NA = not applicable; ND = no data; IV = intravenous; IP = intraperitoneally; PO = oral; q.d. = once a day; b.i.d. = twice a day; t.i.d. = three times a day; q.i.d. = four times a day.

Note: CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens.

Catheter-Related Infections

The incidence of exit-site infection is about 0.8 to 1.2 episodes per patient per year. The incidence is lower in older (>60 year) patients . Causative organisms are different from those associated with peritonitis; the most common is *S.aureus* (about 40% to 50% of episodes), follow by *S.epidermidis*, *Pseudomonas aeruginosa*, and other enteric gram-negative bacilli (about 10% to 20% each) . The diagnostic characteristics of these infections are also vague but generally include the presence of purulent drainage and erythema. The risk of exit-site infections is increased several-fold in patients who are nasal carriers of *S.aureus* . The use of topical antibiotics and disinfectants to treat catheter-related infections is controversial, and there are few adequately controlled studies to determine the effectiveness of systemic antibiotics. Current recommendations suggest that gram-positive organisms should be treated with an oral penicillinase-resistant penicillin or first generation cephalosporin for 2 to 3 weeks, with vancomycin being reserved for recalcitrant infections. Rifampicin may be added if necessary. Gram-negative organisms should be treated with oral quinolones. The effectiveness of this approach may be diminished owing to the chelation drug interactions with divalent and trivalent metal ions, which are commonly taken by dialysis patients (12,35) .

Treatment: Prophylaxis of Peritonitis and Catheter-Related Infections

Attempts to prevent peritonitis and catheter-related infections have includes refinement of connector system technology and the use of prophylactic antibiotic regimens. Several studies have examined the impact of antibacterial agents as prophylaxis against both peritonitis and tunnel-related infections. In one study, CAPD patients were randomized to either no treatment or to intermittent rifampicin, 300 mg. Orally twice daily per day for 5 days, repeated every 3 months. There was no significant change in the incidence of peritonitis; however, there was a significant decrease in the onset and number of catheter-related infections. The catheter-related infection rate per year decreased from 0.65 to 0.22 episode per year for control and treated groups. The treated group had a delayed onset of the first catheter-related infection. This same regimen of rifampicin was compared to topical mupirocin at the exit site. Both reduced the incidence of *S.aureus* catheter infections (35).

Nasal carriage of *S.aureus* is associated with an increased risk of catheter-related infections and peritonitis. Current recommendations suggest that all CAPD patients should have a nasal culture every 2 to 4 weeks, until there is one positive culture of *S.aureus* or until there are three negative cultures . Patients with a positive culture should be defined as carriers and should receive prophylactic therapy. This should include cyclic combinations of oral rifampicin, and mupirocin at the exit site as shown in table 7. Rapid recolonization occurs after rifampicin, necessitating cyclic dosing. This regimen may also reduce bacterial resistance. Unfortunately, up to 12% of patients will have nausea and vomiting, and rifampicin may interact with other agents and discolor dialysate. Topical and intranasal mupirocin both have demonstrated efficacy. Intranasal mupirocin, applied thrice daily for 7 days for each positive nose culture, done monthly, reduced *S.aureus* peritonitis from 0.21 to 0.22 episode per year. In spite of widespread use, these appears to have been little development of resistance to mupirocin in the dialysis population (35).

Table 7. Prophylaxis of Nasal Carriers of *Staphylococcus aureus* in CAPD patients

Agent	Regimen
Rifampin	300 mg. Bid for 5 d every 3 months
Intranasal mupirocin	Bid for 5 d every month
Exit-site mupirocin	Daily

Amikacin

Chemistry

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin A. Amikacin occurs as a white, crystalline powder and is sparingly soluble in water. The drug is commercially available as the sulfate salt. Amikacin sulfate injection is a colorless to light straw-colored solution (38).

Stability

At room temperature less than $40^{O}C$, preferably between 15-$30^{O}C$; freezing should be avoided. At room temperature, amikacin sulfate injection is stable for at least 2 years following the date of manufacture. Commercially available solutions of amikacin sulfate may become a very pale yellow; however, this does not indicate loss of potency (38).

Mechanism of aciton

Amikacin are bactericidal agents that inhibit bacterial protein synthesis by binding irreversibly to the bacterial 30S ribosomal subunit. The aminoglycoside-bound bacterial ribosomes then become unavailable for translation of mRNA during protein synthesis, and this situation leads to cell death. The amikacin also cause misreading of the genetic code, with resultant production of nonsense proteins. To reach the intracellular ribosomal binding targets, and aerobic energy-dependent process is necessary to enable successful penetration of the inner cell membrane by the aminoglycosides. Bacterial uptake of these agents is facilitated by inhibitors of bacterial cell wall synthesis such as beta-lactams and vancomycin. This interaction forms the basis of the antibacterial synergism between aminoglycosides and beta-lactam antibiotics (38-39).

Spectrum

Amikacin are generally active against *Acinetobacter, Citrobacter, Enterobacter, Escherichia coli, Klebsiella,* indole-positive and indole-negative *Proteus, Providencia, Pseudomonas, Salmonella, Serratia,* and *Shigella.* Amikacin are resistant to many of aminoglycoside-modifying enzymes. Therefore, it is active against some strains of bacteria, especially *Proteus, Pseudomonas,* and *Serratia,* which are not susceptible to the other aminoglycosides. In addition, amikacin are also active against *Mycobacterium spp.* Although active against *Staphylococci,* amikacin or other aminoglycosides are not recommended as single agent for the treatment of *Staphylococcal* infections. They must be used with penicillin group or vancomycin for synergy in the treatment of serious infection due to *Staphylococci, enterococci,* or viridans *streptococci* (38-40).

Pharmacokinetics

Absorption

Amikacin are poorly absorbed from GI tract. It is well absorbed following parenteral administration. However, there may be considerable interpatient variation in plasma concentration achieved with a specific IM dose because of differences in rate of absorption from IM injection sites. Following IM administration of a single dose of amikacin of 7.5 mg/kg in adults with normal renal function, peak plasma amikacin concentrations of 17-25 μg/mL are attained within 45 minutes to 2 hours; plasma concentrations of the drug average 2.1 μg/mL at 10 hours. When the same dose is administered by IV infusion over 1 hour, peak plasma concentrations of the drug average 38 μg/mL immediately following the infusion, 5.5 μg/mL at 4 hours, and 1.3 μg/mL at 8 hours (38).

Distribution

Following absorption, aminoglycosides are widely distributed into body fluids including ascitic, pericardial, pentoneal, pleural, synovial and abscess fluids. Amikacin are distributed primarily in the extracellular fluid volume, interstitial and pleural. It diffuse poorly into CSF following IM or IV administration; even in patients with inflamed meninges. A small portion of each aminoglycoside dose accumulates in body tissues and is tightly bound intracellularly. Most body compartments and tissues including the inner ear and kidneys become progessively saturated with an aminoglycoside over the course of therapy, and the drug is slowly released from these areas. It has been postulated that this accumulation may account for the ototoxicity and nephrotoxicity associated with aminoglycosides (38-40).

Amikacin distribution is best described by a modified two-compartment or three-compartment open model, although a one-compartment system is most often used. In the two-compartment model the apparent volume of the central compartment (V_c) approximates the extracellular fluid volume (about 20-30% of lean body weight or ideal body weight in the adult). Animal studies have shown that kidney uptake of amikacin appears saturable at low concentrations and linear at high serum levels. Preliminary data indicate that the same relationship exists for humans, and single doses amikacin, result in lower kidney tissue accumulation than the same dose administered by continuous infusion (39).

Elimination

The plasma elimination half-life of amikacin is usually 2-3 hours in adults with normal renal function and is reported to range from 30-86 hours in adults with severe renal impairment. In adults with normal renal function, 94-98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours (38-40). Complete recovery of the dose in urine requires approximately 10-20 days in patients with normal renal function, and terminal elimination half-lives of greater than 100 hours have been reported in adults with normal renal function following repeated IM or IV administration of the drug (38).

The effect of peritoneal dialysis on the elimination of aminoglycoside antibiotics depends on the dialysis conditions. These conditions include type of dialysis (CAPD, IPD), dialysate composition, dwell time, dialysate volume, dialysate outflow rate and presence of peritonitis. In patients undergoing CAPD, the dialysis clearance of amikacin accounts for approximately 50% of the total body clearance.Drugs that are dialyzable via peritoneal dialysis should be small in size and have a low volume of distribution (39).

Clinical uses

Amikacin is used IM or IV in the short-term treatment of serious infections such as septicemia (including neonatal sepsis), bone and joint infections, skin and soft tissue infections (including those resulting from burns), respiratory tract infections, and postoperative and intra-abdominal infections (including peritonitis) caused by susceptible strains of gram-negetive bacteria. The drugs are also effective in serious, complicated, recurrent urinary tract infections caused by susceptible gram-negative bacteria; however, they are not indicated for the initial treatment of uncomplicated urinary tract infections unless the causative organisms are resistant to other less toxic anti-infectives.

Dosage

The usual dosage of amikacin recommended by the manufacturers for adults, children, and older infants with normal renal function is 15 mg/kg daily given in equally divided doses at 8 or 12 hours intervals. If amikacin is used for uncomplicated urinary tract infections caused by organism not susceptible to less toxic anti-infectives, the usual adult dosage is 250 mg twice daily (38).

Current evidence suggests that once-daily administration of amioglycosides is at least as effective as, and may be less toxic than, conventional dosage regimens employing multiple daily doses of the drugs, however, additional controlled studies in children,patients with renal dysfunction, and other appropriate patient groups are needed to fully define the optimal use of once-daily aminoglycoside dosing regimens (39).

When amikacin is used in conjunction with other antituberculosis drugs in the treatment of clinical tuberculosis,a dosage of 15 mg/kg given IM as a single daily dose 5 times weekly has been recommended (38).

Whenever possible, and especially in patients with life-threatening infections, suspected toxicity or nonresponse to treatment, decreased or varying renal function, and/or when increased aminoglycoside clearance (e.g., patients with cystic fibrosis, burns) or prolonged therapy is likely, peak and trough serum concentrations of amikacin should be de determined periodically and dosage should be adjusted to maintain desired serum concentrations. A causal relationship between maintenance of certain peak or trough serum concentrations or other pharmacodynamic endpoints and clinical response or toxicity has not been established to date for aminoglycoside dosing regimens. However, many clinicians have suggested peak and trough serum concentrations of 15-30 and less than 5-10 μg/ml, respectively, for conventional dose of amikacin (38-40).

Adverse effect

Ototoxicity and nephrotoxicity are the most serious adverse effects of aminoglycoside therapy and are most likely to occur in geriatric or dehydrated patients, patients with renal impairment, or patients who are receiving one of the drugs in high doses or for long periods, or who are also receiving, have received other ototoxic and/or nephrotoxic drugs (38-40).

Otic effects

Eighth cranial nerve damage may be manifested by vestibular symptom such as dizziness, nystagmus, vertigo and ataxia, and/or by auditory symptom such as tinnitus, roaring in the ears, and varying degrees of hearing impairment. Loss of high-frequency perception, detectable only by audiometric testing usually occurs before clinical hearing loss. Loss of hearing may be permanent if damage is extensive. Rarely, progressive eighth cranial nerve damage, with total or partial irreversible bilateral deafness, may occur after amikacin therapy has been discontinued (38-40).

Renal and electrolyte effects

Amikacin-induced nephrotoxicity may be evidenced by tubular necrosis; increases in BUN, nonprotein nitrogen (NPN), and serum creatinine concentration; decreases in urine specific gravity and creatinine clearance, proteinuria; or cells or casts in the urine. Most patients with aminoglycoside nephrotoxicity develop nonoliguric azotemia; oliguria occurs rarely. Aminoglycoside-induced renal toxicity is usually reversible following discontinuance of the drug (38-39).

Nervous system effects

Amikacin produce varying degrees of neuromuscular blockade. Although the blockage induced by an amikacin is generally dose related and self-limiting, it may rarely result in respiratory paralysis. Neuromuscular effects are most administered to patient with neuromuscular disease (e.g., myasthenia gravis) or hypocalcemia or to patient who are receiving general anesthetics, neuromuscular blocking agents or massive transfusions of citrated blood. Drug-induced neuromuscular blockade is not easily reversed and its reversibility seems dependent on the severity of the blockade; calcium salts have been used successfully in some cases but mechanically assisted respiration may be necessary (38-39).

Sensitivity reactions

Occasionally, hypersensitivity reaction including rash, urticaria, stomatitis, pruritus, generalized burning, fever and eosinophilia have occurred in patients receiving an amikacin (38-40).

Other adverse effects

Other less frequently reported adverse effects of amikacin include nausea and vomiting, anemia, leukopenia, granulocytopenia, thrombocytopenia, tachycardia, arthralgia (38-40).

Local irritation, pain, sterile abscess, subcutaneous atrophy, fat necrosis and thrombophlebitis have occurred with IM or IV administration of aminoglycosides (38-40).

Precaution

Patients with preexisting tinnitus, vertigo, subclinical high-frequency hearing loss, or renal impairment and patients who are receiving high dosages and/or prolonged therapy with amikacin or who have received prior ototoxic drugs are especially susceptible to ototoxicity and should be carefully observed for signs of eighth cranial nerve damage during amikacin therapy. The risk of toxicity appears to be low in well-hydrated patients with normal renal function if usual dosage is not exceeded. Patients receiving an amikacin (by any route of administration) should be under close medical supervision. Renal function should be assessed prior to initiation of amikacin therapy and should be monitored at regular intervals during therapy. Eighth cranial nerve function should be monitored in geriatric patients; patients with prior auditory, vestibular or renal impairment; and patients receiving prolonged aminoglycosides therapy. Since geriatric patients may have reduced renal function which is not evident from BUN or serum creatinine concentrations, creatinine clearance may be a more useful indicator of renal function in these patients (38-39).

The difference between therapeutic and toxic serum concentrations of the amikacin may be narrow. Although a causal relationship has not been established, ototoxicity and nephrotoxicity may be related to high peak serum aminoglycoside concentrattions and/or high trough drug concentrations between doses. Therefore, whenever possible and especially in patients with renal impairment, peak and trough serum concentrations of amikacin should be determined periodically and dosage adjusted to maintain desired serum concentrations (38-39).

Pregnancy and lactation

Amikacin can cause fetal harm when administered to pregnant women, but potential benefits from use of the drugs may be acceptable in certain conditions despite possible risks to the fetus (38-40).

Drug interactions

Neurotoxic, ototoxic or nephrotoxic drugs

Since neurotoxic, ototoxic or nephrotoxic effects may be additive, concurrent and/or sequential use of an aminoglycoside and other drugs (administered systemically, orally or topically) with similar toxic potentials (e.g., other aminoglycosides, acyclovir, amphotericin B, bacitracin, capreomycin, cephalosporins, colistin, cisplatin, methoxyflurane, polymyxin B, vancomycin) should be avoided, if possible. In addition, because of the possibility of an increased risk of ototoxicity due to additive effects or altered serum and tissue concentrations of the antibiotics, aminoglycosides should be given concurrently with ethacrynic acid, furosemide, urea or mannitol. The

possibility that dimenhydrinate and other antiemetics may mask symptoms of vestibular ototoxicity should be kept in mind (38-40).

General anesthetics and neuromuscular blocking agents

Concurrent use of an amikacin with general anesthetics or neuromuscular blocking agents (e.g., succinylcholine, tubocurarine) may potentiate neuromuscular blockade and cause respiratory paralysis (38-40).

Anti-infective agents

In vitro studies indicate that the antibacterial activity of amikacin and β-lactam antibiotics or vancomycin may be additive or synergistic against some organisms including *enterococci* and *Ps. aeruginosa*. In vitro studies indicate that amikacin and extended-spectrum penicillins also exert a synergistic bactericidal effects against some Enterobacteriaceae. The synergistic effect of amikacin and these anti-infectives is usually used to therapeutic advantage, especially in the treatment of infections caused by *enterococci* or *Ps. aeruginosa.* Although the exact mechanism of this synergistic effect has not been determined, it appears that by inhibiting bacterial cell-wall synthesis the penicillin allows more effective ingress of the amikacin to the ribosomal binding site (38-39).

Carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin inactivate the aminoglycoside antibiotics when they are mixed together in vitro. The reaction is concentration, temperature, and time related, and appears to be a result of a nucleophilic opening of the beta-lactam ring of the penicillin by a methylamino group of the aminoglycoside. The reaction results in inactivation of both agents. Amikacin and netilmicin are the least inactivated. The interaction is not significant in vivo except in patients with severely diminished renal function. Therefore, concomitant administration of an extended-spectrum penicillin and an amikacin has resulted in decreased serum amikacin concentrations and elimination half-life, especially in patients with renal impairment. Therefore, serum amikacin concentrations should be monitored in patients receiving concomitant therapy, especially when very high doses of an extended-spectrum penicillin are used or when the patient has impaired renal function (39).

When aminoglycosides serum concentrations are determined in patients receiving these beta-lactam antibiotics, it is extremely important to remember that if the assay cannot be performed quickly (ie, within 10 hours), the serum should be frozen (-20 to -70^{O}C) to prevent interaction-induced low aminoglycoside concentrations. It is also advisable to obtain peak and trough levels of the aminoglycoside when the penicillin level is a trough (39).

Therapeutic range and efficacy / Toxicity level

Generally accepted desirable peak and trough concentrations for the parenterally administered agents are listed below. As a range is provided, lower levels in the range are used for less serious infections such as urinary tract infection without sepsis. The higher levels in the range are used in more seriously ill patients or when infection is present in a poorly accessible area, such as the lung (39).

Table 8. Peak and trough concentration of amikacin (38-39)

	Efficacy **Peak (mg/L)**	**Toxicity** **Trough (mg/L)**
Amikacin	15 – 30	5 –10 (Conventional dose) < 5 (Single dose)

Assay methods

This study used the fluorescence polarization immunoassay (FPIA) technique for measurement of amikacin plasma concentrations.

Fluorescence polarization immunoassay (FPIA) and TDX®

The Abbott TDX® system (Abbott Laboratories, North Chicago, IL) is based on FPIA technique. This method combines competitive protein binding with fluorescence polarization to give a direct measurement without the need for a separation procedure. All competitive binding immunoassays for measuring therapeutic drugs are based on competition between the drug in the patient sample and a labeled drug, called tracer. Sample drug and tracer compete for a limited number of binding sites on antibodies specific to the drug being measured. The concentration of unlabled drug from a patient sample will determine how much labeled drug can bind to the specific antibody. In the TDX® system, the label on the tracer drug is the fluorescent dye-fluorescein. The changes of polarization angle reflect tracer binding to antibody. The precise relationship between polarization and concentration of the unlabeled drug is established by measuring the polarization valves of calibrators with known concentrations of the drug. A calibration curve stored in system memory is used to automatically determine the concentrations of unknown patient samples (41).

Clinical pharmacokinetic during continuous ambulatory peritoneal dialysis

Peritoneal clearance of drugs during continuous ambulatory peritoneal dialysis

The net transfer of the drug across the peritoneal membrane from plasma to dialysate potentially contributes to the total body clearance. Factors that affect drug movement across the peritoneal membrane are described as following (42-44):

1. Physiochemical properties of drug, i.e.,

    - molecular weight,
    - spherical size
    - water or lipid solubility
    - ionic charge

2. Physiological aspects of peritoneal membrane, i.e.,

    - the permeability and surface area of the peritoneum
    - membrane thickness
    - vascularity
    - blood flow
    - individual peritoneal resistance to drugs such as stagnant fluid layers

3. Prescribed dialysis regimen, i.e.,

    - dialysate composition (% dextrose)
    - dialysate volume
    - dwell time
    - dialysate outflow rate

4. Pharmacokinetic properties of drug, i.e.,

    - volume of distribution
    - protein binding
    - non-renal clearance

Drug clearance via CAPD (Clpd) is most commonly calculated by dividing the total amount of drug found in the peritoneal effluent of one or more dwell periods [A ($t_1 \rightarrow t_2$)] by the area under the plasma concentration-time curve during the same period [AUC ($t_1 \rightarrow t_2$)]. This clearance term is time dependent, i.e. the longer the dwell time, the higher the Clpd (42).

Drug removal by dialysis is largely a process of the passive diffusion of drug molecules across the dialysis membrane. The rate and extent of diffusion is determined by the concentration gradient of unbound drug between plasma and dialysis fluid. Therefore, the contribution of peritoneal clearance to total plasma clearance is likely to increase according to the fraction of unbound drug (43).

Another important limiting factor for peritoneal clearance is the time-averaged dialysate outflow rate. An adult patient performing 2 L exchanges 4 or 5 times daily attains an average dialysate outflow rate of approximately 8 to 10 L/day (5 to 7 mL/min) (42-43). This low outflow rate of the peritoneal effluent may cause low extraction capacity of many drugs via CAPD. For most drugs, peritoneal clearance is a relative insignificant part of total body clearance. (For peritoneal clearance to be clinically important, its value should be at least 20% of the total body clearance).

Drug that are good dialyzable via peritoneal dialysis should be small in size and have a low volume of distribution and low protein binding (39,42-44). Aminoglycosides are typical of drugs with a significant elimination by CAPD, as a result of their low protein binding (less than 10% bound to plasma protein) and low volume of distribution (0.25 L/kg in healthy subjects) and their physicochemical properties with complex polar molecules (39, 42-44).There were studies found that in CAPD patients with no peritonitis, peritoneal clearance of aminoglycosides accounts for approximately 15-50% of the total body clearance (27,30,39). Although aminoglycosides are significantly removed by CAPD, monitoring for peak and trough concentrations in CAPD patients for adjusting dosage regimen is still very important to avoid nephrotoxicity and ototoxicity (42).

CHAPTER III

PATIENTS AND METHOD

The experimental study was designed and conducted at Medical Ward of Phramongkutklao's Hospital during October 1999 to May 2000.

Patients

Twelve ESRD patients who were infected during undergoing CAPD treatment at CAPD unit, Nephrology Division, Phramongkutklao's Hospital were enrolled in the study. All patients were admitted. Written informed consent was obtained from each patient. Study protocol was approved by ethical committee on human research of Phramongkutklao's Hospital. In this study, patients performed CAPD by using 2 liters of dialysis solution and adhered to their usual schedule of four exchanges per day with dwell periods of 6 hours for each exchange. The criteria for included and excluded patients were :

Inclusion criteria

1. The patient had received CAPD treatment for at least 1 month.

2. The patient was twenty years old or older.

3. The patient had peritonitis and/or exit-site infection and/or tunnel infection and physician ordered amikacin as empirical treatment.

- **Peritonitis** is defined as : cloudy effluent dialysate with white blood cell (WBC) ≥ 100 cell/mm^3 with more than 50% of polymorphonuclear cells (PMN) and with or without clinical symptoms such as abdominal pain, fever, nausea and vomiting.

- **Exit-site infection** is defined as : erythema and purulent or clear discharge at the catheter exit-site.

- **Tunnel infection** is defined as : an infection of subcutaneous catheter with purulent discharge squeezed from subcutaneous tract of catheter with erythema, pain and tenderness.

Exclusion criteria

1. The patient had received amikacin within 1-month prior to study.

2. The patient had history of allergy to amikacin.

3. The patient currently received drugs that can cross reactivity in measuring amikacin concentration by TDx analyzer such as ampicillin, cephalexin, cephalothin, chloramphenicol, clindamycin, erythromycin and tetracycline.

4. The patient had HIV infection.

5. The patient who had been diagnosed as inappropriate to participate in the study.

6. The patient had no willing to participate and did not sign the consent form.

Treatment and Procedure

After admission, blood samples for determination of Hb, Hct, BUN, Cr, Electrolytes (Na, K, Cl, CO_2), Ca, P, total protein(TP) and albumin(ALB) were collected. In addition, cloudy dialysate were collected to investigate the amount of white blood cell counts and PMN and identify the type of pathogen and its susceptibility to antibiotics Culture and antimicrobial susuceptibility test : Dialysate C/S). For exit-site or tunnel infection, purulent or clear discharge were collected for identifying the type of pathogen and its susceptibility to antibiotics (Pus C/S).

Microbiological concepts for dialysate culture and antimicrobial susceptibility test

1. The original bag with cloudy dialysate of CAPD patient with peritonitis was submitted to Microbiology Division, Department of Clinical Pathology, Pramongkutklao's Hospital .

2. A sterile needle and syringe were used to withdraw 10 ml of dialysate fluid for Gram staining and culture.

3. Ten ml of fluid was inoculated into hemoculture bottles and then loaded into shaker incubator of an automated BactT/Alert® hemoculture system for culturing the microorganism.

∗ BactT/Alert® is fully-automated machine and based on a colorimetric detection of CO_2 concentration by means of a sensor internally attached to the bottom of hemoculture bottle. Positive cultures are recognized by a computer driven algorithm that regularly monitors an increased CO_2 concentration as an indicator of bacterial growth ,and the time to detection can be accurately recorded (45).

4. The system was used according to the manufacturer's recommendation. Briefly, the position of the bottles and the time that the bottles were loaded was recorded in a computer. The bottles were incubated at 35-37°C with continuous agitation for seven days or until they were positive. There was an indicator internally attached to the bottom of each bottle that sensed the concentration of CO_2 generated by the growing bacteria in the bottle. A sensor in the shaker incubator colormetrically measured the indicator of each bottle every 10 minutes and the results were recorded by the computer. A computer program analyzed these data and determined whether there was a growth of bacteria in the bottle. The system then alarmed the operator, indicating the bacterial growth was detected in a particular bottle (45).

5. When the system detected bacterial growth, the bottles were removed and subcultured onto three plates (MacConkey agar,blood agar and chocolate agar plates) , simultaneously subcultered in thioglycolate broth and incubated at 35-37°C for identifying causative organism and then tested for antimicrobial susceptibility test biotic sensitivity .

Microbiological concepts for pus culture and antimicrobial susceptibility test

Pus or clear discharge swabbed from exit site or tunnel infection was inoculated in transport medium and delivered to Microbiology Division of Pramongkutklao's Hospital. It was tested for gram staining then subcultured on to three plates (MacConkey agar, blood agar and chocolate agar plates) and simultaneously subcultered in thioglycolate broth and incubated at 35-37°C for identifying causative organism and then tested for antimicrobial susceptibility test.

Drug therapy

Within five days, before C/S became available, antibiotics as empirical treatment should be administered to patients. For peritonitis, each patient received IP cefazolin 1g in the first dialysate bag as a loading dose then 250 mg in subsequent dialysate bag as a maintenance dose for eradicating gram positive bacteria and received a single dose (7.5 mg/kg) of amikacin given by intramuscular route every 48 hours for eradicating gram negative bacteria.

For IP administration, cefazolin and heparin was admixed by sterile technique with 2 liters of dialysate and infused by gravity into peritoneum over 10 minutes.

In case of exit-site or tunnel infection, each patient received oral cloxacillin 500 mg four times per day before meal for eradicating gram positive bacteria and received the same dose and route of amikacin as the case of peritonitis. Those infected-CAPD patients would drain the old dialysate and infused the new dialysate before receiving amikacin intramuscularly.

Sterile technique for admixing cefazolin and heparin with 2 liters of dialysate is in the following order :

1. A nurse who perform this technique should wash her hands and cover the face with mask.

2. Wipe the surface of admixing area with 70% alcohol.

3. Drop povidone-iodine solution on the injection port of dialysate bag and the top of vial of cefazolin and heparin for over 5 minutes. Then cefazolin is reconstituted.

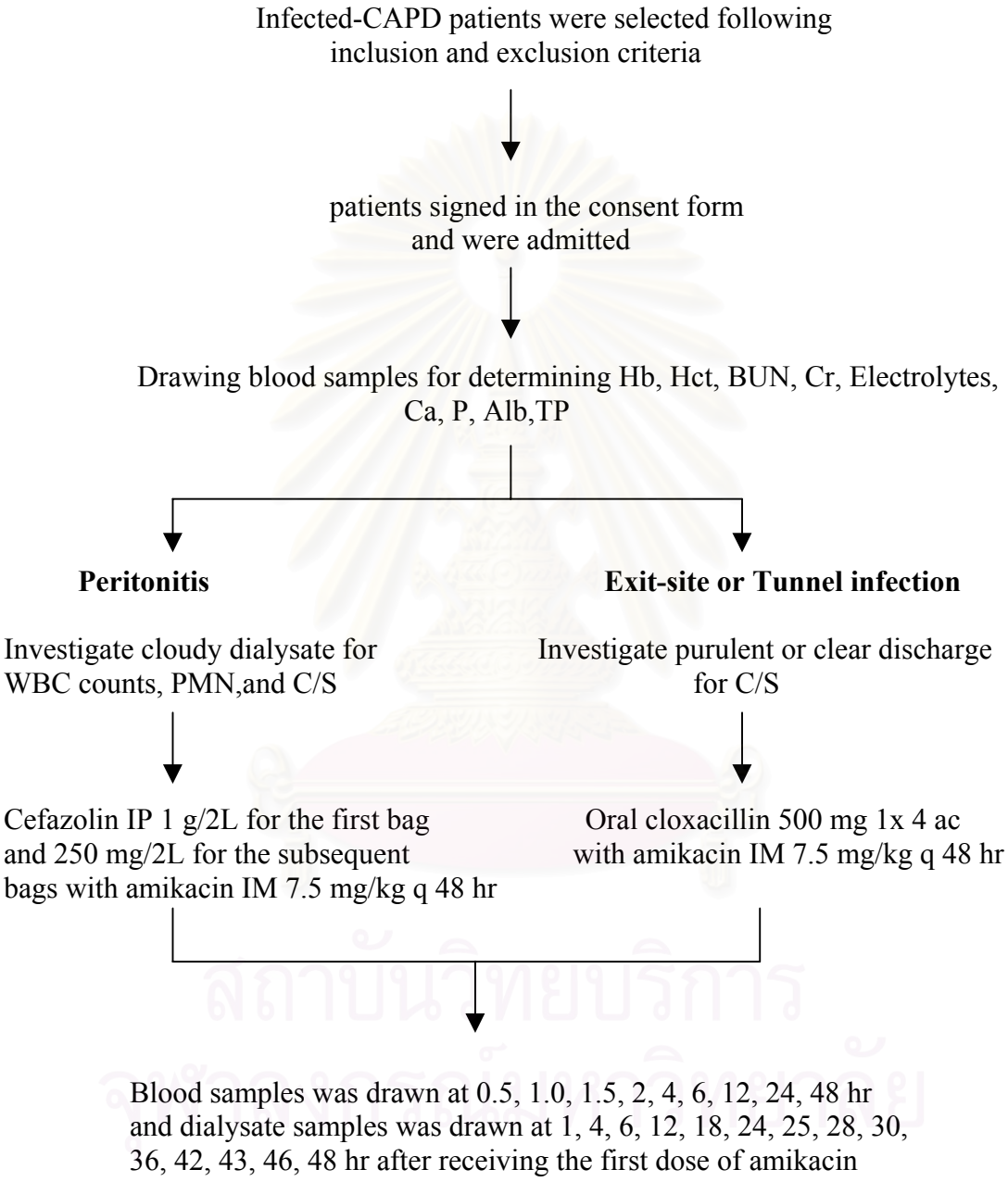
4. Reconstituted cefazolin was injected via injection port followed by heparin and then covers the injection port with micropore.

Collecting blood and dialysate sample

After infected CAPD patients received single dose (7.5 mg/kg every 48 hours) of intramuscular amikacin, 5 ml. of blood sample for determining amikacin level were drawn at 0.5, 1, 1.5, 2, 4, 6 hours from an antebrachial vein via indwelling venous catheter with saline lock and at 12, 24 and 48 hours from antebrachial vein via direct skin. 0.9% Normal saline solution which was replaced heparin lock was drawn away before drawing blood samples. During 48 hours (duration of study), patients used eight bags of dialysate, and 5 ml of dialysate samples were obtained at the end of each dialysate exchange (every 6 hours) at 6, 12, 18, 24, 30, 36, 42, 48 hours after the first dose of intramuscular amikacin. In addition, two dialysate samples per dialysate bag were also collected during the dwell period from the first, the fifth(the middle) and the eighth(the last) dialysate bags. The sampling technique was accomplished by draining approximately 200 ml volume of dialysate from peritoneal cavity into the dialysate bag then 5 ml of dialysate samples was drawn via injection port of dialysate bag using the same sterile technique as those used for admixing antibiotics. These additional samples were therefore collected at 1, 4 hours from the first bag, at 25, 28 hours from the fifth bag and at 43, 46 hours from the eighth bag.

Samples of blood and dialysate were brought to centrifuge by Kubota® machine with 3500 rpm for 5 minutes at room temperature to separate plasma from blood cells and clear dialysate from cell fragments existing in the peritoneal cavity. Plasma and clear dialysate were kept in 1.5 ml microtubes and frozen at –29 °C until assayed. All plasma and dialysate samples were assayed within 2 weeks of collection.

FLOWCHART OF STUDY



Drug analysis

The TDx/TDxFLx amikacin assay is a reagent system for the quantitative measurement of amikacin in serum or plasma.

1. Amikacin calibrators:

Six vials of accurately measured amounts of amikacin in human serum at the following concentrations:

Vial	Amikacin concentration (mg/L)
A	0.0
B	3.0
C	10.0
D	20.0
E	35.0
F	50.0

Preservative : 0.1% Sodium azide

2. Amikacin controls:

Three vials of amikacin in human serum should read within the following ranges:

Vial	Phenytoin concentration (mg/L)
L	4.25 – 5.75
M	13.5 – 16.5
H	27.0 – 33.0

Preservative : 0.1% Sodium azide

3. Amikacin reagent pack

The amikacin reagents consist of the following;

Vial	Contents
S	<1% Amikacin antiserum (Sheep) in buffer with protein stabilizer (4.0 mL). Preservative : Contains Sodium azide.
T	<0.01% Amikacin fluorescein tracer in buffer containing surfactant and protein stabilizer (3.5 mL). Preservative : Contains Sodium azide.
P	Pretreatment solution. Surfactant in buffer containing protein stabilizer (2.5 mL). Preservative : Contains Sodium azide.

Amikacin concentration in both plasma and dialysate samples was measured by using Fluorescence Polarization Immunoassay (FPIA) technique (TDx analyzer, Abbott Laboratories). For plasma samples, sensitivity for this assay was determined to be 0.8 μg/ml and coefficient of variance (CV) within run of amikacin concentration at 5, 10, 30 μg/ml were 2.09, 1.37, 1.78% and CV between day of 5, 10, 30 μg/ml were 0, 1.48, 1.74% respectively.

For dialysate sample, validation method was performed. It was found that CV within run of amikacin concentration at 5, 10, 20 μg/ml were 3.43, 2.75, 0.78% and CV between day at 5, 10, 20 μg/ml were 1, 2.59, 1.98% respectively. Correlation between measured concentration by TDx analyzer and known concentration prepared by manual was 0.98. Average recovery for amikacin in 1.5% dextrose dialysis solution was 99.3%.

Evaluation for efficacy and toxicity of amikacin level in serum and dialysate samples

Peak level of amikacin in plasma concentration was determined as therapeutic level for effective treatment of gram negative bacilli infection. Peak plasma level of amikacin (Cpeak) was targeted to be 15-30 μg/ml (39,46). However there has been no studies determined the target peak dialysate level of amikacin (Ctargetd) as an indicator for effective treatment of peritonitis.

All antibiotics appear to demonstrate an initial increase in eradicating activity as a function of antibiotic concentrations that approach or slightly exceed the MIC (39,47-49). The United States' National Committee for Clinical Laboratory Standards (NCCLS) determined MIC of amikacin for sensitive strain; gram negative rod at the cutoff point ≤16 mg/L (50-51). So in this study, we determined the target peak concentration of amikacin in dialysate for treatment of peritonitis (Ctargetd) equaled to or higher than MIC at 16 mg/L.

Many studies aimed the lowest plasma concentration of single dose of amikacin before giving the next dose (Ctrough) at less than 5 μg/ml to decrease risk of ototoxicity (39,52-54).

This study monitored Cpeak 15-30 mg/L and Ctargetd at ≥ 16 mg/L for efficacy and Ctrough at 48 hours (< 5 μg/ml) for ototoxicity of amikacin.

Pharmacokinetic analysis

Data from plasma concentrations was used to plot concentration-time curve and calculated for pharmacokinetic parameters,i.e., AUC, Ka, α,β, Vd, TBCl, $T_{1/2}$ by using computerized program namely RSTRIPII version 2.2.

Data from dialysate concentration was used to plot concentration-time curve and calculated for pharmacokinetic parameters ,i.e., kd, βd, fd , Clpd.

Statistical analysis

Computerized program namely SPSS for window version 9.0 was used for analyzing unpaired and paired t-test, and correlation (r). $P \leq 0.05$ was considered as significance. Descriptive statistics was used in the study by reporting all data as the mean ± standard deviation (mean ± SD).

CHAPTER IV

RESULTS

12 infected – CAPD patients were enrolled in this study. Each of them signed informed consent form before including in this study.

Patient characteristics

There were eight men (66.7%) and four women (33.3%) with a range of age 30-82 years with the mean age equaled to 56.9 ± 14.8 years. The weight of the patients ranged from 51 kgs to 93 kgs. The mean weight equaled to 64.3 ± 11.2 kgs and the mode was within the range of 50-60 kgs. Of 12 infected-CAPD patients, diabetic nephropathy was the most common cause of ESRD (33.3%) followed by hypertension as the second cause (25.0%). The longest duration of CAPD therapy was 13 years and the shortest was three months (0.21 year). The mean duration of CAPD therapy equaled to 3.5 ± 3.8 years. Most of the patients had hypertension as a co-morbid disease (33.3%) which all of these patients were male. These characteristics of the patients are shown in table 9.

Laboratory findings

As shown in table 10, the mean serum creatinine of these 12 infected-CAPD patients equaled to 861.33 ± 196.78 μmol/l (9.74 ± 2.22 mg/dl). The mean hemoglobin (10.24 ± 1.05 g/dl) and hematocrit (31.04 ± 3.89 %) were lower than the normal range. The mean blood urea nitrogen (6.33 ± 2.50 mmol/l) and serum electrolytes such as sodium (139.24 ± 4.84 mmol/l), chloride (101.12 ± 3.16 mmol/l), bicarbonate (27.28 ± 2.34 mmol/l) were in the normal range except for serum potassium (3.43 ± 0.62 mmol/l) which was slightly lower than the normal range. The mean serum calcium (2.40 ± 0.33 mmol/l) was in the normal range but the mean serum phosphate (1.60 ± 0.57 mmol/l) was slightly higher than the normal range. The mean serum total protein (61.0 ±12.65 g/dl) was within the normal range but the mean serum albumin (33.08 ± 7.0 g/dl) was slightly lower than the normal range.

Table 9. Characteristics of the 12 infected–CAPD patients

Characteristics	Number of patients (%)		
	Total	Male	Female
Sex	12 (100)	8 (66.7)	4 (33.3)
Age (yrs)			
1. 20-30	1 (8.3)	1	-
2. 31-40	1 (8.3)	1	-
3. 41-50	2 (16.7)	1	1
4. 51-60	2 (16.7)	1	1
5. 61-70	4 (33.3)	2	2
6. 71-80	1 (8.3)	1	-
7. 81-90	1 (8.3)	1	-
Mean ± SD	**56.9 ± 14.8**		
Weight (kgs)			
1. 50-60	5 (41.7)	3	2
2. 61-70	3 (25.0)	1	2
3. 71-80	3 (25.0)	3	-
4. 81-90	-	-	-
5. 91-100	1 (8.3)	1	-
Mean ± SD	**64.3 ± 11.2**		
Cause of ESRD			
1. Diabetic nephropathy	4 (33.3)	2	2
2. Hypertension	3 (25.0)	3	-
3. CTIN*	2 (16.7)	2	-
4. CGN**	1 (8.3)	1	-
5. Unknown cause	2 (16.7)	-	2
Duration of CAPD therapy (yrs)			
1. Less than one	2 (16.7)	2	-
2. 1.1-3.0	6 (50.0)	3	3
3. 3.1-5.0	1 (8.3)	1	-
4. 5.1-7.0	1 (8.3)	1	-
5. More than seven	2 (16.7)	1	1
Mean ± SD	**3.5 ± 3.8**		
Co-morbid disease			
1. HTN	4 (33.3)	4	-
2. HTN, DM	3 (25.0)	-	3
3. HTN, Dyslipidemia	1 (8.3)	1	-
4. HTN, DM, Dyslipidemia	1 (8.3)	-	1
5. HTN, IHD, Dyslipidemia	1 (8.3)	1	-
6. HTN, IHD, DM, Dyslipidemia	1 (8.3)	1	-
7. HTN, IHD, DM, CHF	1 (8.3)	1	-

*CTIN = Chronic Tubulointerstitial Nephritis
**CGN = Chronic Glomerulonephritis

Table 10. Mean value of the laboratory data of the 12 infected–CAPD patients

Characteristics	Normal value	Mean ± SD
Hb (hemoglobin)	F (12-16 g/dl) M (13-18 g/dl)	10.24 ± 1.05 g/dl
Hct (hematocrit)	F (36-45%) M (39-50%)	31.04 ± 3.89 %
BUN (blood urea nitroger	3-9 mmol/L	6.33 ± 2.50 mmol/L
Cr (creatinine)	62-124 μmol/L	861.33 ± 196.87 μmol/L
Na (sodium)	135-145 mmol/L	139.24 ± 4.84 mmol/L
K (potassium)	3.5-5.0 mmol/L	3.43 ± 0.62 mmol/L
Cl (chloride)	98-110 mmol/L	101.12 ± 3.16 mmol/L
CO_2 (bicarbonate)	21-31 mmol/L	27.28 ± 2.34 mmol/L
Ca (calcium)	2-2.6 mmol/L	2.40 ± 0.33 mmol/L
P (phosphate)	0.87-1.45 mmol/L	1.60 ± 0.57 mmol/L
TP (total protein)	60-83 g/dl	61.0 ± 12.65 g/dl
Alb (Albumin)	35-47 g/dl	33.08 ± 7.0 g/dl

Infection data

As shown in table 11, seven patients had peritonitis (PT group: 58.3%) which only one had peritonitis with exit-site infection. Five patients had catheter-related infection and no peritonitis (Non-PT group: 41.7%) which three of them had exit site infection, one of them had tunnel infection and the remaining one had both exit site and tunnel infection. Among the eight male patients, five of them had peritonitis, two of them had exit site infection, and the remaining one had both exit site and tunnel infection. Of the four female patients, one of them each had exit site infection, tunnel infection, peritonitis, and peritonitis with exit-site infection.

As shown in table 12, among the 12 infected-CAPD patients, five of them had infection caused by gram positive bacteria (41.7%), four of them had infection caused by gram negative bacteria (33.3%) and the remaining three had negative culture (25.0%). The most common gram positive bacteria isolated was *Staphylococcus aureus*.

As shown in table 13, among the seven infected-CAPD patients who had peritonitis (PT group), five were men, two were women. Three patients in PT group had culture negative (42.8%) and four patients had culture positive (57.2 %). Among all four culture-positive patients; two of them had peritonitis caused by *Staphylococcus aureus* (28.6%), one of them had peritonitis caused by *Acinetobacter baumannii* (14.3%) and the remaining one had peritonitis with exit site infection caused by *Klebsiella pneumoniae* with *Enterobacter cloaceae* (14.3%). Among the five infected-CAPD patients in Non-PT group, three were men, two were women. All five patients in Non-PT group had culture positive ; two of them had exit site infection caused by *Coagulase negative staphylococci* (40%), one of them had exit site infection caused by *Pseudomonas aeruginosa* (20%), one of them had tunnel infection caused by *Escherichia coli* and the remaining one had both exit site and tunnel infection caused by *Staphylococcus aureus*.

As shown in table 14, of these 12 infected-CAPD patients the mean incidence of peritonitis was about 0.6 episodes per year (about one episode every 2 to 3 patient-years). This incidence rate was lower than that in another study (12), which found that the incidence of peritonitis was about 1.1-1.2 episodes per year.

Clinical signs and symptoms

Among the five patients in the Non-PT group, three patients who had exit site infection showed clinical signs and symptoms such as tenderness, purulent drainage, erythema skin with scab and no granulation tissue. The patient who had both exit site and tunnel infection showed the same clinical sign and symptom as those three aforementioned patients plus proud flesh granulation tissue and purulent drainage squeezed from the tunnel tract. The remaining one who had tunnel infection showed tenderness and purulent drainage squeezed from the tunnel tract.

All the seven patients in the PT group had cloudy dialysate with the mean WBC counts equaled to 430 ± 166.8 cell/mm^3 (mean ± SD) and PMN counts equaled to 78 ± 10.3 %. Five of them had both fever and abdominal pain which one of these five patients had nausea and vomiting too. While, there were two patients who had none of these symptoms.

Treatment and outcome

Before the result from C/S were available, some antibiotics as an empirical treatment should be administered to patients. For peritonitis, each patient was treated with cefazolin intraperitoneal (IP) 1g in the first dialysate bag as a loading dose then 250 mg in the subsequent dialysate bags as the maintenance dose for eradicating gram positive bacteria and also received a single dose (7.5 mg/kg) of amikacin administered by intramuscular route (IM) every 48 hours for eradicating gram negative bacteria. In case of either exit-site or tunnel infection, each patient received oral cloxacillin 500 mg four times per day before meal for eradicating gram positive bacteria and received the same dosage regimen and route of amikacin as those with peritonitis.

All 12 infected-CAPD patients had received amikacin 500 mg (every 48 hours). It is not necessary, in practice, to admit patients without peritonitis to a hospital. They can be treated with oral antibiotics as outpatients. However, in order to be able to collect blood and dialysate samples, this study admitted the patients in non-PT group for three days. They received only one dose of amikacin along with four times daily oral cloxacillin during admission. When they were discharged, they were prescribed with oral antibiotics according to their C/S results. The duration for improved clinical outcome of all patients in Non-PT group were 14 days. Except for the patient who had both exit site and tunnel infection caused by *Staphylococcus aureus*, improved clinical outcome was met after three weeks.

In PT group, after they had received one dose of IM amikacin and continuous IP cefazolin, clinical outcome was improved as shown by the reduction in abdominal pain and fever. The mean WBC counts (321 ± 158.16 cell/mm^3) and PMN counts (67 ± 11.50 %) were also reduced significantly ($p = 0.027$). Since the patients should receive empirical treatment continuously until C/S results were available while the trough level of amikacin in blood was still higher than the lower limit of the toxic level (> 5 mg/L) after the first dose of IM amikacin, therefore IP amikacin was administered to the patients continuously in place of IM route in order to reduce risk of ototoxicity. Therefore, the patients in PT group received continuous amikacin IP 25 mg along with continuous cefazolin IP 250 mg in each exchange according to the empirical treatment guideline provided by the International Society of Peritoneal Dialysis Ad Hoc Advisory Committee on Peritonitis Management in 1996 (12) until C/S results were available. However, this study did not extend to investigate amikacin concentration in plasma ans dialysate after this IP administration.

After C/S result were available, all patients with peritonitis were treated with antibiotics according to their C/S results except for three patients who specimen were culture negative, they were continued on the same treatment as the empirical treatment, i.e., : continuous cefazolin IP 250 mg and amikacin IP 25 mg in each exchange for two weeks. The mean duration of therapy for improved clinical outcome (clear dialysate, no finding of WBC and PMN counts, no fever, no abdominal pain) was 16 ± 2 days. Six patients with peritonitis had no recurrent infection while one had recurrent infection caused by *Pseudomonas aeruginosa* after receiving antibiotic treatment for two weeks. This case was cured in four weeks after treatment with continuous amikacin IP 25 mg and ceftazidime IP 250 mg in each exchange.

Table 11. Type of infection of the 12 infected–CAPD patients

Type of infection	Patient No.	No. of patients (%)	Male	Female
Non-PT group :				
Exit site	3, 4, 5	3 (25.0)	2	1
Tunnel	2	1 (8.3)	-	1
Exit site with tunnel	1	1 (8.3)	1	-
PT group :				
Peritonitis	6-8, 10-12	6 (50.0)	5	1
Peritonitis with exit site	9	1 (8.3)	-	1
Total		12 (100)	8(66.7)	4(33.3)

PT = Peritonitis
Non-PT = Non-Peritonitis (exit-site or tunnel infection or both)

Table 12. Causative organisms separated by gram stain of the 12 infected–CAPD patients

Causative organism	No. of patients (%)	Male	Female
Gram-positive organisms:			
Staphylococcus aureus	3 (25)	2	1
Coagulase negative staphylococci	2 (16.7)	1	1
Total	5(41.7)		
Gram-negative organisms:			
Escherichia coli	1 (8.3)	-	1
Klebsiella pneumoniae with *Enterobacter cloaceae*	1 (8.3)	-	1
Pseudomonas aeruginosa	1 (8.3)	1	-
Acinetobacter baumannii	1 (8.3)	1	-
Total	4(33.3)		
No growth	3(25.0)	3	-
Total	12(100)	8(66.7)	4(33.3)

Table 13. Causative organisms separated by type of infection of the 12 infected – CAPD patients

Type of infection	Causative organism	No. of patients (%)	Male	Female
PT :				
Peritonitis	*Staphylococcus aureus*	2 (28.6)	1	1
	Acinetobacter baumannii	1 (14.3)	1	-
Peritonitis with exit site	*Klebsiella pneumoniae with Enterobacter cloaceae*	1 (14.3)	-	1 -
	No growth	3 (42.8)	3	-
	Total	7 (100)	5	2
Non-PT :				
Exit site	*Coagulase negative staphylococci*	2 (40)	1	1
	Pseudomonas aeruginosa	1 (20)	1	-
Tunnel	*Escherichia coli*	1 (20)	-	1
Exit site with tunnel	*Staphylococcus aureus*	1 (20)	1	-
	Total	5 (100)	3	2

Table 14. Past history of incidence of peritonitis in the 12 infected-CAPD patients

Patient No.	Duration of CAPD therapy (year)	Episodes in past history of peritonitis	Incidence of peritonitis (episodes per year)
1	0.21 (3 month)	-	0
2	2.1	-	0
3	13	9	0.7
4	4.0	1	0.25
5	6.2	4	0.6
6	1.8	2	1.1
7	1.4	1	0.7
8	1.2	1	0.8
9	2.1	1	0.5
10	2.5	1	0.4
11	0.3 (4 month)	-	0
12	8.0	6	0.8
Mean	**42.8**	**26**	**0.6**

Pharmacokinetic of amikacin concentrations in plasma

After 12 infected-CAPD patients had received intramuscular amikacin 7.5 mg/kg every 48 hours, its plasma concentration at each sampling time were shown in table 15. The maximum peak plasma concentration of amikacin was 30.5 mg/L and the minimum peak was 18.7 mg/L. The mean peak plasma concentration of amikacin was 25.3 ± 3.21 mg/L (mean ± SD) and the mean time to peak was at 2.6 ± 1.0 hours as shown in table 16. The mean plasma concentrations of amikacin at each sampling time (0.5,1,1.5,2,4,6,12,24,48 hours) were used to plot plasma amikacin concentration versus time curve as shown in figure 5.

All patients had peak plasma concentration of amikacin in the therapeutic range (15-30 mg/L). At 24 hours, the mean plasma concentration of amikacin was 16.2 ± 1.6 mg/L and the trough plasma concentration of amikacin at 48 hours just before the next dose in all patients were higher than 5 mg/L which might predispose patients to higher accumulation of amikacin in the ear which could led to ototoxicity.The maximum trough plasma concentration of amikacin was 14.2 mg/L and the minimum trough was 7.4 mg/L. The mean trough plasma concentration of amikacin was 10.3 ± 1.75 mg/L.

Computerized program namely RSTRIP II version 2.2 was used to determine the equation that best fit the plasma amikacin concentration time curve after IM administration. The result indicated that the plasma amikacin concentration time curve was best described by two-compartment with first order absorption model which the equation was :

$$\mathbf{Cp^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}}$$

This equation is the sum of two linear component representing distribution phase ($Ge^{-\alpha t}$)and elimination phase ($Be^{-\beta t}$) abstracted by absorption phase (Ae^{-kat}) as described in detail in appendix I. The equations that best fit the plasma amikacin concentration time curve of each patients were shown in table 19 and the pharmacokinetic parameters were shown in table 17.

As shown in table 17, the mean absorption rate (ka), distribution rate (α) and elimination rate (β) constant were 1.326 ± 1.820 hr^{-1}, 0.299 ± 0.280 hr^{-1}, 0.019 ± 0.004 hr^{-1} respectively.The mean area under plasma concentration time curve (AUC) of amikacin was 784.38 ± 71.13 mg/L hr. The mean volume of distribution (Vd) was 35.99 ± 9.84 L (0.56 .± 0.11 L/kg). The mean total body clearance was 0.64 ± 0.06 L/hr (10.73 ml/min) with the mean half-life equaled to 38.41 ± 8.94 hour.

As shown in table 18, there were no significant differences in pharmacokinetic parameters of amikacin in plasma between the patients in PT and non-PT group.

Comparison of Cpmeasured and Cpcalculated (calculated from the equation which derived from the mean amikacin concentration of all 12 patients) was shown in table 20 while comparison between Cpmeasured and Cpcalculated of each patients were shown in details in appendix II (table1-12). Correlation between Cpmeasured and Cpcalculated which calculated from the equation that derived from the mean amikacin concentration of all 12 patients was 0.966 while the mean correlation between Cpmeasured and Cpcalculated which calculated from the equation that derived from amikacin concentration of each individual was 0.978 ± 0.023. These high correlation indicated that the equation derived here could be used to calculate the amikacin concentration at any time with good accuracy. The predicted concentration during the first half an hour was the most deviated from the measured concentration.

Table 15. Amikacin concentration in plasma at each sampling time after IM administration a single dose of 7.5 mg/kg to 12 infected-CAPD patients

Pt No. / Time (hr)	Plasma concentration (mg/L)								
	0.5	**1**	**1.5**	**2**	**4**	**6**	**12**	**24**	**48**
1	20.5	24.2	26.1	27.6	23.9	22.5	19.2	18.3	14.2
2	12.7	23.2	25	24.1	23.7	23.3	20.5	17.2	10
3	5.9	15.4	20.2	24.6	30.5	26.8	22.6	19.3	11.7
4	9.3	15.6	21.1	22.4	24	23	19.2	14.6	8.8
5	12.1	22.9	23.7	25.6	24.4	23.5	19.8	15.3	9.5
6	14.8	17	17.6	18.7	17.4	16.5	15	13.5	10.1
7	9.3	17.4	19.3	19.8	23.1	21.8	18.4	14.3	8.7
8	21	23.4	25.4	27	24	23.1	22.2	16.3	7.4
9	8.9	12.5	13.6	19.3	21.3	20	18.7	16.4	9.8
10	10.4	18.6	23	24.3	24.1	23.5	20.5	16.1	10
11	21.8	26.1	29.3	28.5	25.3	24.6	21	16.7	11.2
12	21.6	26.6	27	27.6	25.1	23.1	20.8	16	12.4
mean	**13.4**	**19.9**	**22.6**	**24.1**	**23.9**	**22.6**	**19.8**	**16.2**	**10.3**
SD	**5.6**	**4.7**	**4.4**	**3.4**	**3**	**2.5**	**2**	**1.6**	**1.9**

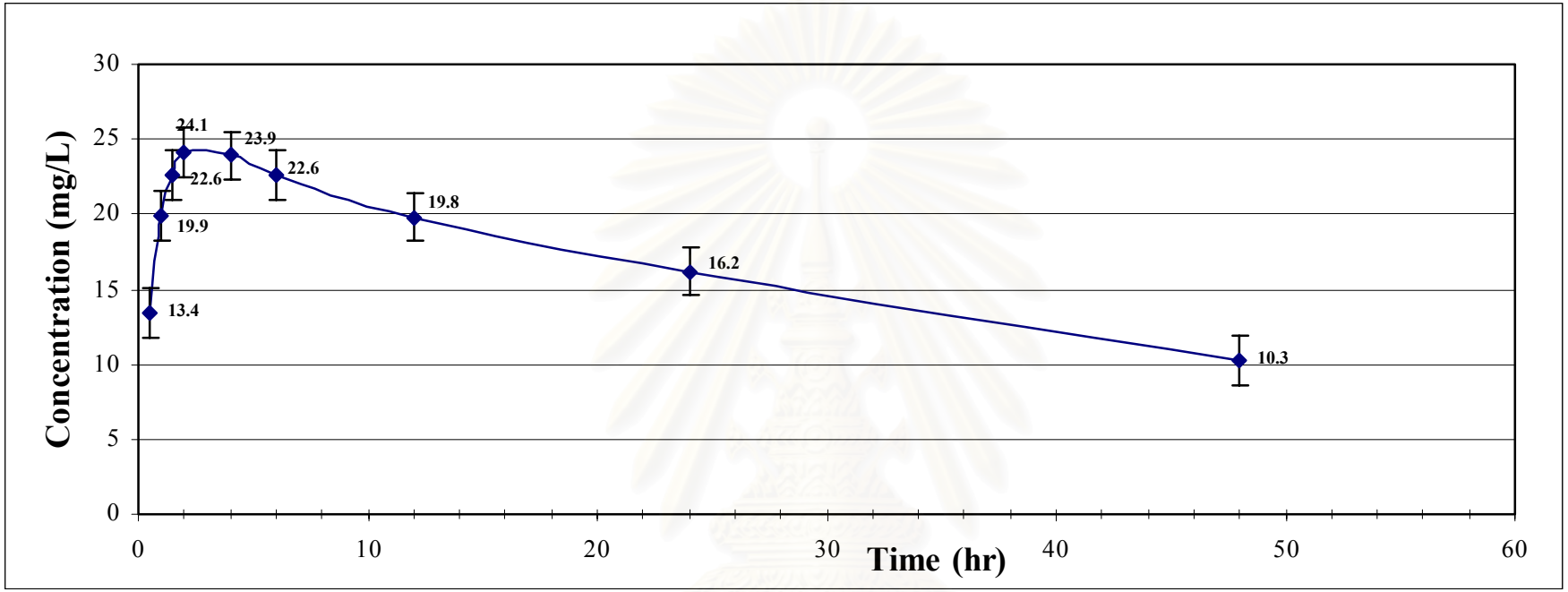


Figure 5. The mean plasma amikacin concentration versus time curve after IM administration a single dose of 7.5 mg/kg to the 12 infeted-CAPD patients

Table 16. Cpeak, Tpeak and Ctrough at 48 hr. of amikacin in plasma after IM administration a single dose of 7.5 mg/kg to the 12 infected-CAPD patients

Patient No.	Cpeak (mg/L)	Tpeak (hr)	Ctrough at 48 hr. (mg/L)
1	27.6	2.0	14.2
2	25.0	1.5	10.0
3	30.5	4.0	11.7
4	24.0	4.0	8.8
5	25.6	2.0	9.5
6	18.7	2.0	10.1
7	23.1	4.0	8.7
8	27.0	2.0	7.4
9	21.3	4.0	9.8
10	24.3	2.0	10.0
11	29.3	1.5	11.2
12	27.6	2.0	12.4
Mean	**25.3**	**2.6**	**10.3**
SD	**3.2**	**1.0**	**1.9**

Table 17. Amikacin pharmacokinetic parameters derived from plasma concentrations after IM administration a single dose of 7.5 mg/kg to the 12 infected-CAPD patients.

Pt No.	Ka* (hr^{-1})	α* (hr^{-1})	β* (hr^{-1})	$AUC_{0 \rightarrow 48}$* (mg/L.hr)	Vd** (L)	Vd (L/kg)	TBCl** (L/hr)	TBCl (ml/min)	$T_{1/2}$** (hr)
1	1.144	0.375	0.013	874.11	45.40	0.71	0.57	9.50	53.30
2	4.358	0.207	0.019	804.34	32.21	0.53	0.62	10.36	36.47
3	0.976	0.022	0.021	905.31	26.55	0.44	0.55	9.20	33.00
4	1.066	1.016	0.023	726.04	29.56	0.45	0.69	11.48	30.13
5	2.278	0.399	0.021	762.36	31.99	0.45	0.66	10.93	33.00
6	2.530	0.013	0.012	649.86	63.59	0.68	0.77	12.82	57.75
7	3.835	0.353	0.023	703.42	31.45	0.45	0.71	11.85	30.13
8	1.360	0.026	0.025	782.44	25.98	0.46	0.65	10.83	27.72
9	0.605	0.576	0.017	734.50	39.12	0.56	0.68	11.34	40.76
10	1.693	0.021	0.020	786.59	32.10	0.58	0.64	10.59	34.65
11	1.695	0.220	0.017	844.03	35.69	0.65	0.59	9.87	40.76
12	2.042	0.363	0.016	839.53	38.18	0.75	0.60	10.00	43.31
Mean	**1.326**	**0.299**	**0.019**	**784.38**	**35.99**	**0.56**	**0.64**	**10.73**	**38.41**
SD	**1.820**	**0.280**	**0.004**	**71.13**	**9.84**	**0.11**	**0.06**	**1.00**	**8.94**

* The value of ka, α, β and $AUC_{0 \rightarrow 48}$ were calculated by computerized program namely RSTRIP II version 2.2.

** The value of Vd, TBCl and $T_{1/2}$ were calculated by the equation 2A, 3A and 4A as described in appendix I respectively.

Table 18. Comparison of the amikacin pharmacokinetic parameters derived from plasma concentrations between the patients in PT and non-PT group after IM administration a single dose of 7.5 mg/kg to the 12 infected-CAPD patients

Pharmacokinetic Parameters	PT group Mean±SD	Non -PT group Mean±SD	P – value
Ka (hr^{-1})	1.966±0.94	1.964±1.293	0.999
α (hr^{-1})	0.224±0.202	0.404±0.335	0.374
β (hr^{-1})	0.018±0.004	0.019±0.003	0.738
$AUC_{0\rightarrow48}$(mg/L.hr)	762.91±66.03	814.43±67.00	0.263
Vd (L/kg)	0.59±0.10	0.52±0.10	0.295
TBCI (L/hr)	0.66±0.06	0.62±0.05	0.238
$T_{½}$ (hr)	39.30±9.26	37.18±8.31	0.715

Table 19. Equations for predicting amikacin concentration in plasma at any time after IM administration a single dose of 7.5 mg/kg to the 12 infected-CAPD patients

Patient No.	Equation for predicting amikacin concentration in plasma at anytime*
1	$Cp^t = 18.16\, e^{-0.375t} + 21.41\, e^{-0.013t} - 28.45\, e^{-1.144t}$
2	$Cp^t = -1.47\, e^{-0.2067t} + 26.17\, e^{-0.019t} - 24.65\, e^{-4.358t}$
3	$Cp^t = -0.77\, e^{-0.022t} + 31.65\, e^{-0.021t} - 30.77\, e^{-0.976t}$
4	$Cp^t = -17.17\, e^{-1.016t} + 25.96\, e^{-0.023t} - 8.78\, e^{-1.066t}$
5	$Cp^t = 1.44\, e^{-0.399t} + 25.12\, e^{-0.021t} - 25.56\, e^{-2.278t}$
6	$Cp^t = 0.08\, e^{-0.013t} + 18.05\, e^{-0.012t} - 11.40\, e^{-2.530t}$
7	$Cp^t = -7.25\, e^{-0.353t} + 24.73\, e^{-0.023t} - 17.48\, e^{-3.835t}$
8	$Cp^t = -0.82\, e^{-0.026t} + 28.29\, e^{-0.025t} - 12.26\, e^{-1.360t}$
9	$Cp^t = 1.42\, e^{-0.576t} + 23.64\, e^{-0.017t} - 20.67\, e^{-0.605t}$
10	$Cp^t = 0.28\, e^{-0.021t} + 25.82\, e^{-0.020t} - 25.94\, e^{-1.693t}$
11	$Cp^t = 6.81\, e^{-0.220t} + 24.90\, e^{-0.017\,t} - 21.00\, e^{-1.695t}$
12	$Cp^t = 7.04\, e^{-0.363t} + 24.96\, e^{-0.016t} - 24.93\, e^{-2.042t}$
1-12	$\mathbf{Cp^t = -0.13\, e^{-0.020t} + 25.45\, e^{-0.019t} - 25.32\, e^{-1.742t}}$ **

***Two-compartment Model:**

$$\mathbf{Cp^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}}$$

** This equation was derived from the mean amikacin concentration in plasma of all 12 patients.

Table 20. Comparison of Cpmeasured and Cpcalculated using equation derived from the mean amikacin concentration in plasma after IM administration a single dose of 7.5 mg/kg to the 12 infected-CAPD patients

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	13.4	14.7	109.70
1	19.9	20.4	102.51
1.5	22.6	22.8	100.88
2	24.1	23.6	97.92
4	23.9	23.5	98.32
6	22.6	22.7	100.44
12	19.8	20.4	103.03
24	16.2	16.4	101.23
48	10.3	10.7	103.88
Mean			**101.96**
SD			**3.32**

r = 0.966 **CV = 3.26 %**

Pharmacokinetic of amikacin concentrations in dialysate

As shown in table 21, after patients received single dose (7.5 mg/kg) of amikacin intramuscularly, amikacin concentration in dialysate at one hour of the first dialysate bag was 5.1 ± 3.5 mg/L at four hours was 13.5 ± 4.5 mg/L and at six hours was 17.6 ± 3.4 mg/L. The mean amikacin conentration in dialysate at the end of the the second (at 12 hour), the third (at 18 hours), the fourth (at 24 hours), the fifthe (at 30 hours), the sixth (at 36 hours), the seventh (at 42 hours) and the eighth (at 48 hours) dialysate bag were 15.6 ± 2.3, 12.5 ± 3.0, 11.0 ± 2.0, 9.8 ± 2.0, 8.5 ± 2.0, 7.5 ± 1.8, 6.6 ± 1.5 mg/L respetively. Amikacin levels in dialysate normally showed peak concentration every six hours at the end of eah dialysate bags. The maximum peak dialysate oncentration was found at the end of the first dialysate bag with the mean equaled to 17.6 ± 3.4 mg/L. This study found that only the first dialysate bag showed the mean peak concentration of amikacin above the predetermined target concentration in dialysate for treatment of peritonitis (Ctargetd ≥ 16 mg/L).

Besides collecting samples at the end of each dialysate bags, this study also collected intervened sampling of dialysate in the first dialysate bag at 1 and 4 hour, in the fifth dialysate bag at 25 and 28 hour and in the eighth dialysate bag at 43 and 46 hours. The results of these sampling times were depited as the curve line of the first (C-D curve), the fifth (E-F urve) and the eighth (H-I curve) dialysate bag as shown in figure 6.

As shown in table 22, amikacin concentration in dialysate at every sampling time of the patients in PT group were higher than amikacin concentration in non-PT group with statistically significant (P = 0.002, unpaired t-test). When considering speifically in the peak concentration in dialysate, it was found that only one of the five patients in non-PT group had peak conentration at six hours at the end of the first dialysate bag which was above Ctargetd indicated that majority of the patients in the non-PT group had peak concentration which was lower than Ctargetd. In contrary, among the patients in PT group, only one out of the seven patients had peak concentration at the end of the first dialysate bag which was lower than Ctargetd indiated that majority of the patients in the PT group had peak conentration which was above the Ctargetd. Besides, the mean peak concentration of the patients in PT group was also above the Ctargetd at 12 hours at the end of the second dialysate bag.

As shown in table 23, The maximum peritoneal amikacin clearance (Clpd) was 0.29 L/hr (4.83 ml/min) and the minimum was 0.16 L/hr (2.67 ml/min) with the mean equaled to 0.23 ± 0.05 L/hr (3.83 ± 0.80 ml/min). This result indiated that the volume of plasma equaled to 0.23 liter which amikacin existing was ompletely removed or cleared by CAPD in each hour.

Table 21. Amikacin concentrations in dialysaste at each sampling time after IM administration a single dose of 7.5mg/kg to 12 infected-CAPD patients

Pt No. / time (hr)	Amikacin concentration in dialysate (mg/L)													
	1	**4**	**6**	**12**	**18**	**24**	**25**	**28**	**30**	**36**	**42**	**43**	**46**	**48**
1	2.9	10.8	14.6	13.2	11.1	9.2	3.4	8	9.5	6.3	4.9	2.2	4	5.2
2	2.3	5.4	13.2	12.8	7	7.9	2.7	4.3	5	6.7	6.3	3.1	4.4	5.8
3*	-	-	14.2	13	10.1	11.2	-	-	10.5	7.7	8.8	-	-	7.1
4*	-	-	14.5	13.7	11.3	9.3	-	-	7.3	7.6	6.1	-	-	5
5	2	10.1	16.6	13.7	8.2	8.1	2.5	3.7	8	4.8	4	1.9	2.8	3.8
6	7.8	10.3	15.1	14.4	13.1	12.4	7.6	10.8	11.8	11.1	9.1	3.7	7.8	8.5
7	5.8	15.7	19.2	17.5	15	12.8	6.6	9.1	10.6	9.9	8.2	3.6	6.2	7.2
8	8.2	18.9	22.5	19.4	15	11.9	4.6	7.3	10	8.3	7.8	4.5	5.4	6.3
9	2	14.7	18.6	16.9	15	13.1	7.2	9	10.9	9.7	8.9	4.1	7	8
10	3	17.1	22.4	17.3	16.5	12	5.6	9.4	11.5	10.1	9.2	4.5	7.4	8.6
11*	-	-	18.3	17.4	12.3	10.6	-	-	8.8	7.2	6.8	-	-	5.6
12	11.6	18.1	21.8	17.6	15.8	13.8	3.9	10.8	11.7	10.9	9.4	4.8	7.3	8
mean	**5.1**	**13.5**	**17.6**	**15.6**	**12.5**	**11**	**4.9**	**8**	**9.6**	**8.4**	**7.5**	**3.6**	**5.8**	**6.6**
SD	**3.5**	**4.5**	**3.4**	**2.3**	**3**	**2**	**1.9**	**2.6**	**2**	**2**	**1.8**	**1**	**1.8**	**1.5**

* The dialysate during intervened sampling times of patient no.3,4 and 11 could not be collected because they used dialysis solution of Baxter Ultrabag System.

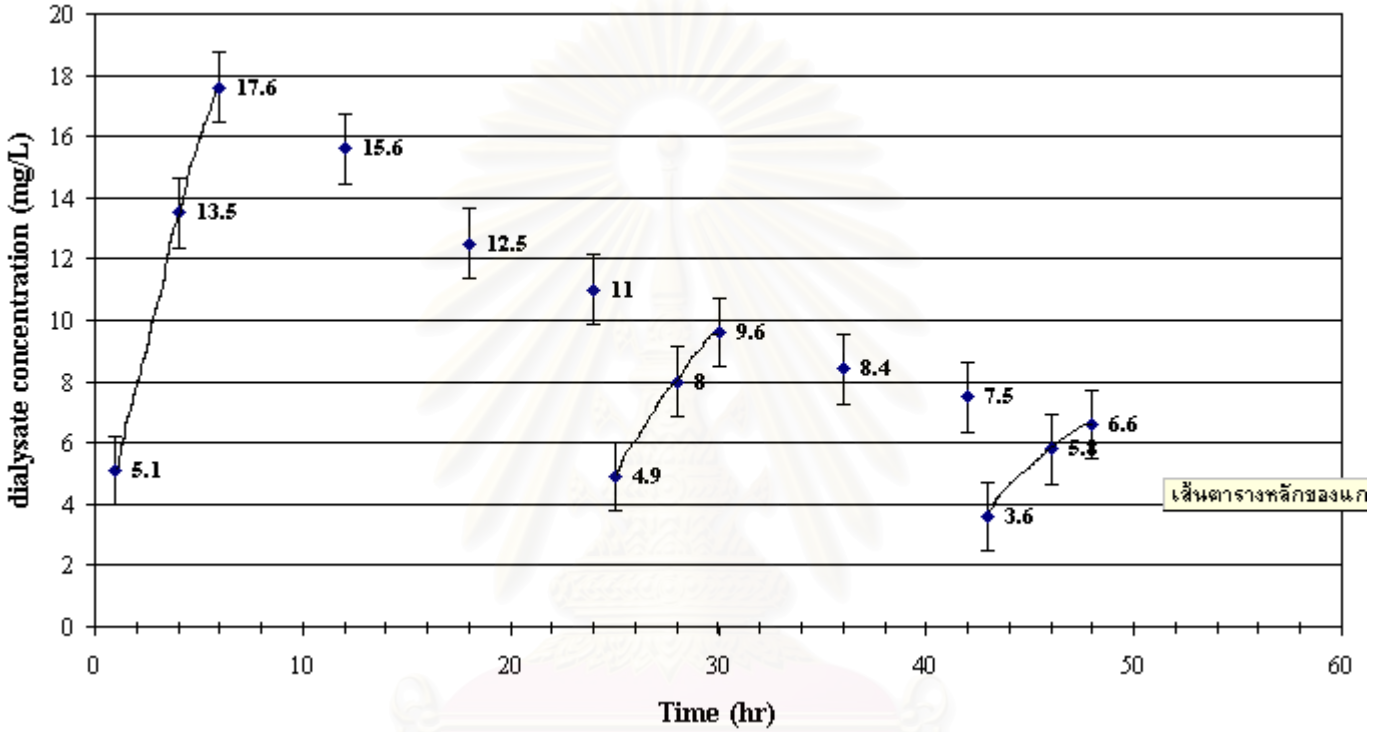


Figure 6. The mean amikacin concentration in dialysate versus time curve after IM administration of 7.5 mg/lkg to 12 infected-CAPD patients

C-D curve = the curve of the first dialysate bag with concentration equaled to 5.1, 13.5, 17.6 mg/L
E-F curve = the curve of the fifth dialysate bag with concentration equaled to 4.9, 8.0, 9.6 mg/L
H-I curve = the curve of the eight dialysate bag with concentration equaled to 3.6, 5.8, 6.6 mg/L

Table 22. Amikacin concentrations in dialysaste at each sampling time after IM administration a single dose of 7.5mg/kg compared between the non-PT group at each sampling time

Pt No. / Time (hr)		Dialysate concentration (mg/L)													
		1	4	6	12	18	24	25	28	30	36	42	43	46	48
(non-PT)	1	2.9	10.8	14.6	13.2	11.1	9.2	3.4	8	9.5	6.3	4.9	2.2	4	5.2
	2	2.3	5.4	13.2	12.8	7	7.9	2.7	4.3	5	6.7	6.3	3.1	4.4	5.8
	3	-	-	14.2	13	10.1	11.2	-	-	10.5	7.7	8.8	-	-	7.1
	4	-	-	14.5	13.7	11.3	9.3	-	-	7.3	7.6	6.1	-	-	5
	5	2	10.1	16.6	13.7	8.2	8.1	2.5	3.7	8	4.8	4	1.9	2.8	3.8
mean		**2.4**	**8.8**	**14.6**	**13.3**	**9.6**	**9.1**	**2.9**	**5.3**	**8.1**	**6.6**	**6**	**2.4**	**3.7**	**5.4**
SD		**0.5**	**2.9**	**1.2**	**0.4**	**1.9**	**1.3**	**0.5**	**2.3**	**2.1**	**1.2**	**1.8**	**0.6**	**0.8**	**1.2**
(PT)	6	7.8	10.3	15.1	14.4	13.1	12.4	7.6	10.8	11.8	11.1	9.1	3.7	7.8	8.5
	7	5.8	15.7	19.2	17.5	15	12.8	6.6	9.1	10.6	9.9	8.2	3.6	6.2	7.2
	8	8.2	18.9	22.5	19.4	15	11.9	4.6	7.3	10	8.3	7.8	4.5	5.4	6.3
	9	2	14.7	18.6	16.9	15	13.1	7.2	9	10.9	9.7	8.9	4.1	7	8
	10	3	17.1	22.4	17.3	16.5	12	5.6	9.4	11.5	10.1	9.2	4.5	7.4	8.6
	11	-	-	18.3	17.4	12.3	10.6	-	-	8.8	7.2	6.8	-	-	5.6
	12	11.6	18.1	21.8	17.6	15.8	13.8	3.9	10.8	11.7	10.9	9.4	4.8	7.3	8
mean		**6.4**	**15.8**	**19.7**	**17.2**	**14.7**	**12.4**	**5.9**	**9.4**	**10.8**	**9.6**	**8.9**	**4.2**	**6.9**	**7.5**
SD		**3.6**	**3.1**	**2.7**	**1.5**	**1.5**	**1**	**1.5**	**1.3**	**1.1**	**1.4**	**0.9**	**0.5**	**0.9**	**1.1**

Table 23. Peritoneal amikacin clearance (Clpd) after IM administration a single dose of 7.5 mg/kg to the 12 infected –CAPD

Patient No.	Clpd (L/hr)	Clpd* (ml/min)
1	0.17	2.83
2	0.16	2.67
3	0.18	3.00
4	0.21	3.50
5	0.18	3.00
6	0.29	4.83
7	0.28	4.67
8	0.26	4.33
9	0.27	4.50
10	0.29	4.83
11	0.21	3.50
12	0.26	4.33
Mean	**0.23**	**3.90**
SD	**0.05**	**0.87**

Calculation method for determining Clpd* was described in details in appendix I

$$\text{Clpd} = \frac{\text{Amount of drug in dialysate from 0 to 48 hours}}{\text{AUC}_{0 \rightarrow 48}}$$

This study hypothesized that there is a relationship between amikacin concentrations in plasma and those in dialysate.The rate of amikacin dialysate excretion is proportional to the amount of amikacin in the body and the equation used to determine amikacin in plasma as described by the two-compartment model with first-order absorption [$C_p^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-k\alpha t}$] should be able to apply for determining amikacin concentration in dialysate .

$$\frac{dXd}{dt} \quad \alpha \quad Xt \qquad \text{- Equation 1}$$

$\frac{dXd}{dt}$ = dialysate excretion rate of amikacin

$$= \frac{\text{(amikacin concentration in dialysate) (dialysate volume)}}{\text{Time interval for collection}}$$

While Xt = The amount of amikacin in the body at any time

$= Vd\ C_p^t$

Therefore $\frac{dXd}{dt} = kdXt = kd(Vd\ C_p^t)$ - Equation 2

While kd = dialysate excretion rate constant

As shown in equation 2 , the dialysate excretion rate of amikacin is proportional to the amikacin concentration in plasma (C_p^t).

Since $C_p^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}$ - Equation 3

Therefore $\frac{dXd}{dt} = kdVd[(Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}]$ - Equation 4

$= (kdVd\ Ge^{-\alpha t} + kdVd\ Be^{-\beta t}) - kdVd\ Ae^{-kat}$

$= (G'e^{-\alpha dt} + B'e^{-\beta dt}) - A'e^{-kadt}$ - Equation 5

if $\beta d << \alpha d << kad$

According to Equation 5, the plot between ln dX/dt versus time will result in a curve which was similar in shape to the plot between plasma concentration time curve using the curve stripping or curve peeling method. One method should be able to get three lines, the first line will give the slope βd with intercept B', the second line will give the slope αd with intercept G' and the third line will give the slope kad with intercept A'.

In this study, however, the computerized program namely RSTRIP II version 2.2 previously used to calculate ka , α , β from data of amikacin concentration in the plasma could not be used to calculate the same pharmacokinetic parameters (kad, αd , βd) from lndx/dt versus time curve as shown in equation 5. Since dialysate samples at intervened sampling times before amikacin concentration in the plasma reached the peak concentration in the absorption phase had not been collected. In addition, collecting intervened dialysate samples required specialized technique and one should be very careful not to increase the risk of infection to the patients by contamination.

From equation 4 , after amikacin had been administered for sometimes, the absorption phase became complete and the distribution phase became equilibrium, then, the exponential terms which stand for the absorption phase and the distribution phase became negligible, the excretion rate of amikacin through dialysate could then be explained by only one exponential term of elimination phase as follow :

$$\frac{dXd}{dt} = kdVdBe^{-\beta d t} \qquad \text{- Equation 6}$$

Taking natural log (ln) to Equation 7

Therefore $\ln (dXd/dt) = \ln kdVdB - \beta dt$ - Equation 7

Starting from the end of the fourth dialysate bag, by linear regression method , the plot of ln dXd/dt versus midpoint time will give the linear curve with slope equal to βd and intercept equal to kdVdB. So kd can be calculated as shown in equation 8.

$$\text{slope} = \beta d$$

$$\text{intercept} = kdVdB$$

While $VdB = \text{Dose}$

Therefore $$kd = \frac{\text{Intercept}}{\text{Dose}}$$ - Equation 8

From equation 7, dialysate excretion rates (dXd / dt) were calculated and then plotted between the mean ln(dXd / dt) (Y-Axis) versus midpoint time (X-Axis) as shown in table 24 and Figure 7 respectively.

In order to find the relationship of the pharmacokinetic parameters between blood and dialysate, the drug concentrations during the same period of time only should be taken into consideration. Due to the same reason as equation 6, equation 3 was simplified as follow :

$$C_p^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}$$ - Equation 3

$$C_p^t = Be^{-\beta t}$$ - Equation 9

Taking natural log (ln) to Equation 9

$$\ln C_p^t = \ln B - \beta t$$ - Equation 10

$$\text{Slope} = B = \frac{\ln C_{p1} - \ln C_{p2}}{\Delta t}$$ - Equation 11

According to equation 10, by linear regression method, the plot of $\ln C_p^t$ versus time will give the linear curve with slope equal to β (as calculated by Equation 11) and intercept equal to ln B.

This study plotted ln C_p^t versus time by using data of amikacin concentration in plasma after the distribution phase was completed . Therefore, amikacin concentration in plasma at 24 hours and at 48 hours only were used to derive the β value and depicted in Figure 8 .

Therefore , in this study, only the βd slope which derived from amikacin concentration in dialysate during the elimination phase was determined and compared with the β slope which derived from amikacin concentration in plasma during the elimination phase by the same linear regression method. The relationship between amikacin concentrations in plasma and its dialysate could then be determined.

As shown in figure 9, the plasma concentration versus time curve and the curve between ln dialysate excretion rate versus midpoint time during elimination phase were paralell and there were no statistical significant difference between β and β_d (P = 0.450, paired t-test) and also between half-lifes calculated by using β and β_d (P = 0.377, paired t-test) as shown in table 25. These results indicated that β_d could be used instead of β to calculate the drug concentration in plasma at any time during elimination phase or vice versa. Therefore, there were relationship between amikacin concentration in plasma and dialysate that is pharmacokinetic characteristics of amikacin in plasma and dialysate were interchangeble .

Table 26 shows the value of dialysate excretion rate (kd) and elimination rate constant (β_d) which derived from data of amikacin concentration in dialysate by plotting the linear curve of ln dXd/dt versus midpoint time to give the slope equal to β_d and the intercept for calculating kd as described in detail by the equation 6-8 above. The maximum kd was 0.014 hr^{-1} and the minimum was 0.007 hr^{-1} with the mean equaled to 0.011 ± 0.002 hr^{-1} . The maximum β_d was 0.038 hr^{-1} and the minimum was 0.012 hr^{-1} with the mean equaled to 0.021 ± 0.007 hr^{-1} .The kd/β_d could represent the fraction of amikacin dose eliminated by CAPD. The maximum percentage of kd/β_d was 73.33 % and the minimum was 34.21 % with the mean equaled to 54.12 ± 10.68 % .

As shown in table 27, there were no statistical significant difference analyzed by unpaired t-test in kd (P = 0.136), β_d (P = 0.847), β (P = 0.935), $\%kd/\beta_d$ (P = 0.149) between the patients in PT and non- PT group except for Clpd which showed statistically significant difference between the patients in PT and non- PT group.

Table 24. Dialysate excretion rate of amikacin versus time at midpoint of each exchange

Pat No. / Tmid (hr)	Dialysate excretion rate (dx/dt) (mg/hr)							
	3	**9**	**15**	**21**	**27**	**33**	**39**	**45**
1	4.87	4.40	3.70	3.07	3.17	2.10	1.63	1.73
2	4.40	4.27	2.33	2.63	1.67	2.23	2.10	1.93
3	4.73	4.33	3.37	3.73	3.50	2.57	2.93	2.37
4	4.83	4.57	3.77	3.10	2.43	2.53	2.03	1.67
5	5.53	4.57	2.73	2.70	2.67	2.27	1.33	1.27
6	5.03	4.80	4.37	4.13	3.93	3.70	3.03	2.83
7	6.40	5.83	5.00	4.27	3.53	3.30	2.73	2.40
8	7.50	6.47	5.00	3.97	3.33	2.77	2.60	2.10
9	6.30	5.63	5.00	4.37	3.63	3.23	2.97	2.67
10	7.47	5.77	5.50	4.00	3.83	3.37	3.07	2.87
11	6.10	5.80	4.10	3.53	2.93	2.40	2.27	1.87
12	7.27	5.87	5.27	4.60	3.90	3.63	3.13	2.67
Mean	**5.87**	**5.19**	**4.18**	**3.68**	**3.21**	**2.84**	**2.49**	**2.20**
SD	**1.13**	**0.77**	**1.03**	**0.66**	**0.68**	**0.57**	**0.61**	**0.51**

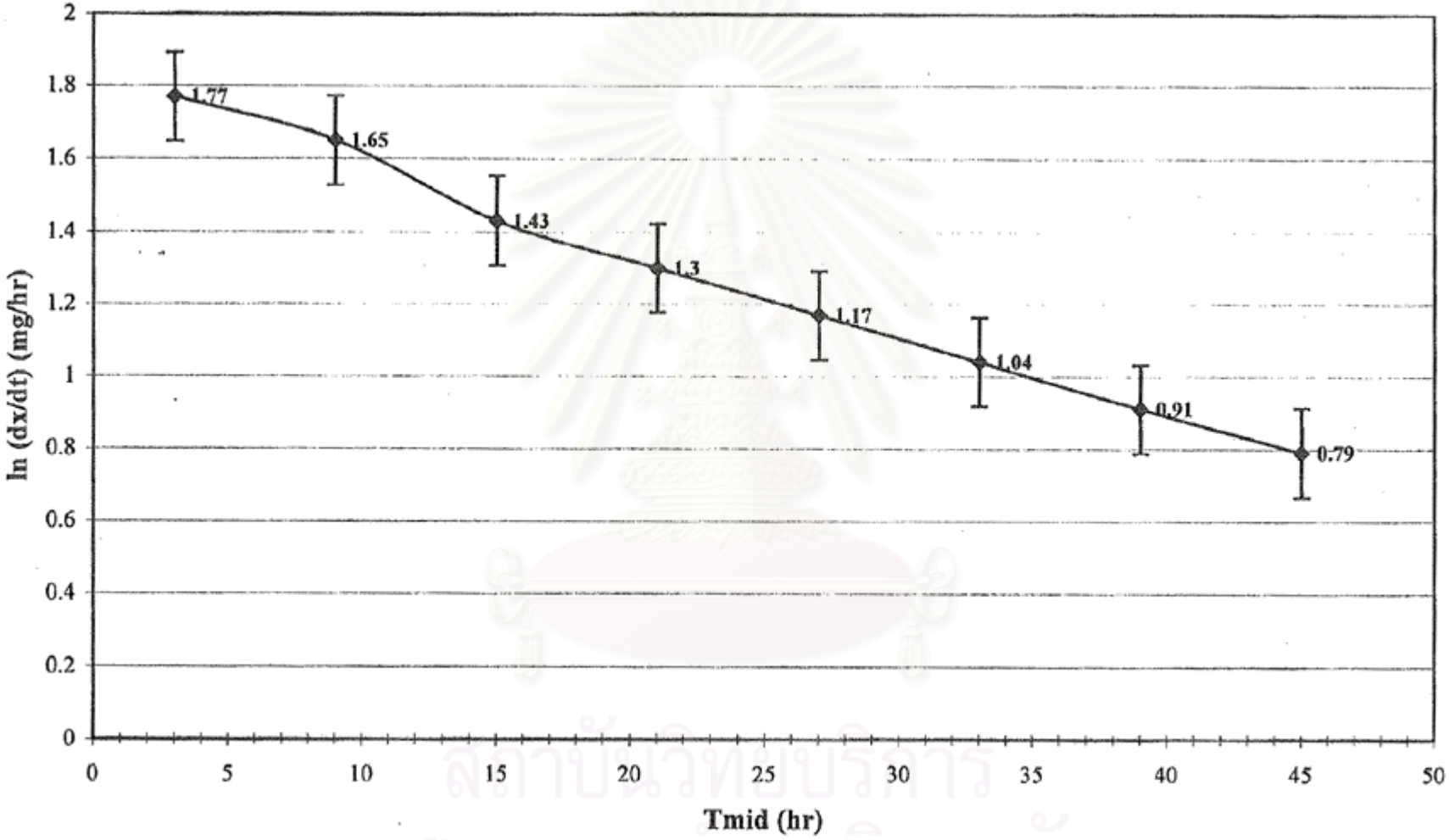


Figure 7. Dialysate excretion rate [In(dxd/dt)] versus midpoint time curve

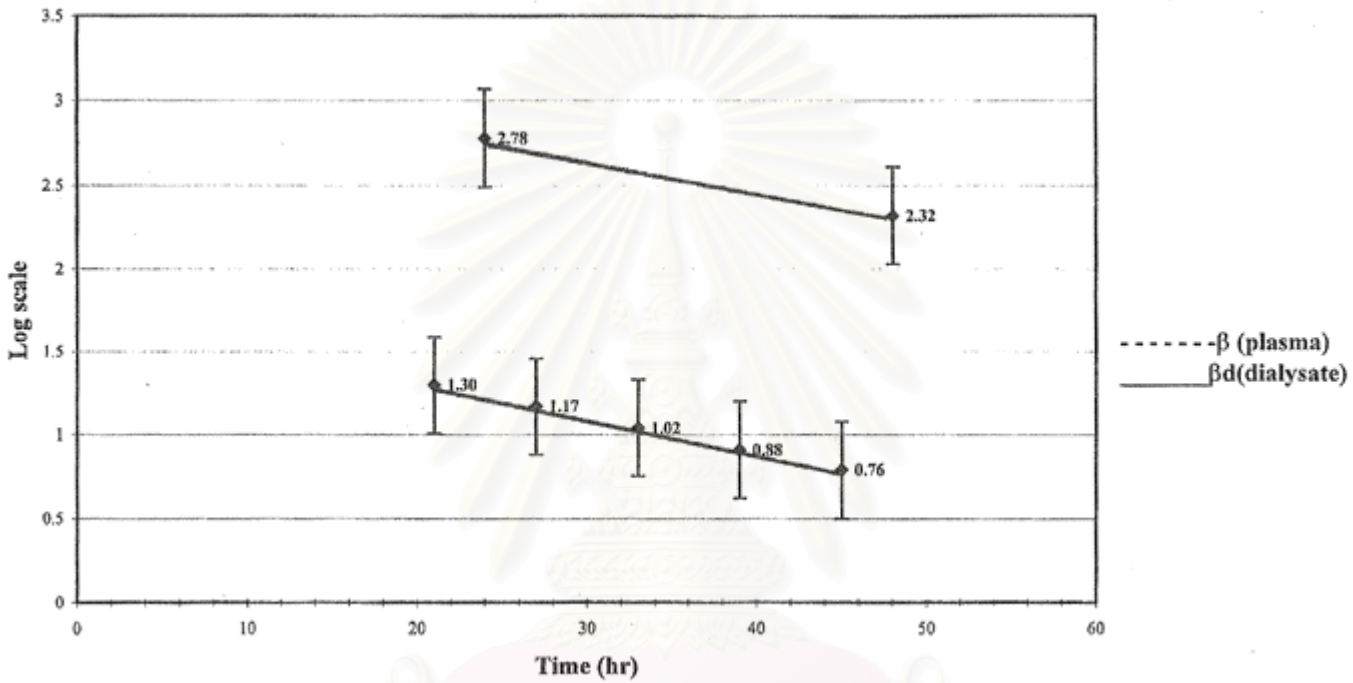


Figure 8. Amikacin concentration in plasma (In c_p^t) versus time curve during elimination phase

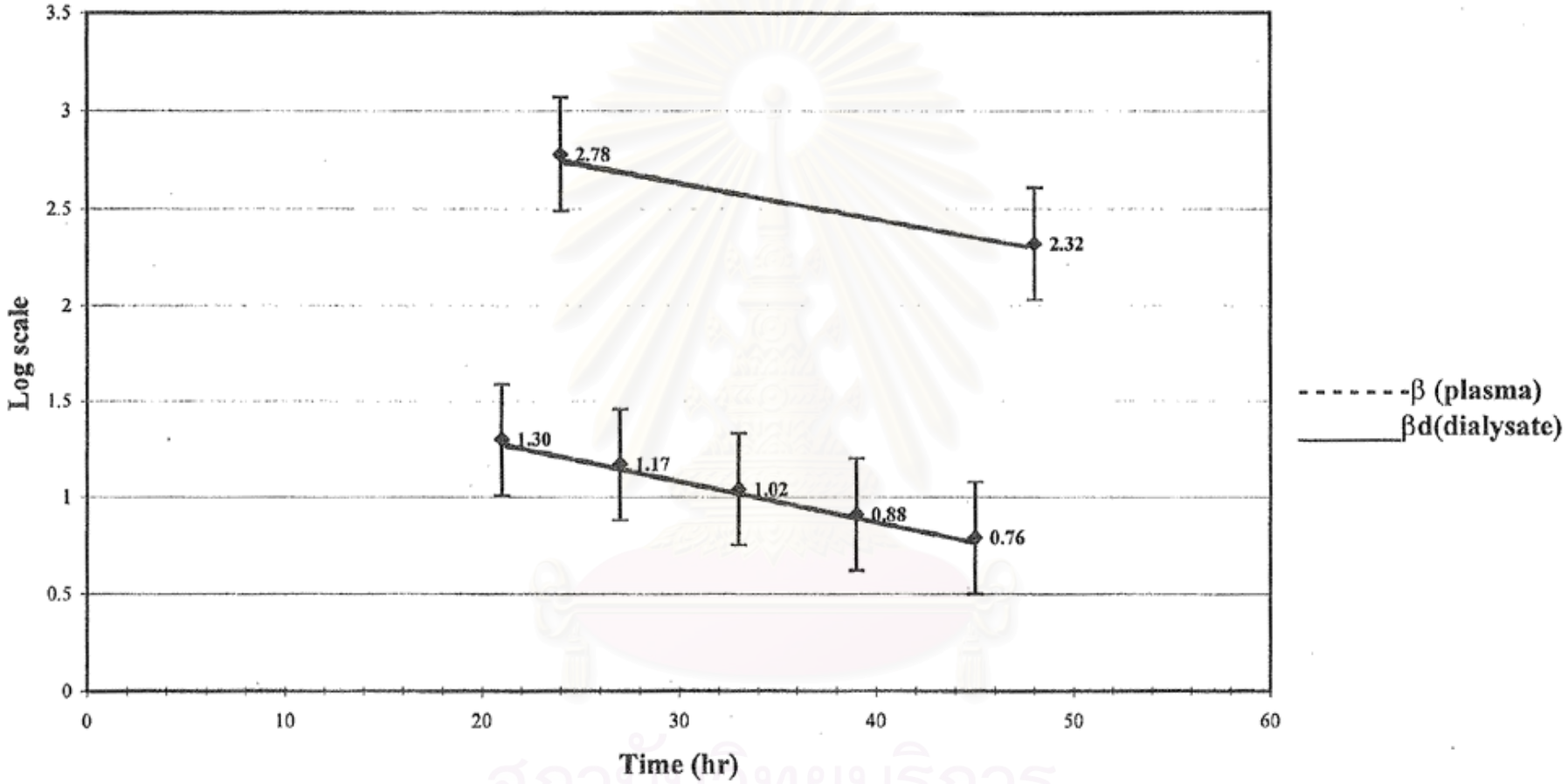


Figure 9. Comparison between plasma amikacin concentration versus time curve and In excretion rate in dialysate versus midpoint time curve during elimination phase.

Table 25. Comparison between elimination rate constant and half-life calculated from data of amikacin concentration in plasma and dialysate

Patient No.	β **(hr^{-1})**	**$T_{1/2\beta}$ = 0.693/β (hr)**	**βd (hr^{-1})**	**$T_{1/2\beta d}$ = 0.693/βd (hr)**
1	0.013	53.30	0.018	38.50
2	0.019	36.47	0.012	57.75
3	0.021	33.00	0.018	38.50
4	0.023	30.13	0.023	30.13
5	0.021	33.00	0.038	18.24
6	0.012	57.75	0.017	40.76
7	0.023	30.13	0.023	30.13
8	0.025	27.72	0.025	27.72
9	0.017	40.76	0.020	34.65
10	0.020	34.65	0.015	46.20
11	0.017	40.76	0.025	27.72
12	0.016	43.31	0.021	33.00
Mean	**0.019**	**38.41**	**0.021**	**35.27**
SD	**0.004**	**8.94**	**0.007**	**10.17**

β = elimination rate constant calculated from data of amikacin concentration in plasma (in the elimination phase)

βd = elimination rate constant calculated from data of amikacin concentration in dialysate (in the elimination phase)

******There were no statistical significant difference analyzed by paired t-test between either β and βd (P = 0.450) or $T_{1/2\beta}$ and $T_{1/2\beta d}$ (P = 0.377)

Table 26. Dialysate excretion rate constant, elimination rate constant and fraction of amikacin removed by CAPD

Patient No.	kd (hr^{-1})	βd (hr^{-1})	kd/βd (%)
1	0.008	0.018	44.44
2	0.007	0.012	58.33
3	0.011	0.018	61.11
4	0.010	0.023	43.48
5	0.013	0.038	34.21
6	0.008	0.017	47.06
7	0.014	0.023	60.87
8	0.013	0.025	52.00
9	0.012	0.020	60.00
10	0.011	0.015	73.33
11	0.012	0.025	48.00
12	0.014	0.021	66.67
Mean	**0.011**	**0.021**	**54.12**
SD	**0.002**	**0.007**	**10.68**

Table 27. Comparison of pharmacokinetic parameters of amikacin in dialysate between the patients in the PT group and non-PT group

Pharmacokinetic Parameters	PT group Mean ± SD	Non – PT group Mean ± SD	P - Value
kd (hr^{-1})	0.012 ± 0.002	0.010 ± 0.002	0.136
βd (hr^{-1})	0.021 ± 0.002	0.022 ± 0.009	0.847
β (hr^{-1})	0.019 ± 0.007	0.019 ± 0.004	0.935
Cl_{pd} (L/hr)	0.27 ± 0.003	0.18 ± 0.002	0.000
% kd / βd	58.27 ± 9.81	48.31 ± 11.20	0.149

CHAPTER V

DISCUSSION

This study found that majority of the 12 infected–CAPD patients were in elderly age and the major cause of ESRD was diabetic nephropathy which was consistent with the previous reports both in Thailand and foreign countries (33-34,55-56).

As shown in table 10, the mean value of sodium, chloride, bicarbonate, and calcium were in the normal range. The mean hemoglobin and hematocrit were lower than the normal range because of anemia complication caused by erythropoietin deficiency in ESRD patients (32). Normally ESRD patients have metabolic acidosis complication with the low serum bicarbonate concentration tends to stabilize at 10 to 20 mmol/L (31-32). For CAPD patients, lactate-containing dialysis solution has been used to provide the benefit effects on the correction of metabolic acidosis and the maintenance of acid-base balance because lactate is a source of bicarbonate in peritoneal dialysis solution (37). Therefore CAPD patients in this study had serum bicarbonate in the normal range. Almost all patients in this study had hyperphosphatemia secondary to hyperparathyroidism as common manifestation in ESRD patients

Another effect of performing CAPD is anorexia especially in CAPD-patients associated with peritonitis (57). This might be the cause of hypokalemia and low serum albumin level found in the patients of this study. Factor related to serum albumin in CAPD patients is dietary protein intake (57) and there was study found that diabetes mellitus and peritonitis were the leading factors related to low serum albumin(58). In addition, serum albumin and other nitrogenous waste product can be removed via CAPD which being removed increasingly in CAPD patients associated with peritonitis and contribution with anorexic condition of CAPD patients (57-58). As a result of all factors causing effect on serum albumin as mentioned above, the 12 infected CAPD patients in this study had low serum albumin level while their BUN were within the normal range. Therefore patients with this condition should be informed to take adequate dietary protein (1.2-1.5 g/kg/day) because low serum albumin level could be the strongest single predictor of decreased survival (35,57-58).The mortality in those CAPD patients who have a serum albumin of less than 3.5 g/dl is increased by 3.5 fold (35). As serum albumin increases, the mortality and morbidity decrease (35,57-58).

The incidence of peritonitis from this study was about 0.6 episodes per per year as shown in table 14.This incidence rate was lower than the other study (12) which found that the incidence of peritonitis was about 1.1-1.2 episodes per year.The reason might due in part to the small sample sizes and most of the patients have been on CAPD therapy for short period of time with the range of 1.1 - 3.0 years Besides, they might have good sanitary.

The C/S test found that 42.8% of the patients in the PT group was culture negative as shown in table 13 which was higher than the previous study which reported culture negative to be 2-20%. The reason could due in part to the sampling which was not taken from the first cloudy dialysate and the 10 ml of cloudy dialysate volume being inoculated to hemoculture bottles were too small (12). Another important cause for culture negative could be that the procedure of centrifugation of 50 ml of cloudy dialysate before inoculation it into hemoculture bottle did not perform (12).

As shown in table 13, Organism causing peritonitis found in this study was consistent with other studies(1,10,12) that gram positive bacteria was the major cause of peritonitis which *Staphylococcus aureus* was the most common pathogen and gram negative bacteria was the second cause of peritonitis which *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the two most common pathogens.

Clinical outcome were improved both in the PT and non-PT groups. The cure rate in both groups after receiving the antibiotics according to their C/S results were 100 %. However, in the first 48 hours using empirical treatment (amikacin IM along with cefazolin IP), WBC and PMNs were reduced significantly. This appearances did not occur due to efficacy of amikacin IM only but due to efficacy of combination between cefazolin IP and amikacin IM.

In the PT group, there was only one patient who had recurrent infection caused by *Pseudomonas aeruginosa* after receiving antibiotic treatment for two weeks. The first peritonitis in this patients was caused by *Staphylcoccus aureus*. Many clinicians suggest that at least two antibiotics with activity against pseudomonas will be necessary for treatmeant of the recurrent type of infection and one of these agents should be aminoglycoside (12). Therapy for pseudomonas peritonitis is recommended for three to four weeks (12). The effect of persistent gram negative, particularly pseudomonas on peritoneal membrane integrity over the long term could lead to loss of peritoneal transport function (12). However, the mechanism of this effect is still unclear, therefore, consideration of early catheter removal is important to preserve peritoneal function and avoid repeated longterm treatment with potentially toxic antibiotic such as aminoglycosides (12). However, in this study, the one patient with recurrent peritonitis caused by *Pseudomonas aeruginosa* had been cured with the

treatment of amikacin 25 mg and ceftazidime 250 mg continuously IP in each exchange for four weeks without catheter removal.

After patients received one dose of intramuscular amikacin 7.5 mg/kg , the mean peak plasma concentration equaled to 25.3 ± 3.2 mg/L which was in the therapeutic range (15-30 mg/L) and closed to peak plasma amikacin concentration of adults with normal renal function (38-39). However, this amikacin peak level obtained from IM administration was lower than the peak level obtained from IV administration which ranged from 30-45 mg/L (38).

In this study, blood samples after IM administration of amikacin were drawn at 1, 1.5, 2, 4 hours to find out the exact time to peak concentration. As shown in table 16, the results found that two patients had peak plasma amikacin concentration at 1.5 hours, six patients at 2 hours and four patients at 4 hours and the mean time to peak plasma concentration (Tpeak) was at 2.6 ± 1.0 hour which was approximately at 3 hours while blood samples at 3 hours had not been collected. In adult with normal renal function, peak plasma amikacin concentration should be achieved within 45 minutes to 2 hours (38-40). Compared with normal adults, almost all patients in this study had slower absorption rate since slower Tpeak (at 3 hours). This results might due to edematous condition of CAPD patients in this study (61).

Since renal function of ESRD patients have already been damaged ,so, nephrotoxicity evaluated from amikacin trough level would be less concerned while ototoxicity still required close monitoring because ESRD may predispose patients to more sustained plasma concentration of amikacin, resulting in high accumulation in the ear lead to ototoxicity (38-40). After single dose of amikacin had been administered , the trough level of amikacin should be less than 5 mg/L to reduce risk of ototoxicity and nephrotoxicity (39, 52-54). In this study, after patients received one dose of intramuscular amikacin 7.5 mg/kg , all of them had trough concentration of amikacin higher than 5 mg/L with the mean concentration equaled to 10.3 ± 1.7 mg/L which may cause ototoxicity .

For the non-PT group, they received only one dose of amikacin during three days of admission after that they were prescribed with oral antibiotics according to their C/S results. Therefore, the patients in the non-PT group were safe for risk of ototoxicity caused by long term use of amikacin. In the PT group, for replacing IM route of amikacin, they received the standard regimen of continuous amikacin IP 25 mg in each exchange according to Ad Hoc Advisory Committee on Peritonitis Management of International Society of Peritoneal Dialysis (ISPD 1996) (12) to reduce risk of ototoxicity along with continuous cefazolin IP 250 mg until C/S results were available. This study administered the patients with the continuous IP dose of amikacin since there had been studies (56,59) found that once-daily IP gentamicin

may not produce the desired therapeutic serum and dialysate concentration for effective treatment of peritonitis. The researcher expected that the results might be the same with once-daily IP of amikacin and recognized that CAPD patients associated with peritonitis should received the best treatment to cure peritonitis and to prevent septicemia . However, there has been no study investigated that whether standard regimen of once-daily or continuous IP dose of amikacin according to ISPD 1996 (12) is effective and safe for CAPD patients associated with peritonitis. Further study is required to answer this question .

The 12 infected-CAPD patients in this study showed the higher Vd (0.56 ± 0.11 L/kg) compared with normal adults (0.20 L/kg) and previously reported value for ESRD patients (0.29 L/kg) (39, 60). This results might be due to increasing of the fractional contribution of total body water (both extracellular and intracellular fluid) to total body weight in CAPD patients which might be caused by addition 2 liters of dialysis solution, ultrafiltration failure which occurred especially during peritonitis (61) and edematous condition of the patients.

In adults with normal renal function, 95-98 % of IM and IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours (38-40,60). The total body clearance of amikacin is occurred via renal clearance as the major pathway and non renal clearance as the minor pathway (less than 5 %). In normal adults, total body clearance as almost equal to renal clearance of amikacin is ranged between 90-120 ml/min and the plasma elimination half-life of amikacin is usually 2-3 hours (38-40,60). Therefore, in ESRD patients with markedly reduced renal function have very low renal clearance (total body clearance) of amikacin and half-life of amikacin in ESRD patients with no dialysis treatment was prolonged to approximately 28-80 hours (38-40).

As compared with normal adults, this study was consistent with other studies (27,38-40,60,62) that the mean total body clearance (10.73 $\pm$ 1.00 ml/min) of amikacin was decreased because of markedly reduced renal function in CAPD patients and the mean half-life was prolonged to 38.41 $\pm$ 8.94 hours which closed to other studies (27,62) which reported that half-life of amikacin in CAPD patients was approximately 45 hours. As described above, this result indicated that half-life of amikacin in CAPD patients was shorter than half-life in ESRD patients with no dialysis treatment .

USRDS indicate that infection is second to cardiovascular disease as the leading cause of death in ESRD patients, occurring in approximately 12 to 22 % of patients (63-64). Infection are also the leading cause of morbidity in CAPD patients (63). In CAPD patients, the potential infection sources as septicemia listed as secondary diagnosis were peritoneal catheter infection (12%), pneumonia (12%),

peritonitis (5%), urinary tract infection (8%), endocarditis (2%), and cellulitis and abscess of foot (2%) (63). Infection in CAPD cause high morbidity and mortality especially in patients with septicemia which had twice the risk of death compared with healthy CAPD patients (64).

Since amikacin had very low total body clearance with prolonged half-life which predisposed CAPD patients to high risk of ototoxicity. By using the mean pharmacokinetic parameters in plasma of this study (Vd,β) by using equation 5A,6A as described in appendix I, if CAPD patients have no choices for using other antibiotics and have infection such as tunnel infection, septicemia, urinary tract infection especially caused by *Pseudomonas aeruginosa* which is necessary to use intramuscular or intravenous route of amikacin in combination with third cephalosporin (i.e. ceftazidime), the appropriate amikacin dosage regimen might be able to be obtained by giving the usaual dose 7.5 mg/kg but extending the dosing interval to at least 72 hours in order to reduce the risk of ototoxicity or avoid using it when is not necessary .

After administering one dose of amikacin (7.5 mg/kg), only the first dialysate bag showed the mean peak concentration of amikacin which was above the therapeutic concentration (Ctargetd ≥ 16 mg/L). When the data was evaluated separately between the PT and non-PT group, it was found that amikacin concentration in the first and the second dialysate bag of the PT group showed the peak concentration which were higher than 16 mg/L and even at 4 hours of the first dialysate bag, concentration of amikacin reached closely to Ctargetd. While amikacin concentration in the first dialysate bag of the non-PT group did not reach Ctargetd. These results suggested that CAPD patients with peritonitis may produce desired therapeutic concentration within four to six hours after the first dose was given as shown in table 22 which was consistent with other studies (27,42). However, the CAPD patients with no peritonitis may not produce desired therapeutic concentration in dialysate.

Since amikacin exhibit concentration dependent-killing gram negative bacilli followed by a prolonged postantibiotic effect which means that the higher the peak the more effective in eradicating the pathogen organism which depended on the time duration pathogen exposed to the high level of amikacin (39). The results from this study showed that the time duration that pathogen organism exposed to high enough amikacin concentration was very short which may result in low effectiveness in eradicating gram negative bacilli.

Although the benefits of administering the drug by IM route are known,i.e., patients can receive the service of treatment near their home in outpatient clinic in remote area which can decrease the risk of contamination from the process of adding

antibiotic into dialysate bag by inexperience nurses and early therapeutic intervention. However, those results as described before, indicated that intramuscular administration of amikacin with the dose of 7.5 mg/kg every 48 hour for treatment of peritonitis in CAPD patients might not be an appropriate dosage regimen since the concentration in the dialysate bag were mostly too low resulted in ineffective eradicating of pathogen organism, at the same time, the trough concentration in plasma was too high resulting in high risk of ototoxicity. Increasing dose of amikacin in order to increasing peak dialysate concentration could not be performed because it may lead to higher trough concentration in plasma resulted in higher risk of ototoxicity.

Therefore, amikacin administered by intraperitoneal route for treatment of peritonitis is more appropriate compared with IM route because IP route give higher dialysate concentrations above the MIC with prolonged time duration which causative pathogen exposed and being eradicated efficiently. However, IM treatment may be beneficial in giving only the first dose to the patients in remote area where no experienced personels are available.

As shown in table 23, the average peritoneal amikacin clearance or amikacin clearance by CAPD (Clpd) was calculated by dividing the total amount of amikacin in dialysate of all eight dwell periods (from time zero to 48 hours) by AUC during the time zero to 48 hours (42). However, Clpd can be calculated by dividing the total amount of amikacin in dialysate of one or more dwell periods by AUC during the same period (42). It was found that amikacin concentration in dialysate of patients in PT group was statistical significantly higher than amikacin concentration in the non-PT group ($P = 0.002$) as a result of the inflammation which increase permeability of amikacin movement across peritoneal membrane (42-44). This result was consistent with the higher Clpd in the PT group as compared to the non-PT group with statistical significance ($P = 0.000$) as shown in table 27. Besides the inflammation induced change in peritoneal permeability. Factors that influence amikacin clearance via CAPD include its physicochemical properties such as being a polar basic compound, its water solubility and its pharmacokinetic parameters such as very low protein binding(< 5 %) and low volume of distribution (42-44).

The mean fraction of amikacin dose eliminated by CAPD (%kd/βd) as shown in table 26 was 54.12 ± 10.68 % which was closed to the prior study (27) which concluded that approximately 50 % of amikacin was excreted by CAPD. This implicated that the other of 50 % amikacin dose could be excreted by the residual function of renal and/or by non-renal clearance.

This study found that there were relationship between amikacin concentration in plasma and dialysate since there were no significant difference in the elimination rate constant either derived from the amikacin concentrations in plasma (β) or derived from the amikacin concentrations in dialysate (βd). The result also showed that there were no significant difference in elimination rate constant (βd) between the PT group and the non-PT group,so, the relationship of amikacin concentration in plasma and dialysate between the PT group and the non-PT group were not different. This result could be an advantage since it could be applied to determine the amikacin concentration in plasma by using the pharmacokinetic parameters obtained from amikacin concentration in dialysate or vice versa.

CHAPTER VI

CONCLUSION

1. Of the 12 infected-CAPD patients, there were eight men (66.7%) and four women (33.3%).Seven patients had peritonitis (PT group : 58.3%) which only one had peritonitis with exit-site infection. Five patients had catheter-related infection (Non-PT group : 41.7%) which three of them had exit site infection, one of them had tunnel infection and the remaining one had both exit site and tunnel infection. Among the 12 infected-CAPD patients, five of them had infection caused by gram positive bacteria (41.7%), four of them had infection caused by gram negative bacteria (33.3%) and the remaining three had negative culture (25.0%). The most common gram positive bacteria found as the causative pathogen was *Staphylococcus aureus* .

2. Besides either cefazolin IP or oral cloxacillin were administered in both PT and non-PT group, the patients also received one dose of amikacin (7.5 mg/kg) administered by intramuscular route. All patients had peak plasma concentration of amikacin in the therapeutic range with the mean peak concentration equaled to 25.3 ± 3.2 mg/L and the mean time to peak was at 2.6 ± 1.0 hour. The trough plasma concentration of amikacin at 48 hours in all patients were higher than 5 mg/L with the mean concentration equaled to 10.3 ± 1.7 mg/L which may cause ototoxicity.

3. The plasma amikacin concentration time curve was best described by two-compartment model with the first-order absorption which the equation was

$$Cp^t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat}$$

The equation which derived from the mean plasma concentration of all the 12 infected-CAPD patients was :

$$Cp^t = (-0.13e^{-0.020t} + 25.45e^{-0.019t}) - 25.32e^{-1.742t}$$

The equation derived here could be used to calculate the amikacin concentration at any time with good accuracy. Correlation between Cpmeasured and Cpcalculated which calculated from equation above was 0.966.

4. The mean absorption rate (ka), distribution rate (α) and elimination rate (β) constant were 1.326 ± 1.820 hr^{-1}, 0.299 ± 0.280 hr^{-1}, 0.019 ± 0.004 hr^{-1} respectively.The mean area under plasma concentration time curve (AUC) from time zero to 48 hours of amikacin administered intramuscularly was 784.38 ± 71.13 mg/l.hr. The mean volume of distribution (Vd) was 35.99 ± 9.84 L.(0.56 ± 0.11 L/kg) The mean total body clearance was 0.64 ± 0.06 L/hr (10.73 ml/min) with the mean half-life equaled to 38.41 ± 8.94 hour.

5. Amikacin concentration in dialysate normally showed the peak concentration every six hours at the end of each dialysate bag and the maximum peak dialysate was found at the end of the first dialysate bag with the mean equaled to 17.6 ± 3.4 mg/ L which was slightly higher than the therapeutic concentration (Ctargetd ≥ 16 mg/L). When considering separately between the patients in PT and non-PT groups, the result showed that even though administration of amikacin by intramuscular route in CAPD patients with peritonitis may produce the desired therapeutic concentration within four to six hours after the first dose was given but these desired concentrations were found only in the first and the second dialysate bags. At the same time, in the non-PT group, the amikacin concentrations in dialysate even the peak concentration at the end of the first dialysate bag were never reached Ctargetd. Therefore intramuscular administration of amikacin with the dose of 7.5 mg/kg every 48 hour for treatment of peritonitis in CAPD patients might not be an appropriate dosage regimen since the concentration in the dialysate bag were most of the time too low resulted in ineffective eradicating pathogen organism, at the same time, the trough concentration in plasma was too high resulting in high risk of ototoxicity.

6. The mean averaged peritoneal amikacin clearance or amikacin clearance by CAPD was 0.23 ± 0.05 L/hr (3.90 ± 0.87 ml/min) . Approximately 54 % of the dose of amikacin was removed by CAPD.Comparison between the PT and non-PT group showed that amikacin concentration and amikacin clearance in dialysate of the patients in PT group were higher than patients in non-PT group.

7. There were relationships between amikacin concentrations in plasma and dialysate. Pharmacokinetic parameters of amikacin (elimination rate constant ,β) obtained from the samples collected from plasma and dialysate were the same. This result could bring advantage for application in clinical practice since amikacin concentrations in plasma could be determined by using data of amikacin concentration in dialysate.

8. If CAPD patients got infection such as tunnel infection, septicemia, urinary tract infection especially those caused by *Pseudomonas aeruginosa* which is necessary to use intramuscular or intravenous route of amikacin in combination with third generation cephalosporin (i.e. ceftazidime), the more appropriate dosage regimen should be the one that extending the dosing interval to be at least 72 hours in order to reduce risk of ototoxicity. In the case of peritonitis, the intraperitoneal route should be more appropriate.

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APPENDIX

APPENDIX I

APPENDIX I

1. For two compartment model with absorption part of IM administration, the plasma concentration (C) at any time (t) can be described by (65,68) :

$$C_t = (Ge^{-\alpha t} + Be^{-\beta t}) - Ae^{-kat} \quad \textbf{- Equation 1A}$$

Equation 3 is the sum of two linear components representing distribution ($Ge^{-\alpha t}$) and elimination phase ($Be^{-\beta t}$) abstracted by linear component of absorption phase (Ae^{-kat}). In each case, A or G or B was represented for y-intercept of each linear component.

ka = absorption rate constant (hr^{-1})
α = distribution rate constant (hr^{-1})
β = elimination rate constant (hr^{-1})

Computerized program as RSTRIP II version 2.2 is used for fitting equation 3 for individual patient by stripping method. RSTRIP II version 2.2 give the result in value of A, G, B, ka, α and β by entering data of amikacin plasma concentration at every sampling time of individual patient .

2. Calculating for pharmacokinetic parameters in plasma of individual patient

2.1 Area under the plasma concentration versus time curve or AUC can be calculated by a method of "trapezoidal rule"

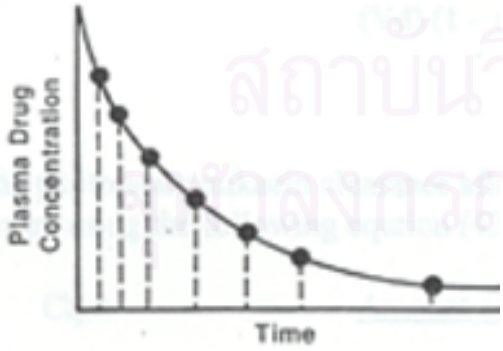
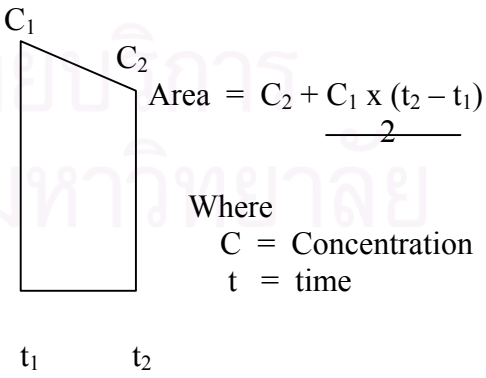


Figure 1



$$\text{Area} = \frac{C_2 + C_1}{2} \times (t_2 - t_1)$$

Where
C = Concentration
t = time

Figure 2

If a line is drawn vertically to the x-axis from each measured concentration, a number of smaller areas is described (Figure 2). The area of each shape can be estimated by drawing a straight line between adjacent concentration and calculating the area of the resulting trapezoid (Figure 2). If the time between measurements is small, only a slight error results. These smaller areas can be summed to estimate the AUC (66).

2.2 Volume of distribution (Vd) can be calculated by (65):

$$Vd = \frac{dose}{AUC \times \beta}$$ **- Equation 2A**

2.3 Total body clearance (TBCl) can be calculated by (65-67):

$$TBCl = Vd \times \beta$$ **- Equation 3A**

2.4 Half-life ($T_{1/2}$) can be calculated by (65-67):

$$T_{1/2} = \frac{0.693}{\beta}$$ **- Equation 4A**

3. Equation for adjusting appropriate dose or dosing interval at steady state of amikacin in plasma concentration are shown as following (67):

$$Dose = \frac{(C_{pss}t)\,(Vd)\,(1 - e^{-\beta\tau})}{e^{-\beta t}}$$ **- Equation 5A**

C_{pss} = plasma concentration at steady state

$$C_{pss} = \frac{Dose \times e^{-\beta t}}{(Vd)\,(1 - e^{-\beta\tau})}$$ **- Equation 6A**

4. The peritoneal amikacin clearance after IM administration can be calculated from 0 to 48 hours by using the following eqution (42) :

$$Clpd = \frac{\text{Amount of drug in dialysate from 0 to 48 hours}}{AUC_{0 \rightarrow 48}}$$

$$Clpd = \frac{Xdia^{\,t = 0 \rightarrow 48}}{AUC_{0 \rightarrow 48}}$$ **- Equation 7A**

For example : data from patient no. 1

$$Xdia^{t=0\rightarrow 48} = (14.6 \times 2) + (13.2 \times 2) + (11.1 \times 2) + (9.2 \times 2) + (9.5 \times 2) + (6.3 \times 2) + (4.9 \times 2) + (5.2 \times 2) = 148 \text{ mg}$$

$$AUC_{0\rightarrow 48} = 874.11 \text{ mg/L.hr}$$

$$Clpd = \frac{148}{874.11} = 0.17 \text{ L/hr}$$

APPENDIX II

APPENDIX II

Comparison between Cpmeasured and Cpcalculated of each patients

Table 1. Comparison between Cpmeasured and Cpcalculated of patient no. 1

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	20.5	20.3	99.02
1	24.2	24.6	101.65
1.5	26.1	26.2	100.38
2	27.6	26.6	96.38
4	23.9	22.1	92.47
6	22.5	27.7	96.44
12	19.2	18.6	96.88
24	18.3	16.2	88.52
48	14.2	12.6	88.73
Mean			**95.61**
SD			**4.49**

r = 0.986 **CV = 4.69 %**

Table 2. Comparison between Cpmeasured and Cpcalculated of patient no. 2

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	12.7	19.5	153.54
1	23.2	24.2	104.31
1.5	25.0	24.3	97.20
2	24.1	24.3	100.83
4	23.7	23.8	100.42
6	23.3	22.8	97.85
12	20.5	20.7	100.98
24	17.2	16.5	95.93
48	10.0	10.4	104.00
Mean			**106.12**
SD			**16.98**

r = 0.905 **CV = 16.00 %**

Table 3. Comparison between Cpmeasured and Cpcalculated of patient no. 3

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	5.9	10.2	172.88
1	15.4	14.2	92.21
1.5	20.2	22.6	111.88
2	24.6	25.3	102.85
4	30.5	28.1	92.13
6	26.8	27.2	101.49
12	22.6	24.1	106.64
24	19.3	18.8	97.41
48	11.7	11.4	97.44
Mean			**108.32**
SD			**23.62**

r = 0.969 **CV = 21.80 %**

Table 4. Comparison between Cpmeasured and Cpcalculated of patient no. 4

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	9.3	10.25	110.22
1	15.6	16.1	103.21
1.5	21.1	19.6	92.89
2	22.4	21.5	95.98
4	24.0	23.2	96.67
6	23.0	22.5	97.83
12	19.2	16.6	102.08
24	14.6	14.8	101.37
48	8.8	8.5	96.59
Mean			**99.65**
SD			**4.87**

r = 0.994 **CV = 4.89 %**

Table 5. Comparison between Cpmeasured and Cpcalculated of patient no. 5

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	12.1	16.5	136.36
1	22.9	22.9	100.00
1.5	23.7	24.2	102.11
2	25.6	24.3	94.92
4	24.4	23.3	95.49
6	23.5	22.2	94.47
12	19.8	19.7	99.49
24	15.3	15.4	100.65
48	9.5	9.4	98.95
Mean			**102.49**
SD			**12.24**

r = 0.961 **CV = 11.95 %**

Table 6 . Comparison between Cpmeasured and Cpcalculated of patient no. 6

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	14.8	14.8	100.00
1	17.0	17.0	100.00
1.5	17.6	17.5	99.43
2	18.7	17.6	94.12
4	17.4	17.3	99.43
6	16.5	16.9	102.42
12	15.0	15.7	104.67
24	13.5	13.6	100.74
48	10.1	10.5	103.96
Mean			**100.53**
SD			**2.92**

r = 0.985 **CV = 2.90 %**

Table 7. Comparison between Cpmeasured and Cpcalculated of patient no. 7

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	9.3	14.8	159.14
1	17.4	18.7	107.47
1.5	19.3	19.4	100.52
2	19.8	19.9	100.51
4	23.1	20.5	88.74
6	21.8	20.2	92.66
12	18.4	17.9	97.28
24	14.3	13.1	91.61
48	8.7	8.4	96.55
Mean			**103.83**
SD			**20.25**

r = 0.901 **CV = 19.51 %**

Table 8. Comparison between Cpmeasured and Cpcalculated of patient no. 8

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	21.0	20.9	99.52
1	23.4	25.2	107.69
1.5	25.4	24.9	98.03
2	27.0	25.3	93.70
4	24.0	24.8	103.33
6	23.1	23.7	102.60
12	22.2	20.5	92.34
24	16.3	15.2	93.25
48	7.4	8.4	113.51
Mean			**100.44**
SD			**6.71**

r = 0.978 **CV = 6.68 %**

Table 9. Comparison between Cpmeasured and Cpcalculated of patient no. 9

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	8.9	9.2	103.37
1	12.5	13.3	106.40
1.5	13.6	15.3	112.50
2	19.3	17.1	88.60
4	21.3	20.8	97.65
6	20.0	20.3	101.50
12	18.7	19.2	102.67
24	16.4	15.6	95.12
48	9.8	10.3	105.10
Mean			**101.44**
SD			**6.54**

r = 0.972 **CV = 6.44 %**

Table 10. Comparison between Cpmeasured and Cpcalculated of patient no. 10

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	10.4	14.2	136.54
1	18.6	20.8	111.83
1.5	23.0	23.3	101.30
2	24.3	24.2	99.59
4	24.1	24.1	100.00
6	23.5	23.2	98.72
12	20.5	20.6	100.49
24	16.1	16.2	100.62
48	10.0	10.1	101.00
Mean			**105.57**
SD			**11.55**

r = 0.973 **CV = 10.94 %**

Table 11. Comparison between Cpmeasured and Cpcalculated of patient no. 11

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	21.8	21.8	100.00
1	26.1	26.1	100.00
1.5	29.3	27.5	93.86
2	28.5	27.8	97.54
4	25.3	26.1	103.16
6	24.6	24.4	99.19
12	21.0	20.9	99.52
24	16.7	16.8	100.60
48	11.2	11.2	100.00
Mean			**99.32**
SD			**2.38**

r = 0.993 **CV = 2.39 %**

Table 12. Comparison between Cpmeasured and Cpcalculated of patient no. 12

Time (hr)	Cpmeasured (mg/L)	Cpcalculated (mg/L)	Ccal x 100 (%) Cmea
0.5	21.6	21.7	100.46
1	26.6	26.2	98.50
1.5	27.0	27.3	101.11
2	27.6	27.2	98.55
4	25.1	25.1	100.00
6	23.1	23.5	101.73
12	20.8	20.6	99.04
24	16.0	17.2	107.50
48	12.4	11.8	95.16
Mean			**100.22**
SD			**3.14**

r = 0.994 **CV = 3.14 %**

APPENDIX III

APPENDIX III

Demographic data of all 12 infected-CAPD patients

Patient No. 1

Sex : male **Age :** 38 years **Weight :** 64 kgs
Cause of ESRD : Chronic Glomerulonephritis
Co-morbid disease : HTN
Duration of CAPD therapy : 3 months
Type of infection : Exit-site with tunnel infection
Causative pathogen : *Staphylococcus aureus*
Past history of incidence of peritonitis : None
Empirical treatment : Oral cloxacillin 500 mg 1x4 ac with amikacin IM 500 mg q 48 hr

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
12.5	39	6.1	857.5	144.5	3.0

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
103	27.3	2.12	1.38	53	28

Patient No. 2

Sex : female **Age :** 61 years **Weight :** 61 kgs
Cause of ESRD : Diabetic Nephropathy
Co-morbid disease : HTN, DM, Dyslipidemia
Duration of CAPD therapy : 2.1 years
Type of infection : Tunnel infection
Causative pathogen : *Escherichia coli*
Past history of incidence of peritonitis : None
Empirical treatment : Oral cloxacillin 500 mg 1x4 ac with amikacin IM 500 mg q 48 hr

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
9.5	27	4.1	857	148	4.0

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
104.5	26.5	2.46	2.21	80	43

Patient No. 3

Sex : female **Age :** 68 years **Weight :** 60 kgs
Cause of ESRD : Unknown cause
Co-morbid disease : HTN, DM
Duration of CAPD therapy : 13 years
Type of infection : Exit-site infection
Causative pathogen : *Coagulase negative staphylococci*
Past history of incidence of peritonitis : 0.7 episodes/year
Empirical treatment : Oral cloxacillin 500 mg 1x4 ac with amikacin IM 500 mg q 48 hr

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
10.4	7.7	17.7	804.4	145	3.5

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
103	28	2.42	0.8	84	39

Patient No. 4

Sex : male **Age :** 74 years **Weight :** 65 kgs
Cause of ESRD : Chronic Tubulointerstitial Nephritis
Co-morbid disease : HTN, IHD, Dyslipidemia
Duration of CAPD therapy : 4 years
Type of infection : Exit-site infection
Causative pathogen : *Coagulase negative staphylococci*
Past history of incidence of peritonitis : 0.25 episodes/year
Empirical treatment : Oral cloxacillin 500 mg 1x4 ac with amikacin IM 500 mg q 48 hr

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
9.5	29	4.0	780	136	2.92

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
98.3	29.1	2.20	2.0	54	29

Patient No. 5

Sex : male **Age :** 48 years **Weight :** 71 kgs
Cause of ESRD : HTN
Co-morbid disease : HTN, Dyslipidemia
Duration of CAPD therapy : 6.2 years
Type of infection : Exit-site infection
Causative pathogen : *Pseudomonas aeruginosa*
Past history of incidence of peritonitis : 0.6 episodes/year
Empirical treatment : Oral cloxacillin 500 mg 1x4 ac with amikacin IM 500 mg q 48 hr

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
9.6	29	4.2	1207	134.6	2.81

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
98	26.7	3.36	2.0	67	41

Patient No. 6

Sex : male **Age :** 62 years **Weight :** 93 kgs
Cause of ESRD : Diabetic Nephropathy
Co-morbid disease : HTN, DM, IHD, Dyslipidemia
Duration of CAPD therapy : 1.8 years
Type of infection : Peritonitis
Causative pathogen : *Culture negative*
Past history of incidence of peritonitis : 1.1 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
10.5	37	6.4	655	138.5	2.88

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
95.9	29.8	2.34	0.97	48	22

Patient No. 7

Sex : male **Age :** 55 years **Weight :** 70 kgs
Cause of ESRD : Diabetic Nephropathy
Co-morbid disease : HTN, DM, IHD, Dyslipidemia, Gout, CHF
Duration of CAPD therapy : 1.3 years
Type of infection : Peritonitis
Causative pathogen : *Staphylococcus aureus*
Past history of incidence of peritonitis : 0.7 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
8.9	28	9.8	914	135.5	4.25

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
100.5	22.8	2.32	2.59	69	39

Patient No. 8

Sex : male **Age :** 30 years **Weight :** 56 kgs
Cause of ESRD : Chronic Tubulointerstitial Nephritis
Co-morbid disease : HTN, TB
Duration of CAPD therapy : 1.2 years
Type of infection : Peritonitis
Causative pathogen : Culture negative
Past history of incidence of peritonitis : 0.8 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
9.8	29	11.7	1091	138.7	4.43

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
106.4	22.7	2.17	2.06	42	22

Patient No. 9

Sex : female **Age :** 45 years **Weight :** 70 kgs
Cause of ESRD : Unknown cause
Co-morbid disease : HTN, DM
Duration of CAPD therapy : 2.1 years
Type of infection : Peritonitis with exit site infection
Causative pathogen : *Klebsiella peumoniae* and *Enterobacter cloaceae*
Past history of incidence of peritonitis : 0.5 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
10.2	30.5	21.5	670	139.7	4.1

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
103.3	29.3	2.46	1.63	50	32

Patient No. 10

Sex : female **Age :** 59 years **Weight :** 55 kgs
Cause of ESRD : Diabetic Nephropathy
Co-morbid disease : HTN, DM
Duration of CAPD therapy : 2.5 years
Type of infection : Peritonitis
Causative pathogen : *Staphylococcus aureus*
Past history of incidence of peritonitis : 0.4 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
11.2	30	3.8	616	135	2.9

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
100	29	2.19	0.97	63	31

Patient No. 11

Sex : male **Age :** 82 years **Weight :** 55 kgs
Cause of ESRD : HTN
Co-morbid disease : HTN
Duration of CAPD therapy : 4 months
Type of infection : Peritonitis
Causative pathogen : Culture negative
Past history of incidence of peritonitis : None
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
11.5	33	4.9	731	144	2.9

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
102.6	28.1	2.32	1.18	60	35

Patient No. 12

Sex : male **Age :** 61 years **Weight :** 52 kgs
Cause of ESRD : HTN
Co-morbid disease : HTN
Duration of CAPD therapy : 8 years
Type of infection : Peritonitis
Causative pathogen : Acinetobacter baumannii
Past history of incidence of peritonitis : 0.8 episodes/year
Empirical treatment : cephazolin IP 1 g/2L for the first bag and 250 mg/2L for the subsequent bags with one dose of amikacin IM 500 mg within 48 hr then continuous amikacin IP 25 mg/2L in each dialysate bag

Laboratory data

Hb (g/dl)	Hct (%)	BUN (mmol/L)	Cr (μmol/L)	Na (mmol/L)	K (mmol/L)
9.3	27	5.5	1153	133.5	3.5

Cl (mmol/L)	CO_2 (mmol/L)	Ca (mmol/L)	P (mmol/L)	TP (g/dl)	Alb (g/dl)
98	28	24.5	1.34	62	36

VITAE

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