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CORRELATION BETWEEN AMIKACIN AND CEFTAZIDIME PHARMACOKINETIC PARAMETERS

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วัตถุประสงค์: ยาเซฟเทซิดิม และยาอะมิเคซินมักใช้ร่วมกันเพื่อรักษาโรคติดเชื้อแบคทีเรียแกรมลบรูปแท่ง ยาทั้งสองชนิดนี้มีคุณสมบัติทางเคมีกายภาพคล้ายกัน จึงมีความเป็นไปได้ว่าค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาทั้งสองชนิดนี้จะมีความสัมพันธ์กัน ดังนั้นจึงทำการศึกษาเพื่อทดสอบสมมุติฐานนี้ ตลอดจนสร้างสมการเพื่อทำนายค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของกันและกันระหว่างยาทั้งสองชนิดนี้

วิธีการศึกษา: เป็นการศึกษาเชิงสังเกตแบบไปข้างหน้าในผู้ป่วยโรคติดเชื้อ 19 คนซึ่งนอนรักษาตัวที่โรงพยาบาลพระมงกุฎเกล้า และได้รับยาเซฟเทซิดิมร่วมกับยาอะมิเคซินเพื่อรักษาโรคติดเชื้อ ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาทั้ง 2 ชนิด คำนวณจากระดับยา 2 จุดที่ได้จากผู้ป่วยเมื่อระดับคงที่ นำค่าพารามิเตอร์ที่ได้มาทดสอบหาความสัมพันธ์และหาสมการสำหรับใช้ทำนายค่าพารามิเตอร์ของกันและกันโดยการวิเคราะห์ความถดถอย

ผลการศึกษา: ค่าการขจัดยา (Cl) ค่าคงที่ในการขจัดยา (K_e) และค่าครึ่งชีวิต ($t_{1/2}$) ของยาเซฟเทซิดิมและยาอะมิเคซิน มีความสัมพันธ์เชิงอย่างมีนัยสำคัญ โดยค่าสัมประสิทธ์สหสัมพันธ์ (r) ของ Cl เท่ากับ 0.966 ของ K_e เท่ากับ 0.942 และของ $t_{1/2}$ เท่ากับ 0.891 ความสัมพันธ์ระหว่าง Cl ของยาทั้ง 2 ชนิดมีค่าสูงกว่าความสัมพันธ์ระหว่าง Cl ของยาแต่ละชนิดกับ Cl_{cr} พบความสัมพันธ์ระดับปานกลางสำหรับค่าปริมาตรการกระจายยา (ลิตร/กก) ระหว่างยาทั้ง 2 ชนิด (r เท่ากับ 0.671)

สรุปผลการศึกษา: Cl K_e และ $t_{1/2}$ ของยาเซฟเทซิดิมและ ยาอะมิเคซินมีความสัมพันธ์กันอย่างสูง และสามารถนำค่า Cl K_e และ $t_{1/2}$ ของยาอะมิเคซินมาทำนายค่าพารามิเตอร์ดังกล่าวของยาเซฟเทซิดิมได้ (หรือ ทำนายในทางกลับกัน) วิธีนี้จะช่วยเพิ่มความสะดวกในการกำหนดขนาดยาเซฟเทซิดิมในผู้ป่วยแต่ละรายอย่างเหมาะสมเพื่อให้ได้ระดับยาที่ให้ผลการรักษาสูงสุดและลดอัตราการเกิดเชื้อแบคทีเรียที่ดื้อต่อยาเซฟเทซิดิม

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

สาขาวิชา.....เภสัชกรรมคลินิก..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

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KEY WORD: PHARMACOKINETIC PARAMETER / CEFTAZIDIME / AMIKACIN / CORRELATION

SAM-ANG KIATJAROENSIN: CORRELATION BETWEEN AMIKACIN AND CEFTAZIDIME PHARMACOKINETIC PARAMETERS. THESIS ADVISOR: ASSOC. PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D., THESIS COADVISOR : DANABHAND PHIBOONBANAKIT, M.D., 97 pp. ISBN 974-14-2531-7.

Aim: Ceftazidime and amikacin are usually prescribed together for the treatment of suspected or documented gram-negative bacilli infection. Similar physicochemical properties of ceftazidime and amikacin may contribute to good relationship of their pharmacokinetic parameters. This study was conducted to prove this hypothesis and create predictive pharmacokinetic parameter equations for each other.

Method: Prospective observative pharmacokinetic study was performed in nineteen patients who received ceftazidime and amikacin as part of therapy at Phramongkutklao Hospital. Two plasma concentrations at steady state of both antibiotics were used for calculating the pharmacokinetic parameters. Regression analyses were performed to determine a correlation and predictive equation between ceftazidime and amikacin pharmacokinetic parameters.

Results: Regression analysis showed a significant linear with high correlation between total drug clearance (Cl), elimination rate constant (K_e) and elimination half life ($t_{1/2}$) of ceftazidime and amikacin (r = 0.966, 0.942, 0.891 for Cl, K_e and $t_{1/2}$, respectively). The correlation between clearance of amikacin and ceftazidime was better than the correlation between either drug clearance and creatinine clearance. A fair correlation was found between the volume of distribution (L/kg) of the two drugs (r = 0.671).

Conclusion: A high correlation between pharmacokinetic parameters of ceftazidime and amikacin in this study indicated that ceftazidime pharmacokinetic parameters could be accurately predicted from those of amikacin and vice versa. This will help in modification of drug dosage regimen for individual patient in order to maximize therapeutic effect and minimize antimicrobial-resistant bacteria.

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Field of study...Clinical Pharmacy...Advisor's signature.....Duangchit Panomvana.....
Academic year .....2006 .....Co-advisor's signature.....Danabhand Phiboonbanakit.....

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ABBREVIATIONS

τ	Dosing interval
AUC	Area under the concentration-time curve
amk	Amikacin
BMI	Body mass index
°C	Celsius
CAPD	Continuous Ambulatory Peritoneal Dialysis
Cl	Clearance
CLSI	Clinical and laboratory standards institute
Cl_{cr}	Creatinine clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
C_t	Concentration of drug at t
ctz	Ceftazidime
CV	Coefficient of variation
ESBL	Extended spectrum bata-lactamase
F	Bioavailability factor
FPIA	Fluorescence polarization immunoassay
g	Gram
GFR	Glomerular filtration rate
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
hr	Hour
IBW	Ideal body weight
IV	Intravenous
IM	Intramuscular
IS	Internal standard
K_e	Elimination rate constant
kg	Kilogram
L	Liter
LLOQ	Lower limit of quantification
Max	Maximum
MDR	Multi drug resistant

μg	Microgram
mg	Milligram
MIC	Minimum inhibitory concentration
Min	Minimum
min	Minute
mL	Milliliter
mM	Millimolar
PAE	Post antibiotic effect
PTBD	Percutaneous transhepatic biliary drainage
PBP	Penicillin-binding protein
QCH	High concentration quality control sample
QCL	Low concentration quality control sample
QCM	Medium concentration quality control sample
QCs	Quality control sample
r	Correlation coefficient
rpm	Round per minute
S	Chemical form factor
SCI	Spinal cord injury
SD	Standard deviation
SE	Standard error
sec	Second
S_{cr}	Serum creatinine
T	Time
$t_{1/2}$	Half life
t_{max}	Time to reach the maximum concentration
V_d	Volume of distribution

CHAPTER I

INTRODUCTION

Background and Rational

Amikacin is a semisynthetic aminoglycoside antibacterial agent. It has broad spectrum of *in vitro* activity against staphylococci and *Enterobacteriaceae* including *Pseudomonas aeruginasa (1)*. It has been used for decades in the treatment of febrile neutropenic patient and in patients with hospital acquired infection. In addition, amikacin exhibit the synergistic effect against Enterobacteriaceae in combination with β-lactam antibiotic *(2)*. Because of the incidence of toxicity and the relationship between toxicity and plasma concentration of aminoglycoside, monitoring drug concentration are recommend in high risk patient to avoid ototoxicity and nephrotoxicity *(3)* .

Ceftazidime is a third generation cephalosporin. It has broad spectrum *in vitro* activity against gram positive and gram negative bacteria, particularly *Pseudomonas aeruginosa*. Ceftazidime is commonly used in the treatment of nosocromial infection and infections associated with neutropenic fever *(4-6)*. Time above the minimum inhibitory concentration (t > MIC) is considered to be the best prediction for therapeutic efficacy of ceftazidime. Study of the *in vitro* pharmacokinetic model summarized that maximum killing was achieved when the concentration was four to five times over the MIC and this level should be maintain for 90%-100% of the dosing interval because of cephalosporins produced no or slightly postantibiotic effect (PAE) against gram-negative bacteria and leukocyte had no significant effect on the *in vivo* PAEs of cephalosporins *(7, 8)*.

Dose and method of administration of ceftazidime play the important role to achieve the pharmacodynamic index and maximize efficacy of therapy. The emergence of resistant bacteria to ceftazidime together with the results from pharmacokinetic study concluded that there were different pharmacokinetic parameters of ceftazidime between healthy volunteer and specific group of patients *(9-11)*. These facts emphasized the need for individual pharmacokinetic parameters to modify dose and select the method of administration. Young and Pea suggested that

the routine monitoring of plasma ceftazidime concentration in critical ill and hematological malignancy patient respectively would be helpful in avoiding the treatment failure from the unpredicted low level *(11, 12)*. The problem is the inconvenience in measuring ceftazidime concentrations by HPLC method.

Amikacin and ceftazidime are commonly prescribed concomitantly to treat suspected or documented gram-negative bacilli infection, particularly those caused by *Pseudomonas aeruginosa (13-17)*. Several pharmacokinetic properties of aminoglycosides and ceftazidime are similar *(1, 5)*. Furthermore, the measurment of aminoglycoside plasma level by FPIA method is routinely used. If ceftazidime pharmacokinetic parameters could be accurately predicted from aminoglycosides pharmacokinetic parameters, the predictive pharmacokinetic parameters could then be used to calculate ceftazidime concentration and conveniently adjust dosage regimen for each patient.

This study was designed to investigate a correlation between pharmacokinetic parameters of both antibiotics. Furthermore, the clinical outcome would also be observed and recorded.

Objective

1) To investigate the relationships between the pharmacokinetic parameters of amikacin and those of ceftazidime.

2) To create an equation for the prediction of ceftazidime pharmacokinetic parameters from amikacin pharmacokinetic parameters and vice versa.

The Significance of the study

This study will provide an equation to predict patient- specific ceftazidime pharmacokinetic parameters from amikacin pharmacokinetic parameters (and vice versa). This will help in the production of the rapid attainment of ceftazidime (or amikacin) target concentration in an individual patient who receives concomitant therapy with amikacin and ceftazidime.

CHAPTER II

REVIEW OF LITERATURE

Review of amikacin

1. Chemistry

Amikacin is a semisynthetic aminoglycoside antibiotics derived from kanamycin A which is isolated from *Streptomycetes kanamyceticus*. The structure of all aminoglycosides has an essential six-member ring with amino-group substituents- hence the name *aminocyclitol* for this structure. Amikacin is kanamycin A with semisynthetic addition of 2-hydroxy-4-aminobutyric acid to the aminogroup at position 1 of the aminocyclitol. The chemical structure of amikacin is showed in Figure 1. Like others aminoglycosides, amikacin is highly soluble in water and insoluble in organic solvents. The latter property correlates with the limited ability of amikacin to cross lipid-containing cellular membranes. Hence, at pH 7.4, amikacin have a very high positive charge and are cationic *(18)*. Amikacin is commercially available as the sulfate salt which is formed in *situ* during the manufacturing process *(1)*.1.3 g of amikacin sulfate is approximately equivalent to 1 g of amikacin *(19)*.

The stability of aqueous solutions of amkacin sulfate was summarized as follows: The amikacin activity was maintained at greater than 90% of the originally present amount after elevated temperature at 56 ºC and 45 ºC for 4 months, 37 ºC for 12 months, and 25 ºC for up to 36 months *(20)*.

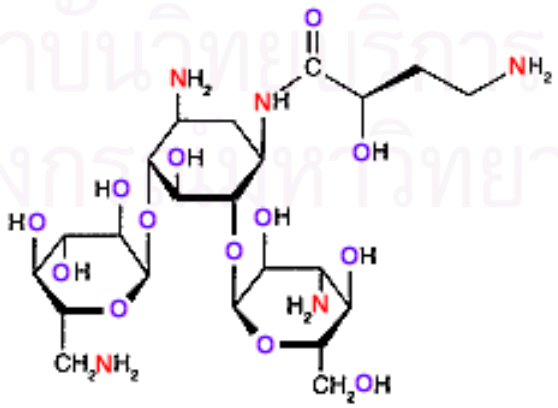

Figure 1 The structure of amikacin

2. Mechanism of antibiotic activity and antibacterial spectrum

The bactericidal activity of aminoglycosides, including amikacin, is thought to be ribosomally mediated. Their activity results from inhibition of protein biosynthesis by irreversible binding of the aminoglycosides to the bacterial ribosome. The process of activity includes an initial ionic interaction with the external surface of the bacterial cell, two energy-dependent uptake phase, and binding to ribosomes. The intact bacterial ribosome is a 70S particle that consists of two subunits (50S and 30S). The smaller 30S ribosomal subunit, which contains the 16S rRNA, has been identified as a primary target for aminoglycosides that ultimately induces mistranslation on prokaryotic ribosomes. Amikacin induces misreading of mRNA codons during translation and also inhibit translocation *(21)*.

In general, aminoglycosides are active against many aerobic gram negative bacteria and some aerobic gram positive bacteria. However, there are differences in spectrum of activity of individual drugs. The susceptibility of organism to amikacin were presented in Table 1. An energy- and oxygen- dependent transport mechanism is required for aminoglycosides to penetrate the outer bacterial membrane of susceptible bacteria. It is for this reason that this class of antibiotics demonstrates poor activity against anaerobes and has decreased ability to penetrate the bacteria within abscesses that may have limited oxygen. Bacteria defend themselves against aminoglycosides by some combination of three mechanisms: alteration in uptake, synthesis of modifying enzymes, or a change in ribosomal binding site. Enzymatic modification is the most common mechanism *(18)*.

Table 1 The susceptibility of the pathogens to amikacin and ceftazidime *(22)*

Organisms	Amikacin	Ceftazidime
Gram-positive		
Strep Group A,B,C,G	0	+
Strep. pneumoniae	0	+
Enterococcus faecalis	S	0
Enterococcus faecium	0	
Staph. aureus (MSSA)	+	±
Staph. aureus (MRSA)	0	0
Staph. epidermidis	±	±
L. monocytogenes	S	0
Gram-negative		
N. gonorrhoeae	0	±
N. meningitides	0	±
M. catarrhalis	+	+
H. influenzae	+	+
E. coli	+	+
Klebsiella sp.	+	+
Enterobacter sp.	+	+
Serratia sp.	+	+
Salmonella sp.		
Shigella sp.	+	
Proteus mirabilis		+
Proteus vulgaris	+	+
Citrobacter sp.		+
Acinetobacter sp.	0	+
Ps. aeruginosa	+	+
Y. enterocolitica	+	±

+ = usually effective clinical or > 60% susceptible

± = clinical trials lacking or 30-60% susceptible

0 = not effective clinically or < 30% susceptible

blank = data not available

3. Pharmacokinetic

All of the aminoglycosides have similar pharmacokinetic and toxic properties.

3.1 Absorption

Because of all aminoglycosides are high charged in nature, they are poorly absorbed orally and must be used parenterally for the treatment of systemic infection. The intramuscular route is well tolerated and results in essentially complete absorption, but intravenous administration is generally preferred because of the rapid and predictable serum profile *(1, 18, 21)*.

3.2 Distribution

Due to their chemical property, low level of protein binding and a high level of solubility in water, the aminoglycosides are distributed freely in the vascular space and relatively freely in the interstitial spaces of most tissues *(23)*. After intravenous or intramuscular dose of aminoglycosides, peak serum concentrations occur in 30 and 45 minutes *(1)*. Aminoglycosides cross biologic membranes poorly, with the exception of renal tubular cells and perhaps inner ear cells. Parenteral aminoglycoside administration results in low concentrations of active drug in bronchial secretions. Aminoglycosides traverse the blood-cerebrospinal fluid and blood-brain barriers poorly. Urine concentrations of aminoglycosides exceed peak plasma levels 25 to 100 fold within 1 hour of drug administration. Aminoglycosides enter synervial fluid easily. The biliary tract is poorly penetrated by aminoglycosides, with bile drug levels only 30% of concomitant serum concentrations *(18)*. Because aminoglycosides are highly water soluble, their volume of distribution (V_d) is similar to that of the extravascular compartment. Studies performed in normal adult volunteers have found a V_d of 0.2 – 0.3 L/kg. Inpatients with excess fluid in the extravascular space the V_d is increased *(2)*. Since aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight should result in a more accurate approximation of volume of distribution in obese patient *(24)*. A rapid distribution phase of aminoglycosides is approximately 15-30 minutes.

3.3 Metabolism

No evidence of *in vivo* metabolism of the aminoglycosides has been reported *(1, 2)*.

3.4 Excretion

After parenteral administration of aminoglycosides, 99% is excreted unchanged by the kidney, via glomerular filtration *(2)*. Less than 1% is eliminated in the feces and 1% in saliva *(25)*. However, the study of renal disposition of amikacin in rabbit and human indicated that small fraction of amikacin undergo tubular reabsorption according to the dose *(26)*. In adults with normal renal function, the plasma elimination half-life of amikacin is usually 2-3 hours and is reported to range from 30-86 hours in adults with severe renal impairment. Complete recovery of the dose in urine requires approximately 10-20 days in patient with normal renal function who received amikacin *(1)*.

4. Pharmacodynamic

Aminoglycosides have concentration-dependent bactericidal activity, the rate of bacterial eradication increases with increasing concentration above their MICs. Due to this property, the pharmacodynamic parameter that is believed to best characterize the profile of the aminoglycosides *in vivo* is the C_{max}/MIC ratio. The results from the clinical trial indicated that to obtain a clinical response of ≥ 90%, the peak level needed to exceed the MIC by 8-10 folds *(7)*. However, study by Moore and colleagues are often quoted as the basis for use of a C_{max}/MIC target of 10 or higher in clinical setting. The study by Kushuba and coworkers described that a C_{max}/MIC ratio of 10 or higher gave a 90% probability of normalization of temperature by day 7 *(27)*. The once-daily dosage regimen for aminoglycosides was designed to enhance peak serum concentration *(7, 21)*.

The post antibiotic effect (PAE) is defined as the persistent suppression of bacterial growth after limited exposure of bacteria to an antibiotic. Several factors are known to influence the presence and duration of the PAE. They include type of organism, class and concentration of antibiotic, duration of antimicrobial exposure.

The higher the aminoglycosides concentration, the longer the PAE. The smaller the inoculums and the higher the oxygen tension, the longer the PAE. Aminoglycosides exhibit a PAE on both gram-positive and gram-negative organisms *(28)*. PAE can be measured *in vitro* or in animal model of infection. *In vitro*, the aminoglycosides consistently demonstrate a PAE that varies from 1 to 3 hours in broth and serum for *P. aeruginosa* and from 0.9 to 2.0 hours for other Enterobacteriaceae *(29)*. The existence of PAE for ceftazidime combined with amikacin on multidrug-resistant *P. aeruginosa* was found, the mean PAEs (± SE) were 3.1 ± 0.71 hours *(30)*.

5. Dosage and Administration

Amikacin sulfate is administered by IM injection or IV infusion. Dosage of amikacin should be based on an estimation of ideal body weight. Amikacin can be administered either twice a day or once a day *(18)*.

In patient with normal renal function, twice a day regimen is divided into an initial dose of 7.5 mg/kg and maintenance dose 7.5 mg/kg q 12 hours to give desired peak serum concentration at 15-30 μg/mL and trough serum concentration at 5-10 μg/mL. The single daily dose of amikacin is 15 mg/kg/day to give desired peak serum concentration at 60 μg/mL and undetectable trough serum concentration. The manufacturers state that daily dosage should not exceed 15 mg/kg or 1.5 g *(18)*.

In patient with impair renal function. There are two general methods for dosage adjustment. The first method is continuation of the same dose and extending the dosage interval. The second method is reduction the dose and continuing the same dosing interval. The first one is favored in that higher peak levels are achieved with enhanced bactericidal activity. Suggested intervals are summarized by the degree of renal impairment in Table 2 and 3. However, even when one of these methods is used, peak and trough serum concentrations of the drug should be monitored *(18)*.

Table 2 Twice a day regimen of amikacin: Adjustment of dosage interval in patients with variable degrees of impaired renal function *(18).*

Maintenance dose for normal renal function (mg/kg)	Dosage interval based on estimated creatinine clearance (mL/min)			
	80-90	50-79	10-49	< 10
7.5 q 12 h	q 12 h	q 12-24 h	q 24-48 h	q 48-72 h

Table 3 Once a day regimen of amikacin: Adjustment of dose in patients with variable degrees of impaired renal function *(31).*

estimated creatinine clearance (mL/min)	> 90	70-90	50-69	40-49	<40
Dose in mg/kg (given q 24 h)	15	12	7.5	4	Individualize pharmacokinetic advised

6. Adverse Effect / Toxicity

The major adverse effects associated with aminoglycosides include: neuromuscular blockade, nephrotoxicity, and ototoxicity. Aminoglycosides seldom produce hypersensitivity reaction, hematologic dyscrasias, hepatitis, and drug fever. Because they do not produce inflammatory reaction, they seldom produce phlebitis on intravenous injection, pain on intramuscular injection, and irritation of serosal surfaces on direct instillation in to pleural space, joint space, and the peritoneal cavity. In addition, they are extremely well tolerated when injected into the CSF and have not been associated with epileptogenic reaction *(1, 18).*

Neuromuscular blockade after aminoglycosides, including amikacin, administration is a rare but serious and potential lethal adverse effect. In general, blockade has occurred in clinical situations in which a disease state or a concomitant drug interferes with neuromuscular transmission. Clinical manifestations of blockade may include weakness of respiratory musculature, flaccid paralysis, and dilated pupils. The risk of blockade is amplified in patients also administered D-tubocurarine, succinylcholine, and similar agent. Hypomagnesemia, hypocalcemia, and calcium

channel blockers amplified the risk. Blockade is preventable by intravenously infusing aminoglycosides over a period of 20-30 minutes or more *(18)*.

The reported incidence of aminoglycosides-induced nephrotoxicity varies from 0 to 50%, with most reports in the 5 to 25% range. The variability results from differences in the definition of nephrotoxicity and the poor risk factor assessment of the affected patient population *(18, 21)*. In review study shown that the incidences of amikacin induce nephrotoxicity were 9.4%, and a subgroup analysis distinguished reactions 'definitely/probable' from 'possible' reported the incidences of nephrotoxicity were 3.9% *(32)*. At present, it is though that nephrotoxicity is due to aminoglycosides accumulation in the lysosomes of the renal proximal tubule cells, which results in necrosis of the tubular cell. The clinical presentation of acute tubular necrosis manifested by non-oliguric renal failure within a week. This toxicity is usually reversible following discontinuance of the drug *(2)*.

Aminoglycosides may cause cochlear and vestibular damage in both experimental animal and humans. This toxicity is of particular concern because it usually irreversible and can appear after the end of treatment and repeated exposure engenders cumulative risk. In review study shown that the incidences of amikacin induce cochlear damage were 13.9% which were the highest incidence when comparing to gentamicin, tobramycin, and netilmycin, and the incidences of amikacin induce vestibular damage were 2.8% which were higher than netilmycin but lower than gentamicin and tobramycin *(32)*.

7. Determination in body fluid

There are twelve quantitative methods for determination of aminoglycoside level in biological fluid. These are microbiological assay, radiochemical assay, radioimmunoassay, enzyme immunoassay, fluoroimmunoassay, direct chemilunescence immunoassay, Nephelometric and turbidimetric immunoassay, Immunohistochemical techniques, spectrophotometric and other non-separative physiochemical methods, gas chromatography, thin-layer chromatography, high performance liquid chromatography *(33)*.

The fluoroimmunoassay (FIA) was chosen for this study because it found to be accurate, precise (RSDs<5%), rapid and simple to use. Homogeneous FIA is exemplified by fluorescence polarization immunoassay (FPIA). Abbott (Abbott Park, IL, USA) introduced the TDx® system in 1981. This batch analyzer system uses FPIA methodology for determination of aminoglycosides quantity.

The principle of FPIA is as follows. Sample (drug), tracer (fluorescein-labelled drug), and anti-drug antibody are incubated together in the reaction cell until competition for the limited number of antibody binding sites reach equilibrium (3 min). Illumination of the reaction cell with vertically polarized light causes the fluorescein label to emit light at longer wavelength that is detected through another vertical polarizing filter. Free tracer molecules rotate rapidly in solution; their emitted light is orientated in different planes from the incident light and is not detected. Tracer that is bound to antibody has much slower rotation; its emitted light is in almost the same plane as the incident light and is therefore detected. Increasing the concentration of drug in the sample limits the binding of tracer to the antibody and therefore causes a decrease in the measured fluorescence *(33)*. Serum or plasma specimens may be used with this assay and plasma which collected by heparin tube did not influence amikacin determination by FPIA *(34, 35)*.

Review of ceftazidime

1. Chemistry

Cephem nucleus is a basic structure of cepharosporin (Figure 2). It is a product of fusing beta-lactam ring with a six-member dihydrothiazine ring. The basic molecule of cephalosporins is numbered beginning in the dihydrothiazine ring with the sulfur moiety at position 1. The modification of this structure by substitutions at position 3 or 7, or by the addition of different acyl side chains from position 7 has given rise to the family of cephalosporin antibiotics. Ceftazidime is a semisynthetic cephalosporin antibiotic (Figure 3). It contains an aminothiazolyl side chain at position 7 of cephem nucleus. The aminothiazolyl side chain enhances antibacterial activity and stability against beta-lactamase. Ceftazidime contains a carboxypropylnoxyimino group in the side chain rather than the methoxyimino group contained in many aminothiazolyl cephalosporins. This difference results in increasing stability against hydrolysis by beta-lactamases, increasing activity against *Pseudomanas*, and decreasing activity against gram-positive bacteria *(1, 4)*.

Ceftazidime occurs as a white to off-white powder. The drug has solubility of 5 mg/mL in water and less than 1 mg/mL in alcohol. Ceftazidime has pK_as of 1.9, 2.7, and 4.1. Ceftazidime for injection is available as dry powder containing ceftazidime together with sodium carbonate. When reconstituted ceftazidime sodium is formed with the evolution of carbon dioxide, and the solution have pHs of 5-8 *(1, 19)*.

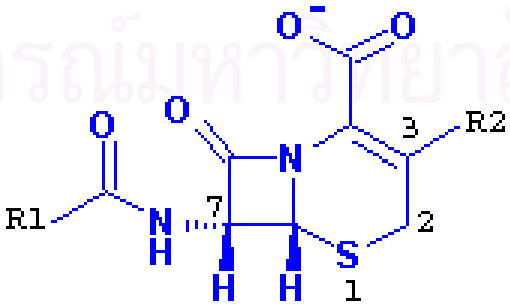

Figure 2 Cephem nucleuses, a basic structure of a cephalosporin

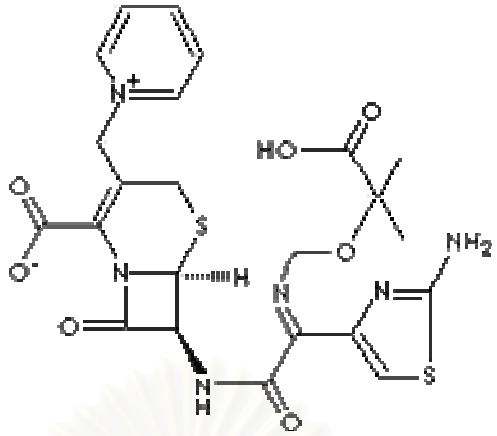

Figure 3 The structure of ceftazidime

2. Mechanism of antibiotic activity and antibacterial spectrum

The antimicrobial activity of ceftazidime, like that of other beta-lactam antibiotics, the drug binds to penicillin-binding proteins (PBPs) and inhibits the biosynthesis of the peptidoglycan component of the bacterial cell wall, causing inhibition of bacterial growth or cell lysis and death *(5, 6)*.

Ceftazidime remains active *in vitro* against most major aerobic nosocrobial bacterial pathogens. Common nosocromial gram-negative organisms susceptible to ceftazidime include *Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris* and *Providencia stuartii.* Of the gram-positive bacteria, most streptococci remain susceptible to ceftazidime but there are an increasing number of penicillin-resistant strains also resistant to ceftazidime *(5).* The susceptibility of organism to ceftazidime were shown in Table 1.

Resistance to ceftazidime is evident in bacterial species possessing extended spectrum beta-lactamases which are geographically wide spread. Microbial resistance to ceftazidime can be mediated through three mechanisms: alteration of a PBP target, production of beta-lactamase, and decrease ability of the drug to reach its PBP target. Often multiple mechanisms may work in concert to render a cell resistant *(4)*.

3. Pharmacokinetic

3.1 Absorption

Ceftazidime is not absorbed from the GI tract and must be given parenterally. The drug is usually administered by intravenous (IV) bolus or short infusion, or intramuscular (IM) injection; absorption is complete from IM injection sites. Administration of lidocaine 1% with ceftazidime e.g. intramuscularly did not significantly alter the peak plasma concentration of the drug. Following IM injection into the gluteus maximus or vastus lateralis, ceftazidime may be absorbed more slowly in women than in men *(6)*.

3.2 Distribution

Following IM or IV administration, ceftazidime is widely distributed into the body tissues and fluids including the gallbladder, bone, bile, skeletal muscle, prostatic tissue, endometrium, myometrium, heart, skin, adipose tissue, aqueous humor, sputum, pleural fluid, peritoneal fluid, synovial fluid, ascetic fluid, lymphatic, and blister fluid *(1)*.The half-life of distribution ($t_{½\,\alpha}$) is about 0.1-0.6 hour , and the drug exhibits low protein binding (10 to 17%) *(5)*. Sommer and coworkers reported a significantly ($p<0.01$) smaller peripheral compartment volume of distribution for women than men , because of a smaller extra cellular fluid volume *(36)*. The degree of protein binding is independent of the concentration of the drug. The volume of distribution of ceftazidime at steady state averages 0.18-0.31 L/kg in healthy adult. In neonates 2-9 days of age, the volume of distribution at steady state averages 0.42-0.55 L/kg. In patients with cystic fibrosis, the volume of distribution at steady state averages 0.15-0.19 L/kg in the central compartment and 0.17-0.27 L/kg in the peripheral compartment *(1)*.

3.3 Metabolism

Metabolites of ceftazidime were not detected in either plasma or urine of healthy subject administered single or multiple doses *(1, 6)*.

3.4 Elimination

Ceftazidime is excreted almost entirely (>95%) by renal elimination. The lack of significant effect of probenecid on the clearance of ceftazidime in healthy subjects indicates that the drug is excreted primarily by glomerular filtration *(6)*. In adults with normal renal and hepatic function, the elimination half-life is 1.4-2 hours. Renal function influences the pharmacokinetics of the drug, the elimination half-life of ceftazidime ranged from 3-6 hours in patients with creatinine clearances of 29.5-53 mL/min and 9.4-24.6 hours in patients with creatinine clearances of 5.4-27 mL/min, and dosage reductions are essential in patients with renal impairment to avoid accumulation of the drug *(1, 37, 38)*. Ceftazidime is removed by continuous ambulatory peritoneal dialysis and continuous arteriovenous haemodialysis. In patients with liver cirrhosis and ascites, the volume of distribution at steady state and elimination half-life are increased. This is mainly due to ascetic fluid acting as a reservoir from which the drug returns slowly to the circulation. The hepatic dysfunction, the volume of distribution at steady state and elimination half-life are not as pronounce in patients with chronic dysfunction without cirrhosis. Increased glomerular filtration rate accounts for increased clearance of ceftazidime in patients with cystic fibrosis *(5, 6)*.

4. Pharmacodynamic

The beta-lactam antibiotics exhibit time-dependent killing. Saturation of the killing rate occurs at low multiples of the MIC (usually around four to five times the MIC). Short PAEs or no PAEs are observed for gram-negative bacilli after exposure to beta-lactam antibiotics and leukocytes have no major effect on the minimal *in vivo* PAEs observed for gram-negative bacilli *(7)*. Thus the goal of a dosing regimen for these drugs would be to optimize the duration of exposure. Studies in animal infection models have demonstrated that for beta-lactam/organism combinations in which there is no PAE in vivo, maximum killing is achieved when the time above MIC approaches 90%-100% of the dosing interval. for beta-lactam/organism combinations that do have *in vivo* PAE, maximum killing is achieved when the time above MIC is only 50%-60% of the dosing interval *(8)*. Administration of beta-lactams antibiotic by continuous infusion facilitates

maintaining serum levels above the MIC *(7, 39)*. Many clinical studies have been shown that continuous infusion and intermittent bolus injection of ceftazidime were equally effective for the treatment of susceptible gram-negative bacteria, but continuous infusion provided significant dose reduction and cost saving *(9, 40-43)*.

5. Dosage

Ceftazidime is administered by IV injection, IV infusion or by deep IM injection. Continuous intravenous infusion of ceftazidime has also been suggested to provide an optimum pharmacodynamic profile *(5)*. If an aminoglycoside is administered concomitantly with ceftazidime, Its should be administered at separate sites *(1)*.

The dosage of ceftazidime most commonly recommended for patients with aged > 12 years is 1 g every 8 or 12 hours. However, dosage may vary, according to site, severity of infection, the susceptibility of the causative organism, and renal function of the patient. The maximum adult dosage of ceftazidime recommended by the manufacturers is 6 g daily. Dosage reductions, based on creatinine clearance, are recommended in patients with renal impairment *(5)*. Modifications in dose and/or frequency of administration of ceftazidime that are recommended in various references are different *(44)*, as shown in Figure 4.

Ceftazidime is removed by haemodialysis. In this setting a 1 g loading dose and a further 1 g after each dialysis period is recommended. In adults undergoing intra peritoneal dialysis or CAPD, the suggested parenteral ceftazidime regimen is a 1 g loading dose followed by 0.5 g every 24 hour *(1, 5)*.

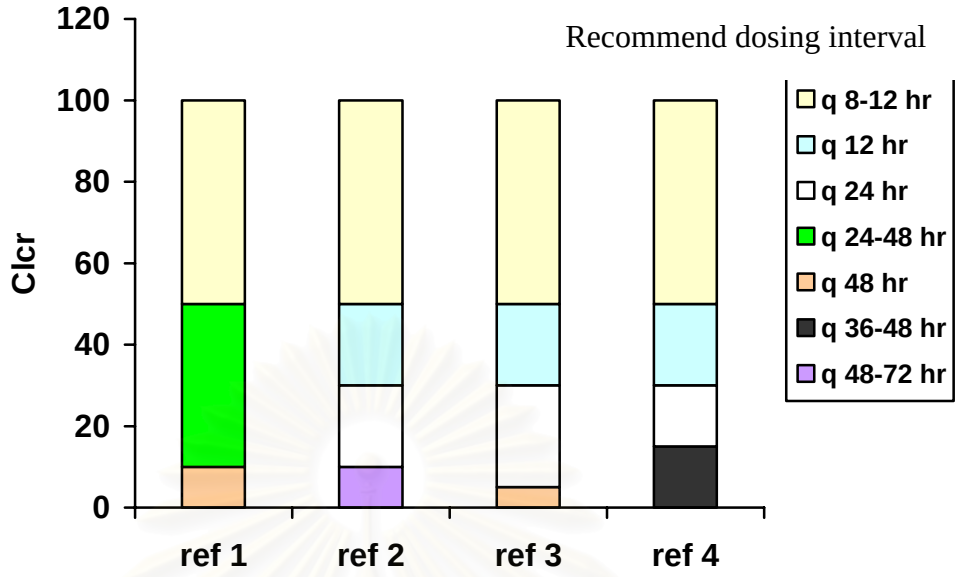

Figure 4 Ceftazidime dosage recommended in 4 references

Ref 1 = The Sanford guide to antimicrobial therapy*(22)* Ref 2 = Handbook of antibiotics*(31)*

Ref 3 = AHFS Drug Information 2004*(1)* Ref 4 = The study by Welage LS et al.*(37)*

6. Adverse Effect / Toxicity

In common with other third generation cephalosporins, ceftazidime is generally well tolerated. Adverse event that do occur are usually mild in severity. The incidence of ceftazidime-related adverse events is estimated at approximately 9%. Ceftazidime can cause skin-related adverse events including pruritus, rash, fever, and other hypersensitivity reactions including anaphylaxis (1 to 3%), local pain on administration and phlebitis (< 3%) and thrombophlebitis (1 to 2%). Gastrointestinal reactions such as nausea, vomiting, diarrhea occurred in 2.4% of patients. Ceftazidime causes transient rises in liver function test in 3 to 9% of patients, but increased serum bilirubin levels are seen in < 1% of patients with transient abnormal liver function test (3 to 9%) *(1, 5, 6).*

The others important adverse effects related to ceftazidime are neurotoxic, haematological effect, and nephrotoxic. Nervous system adverse events causes by ceftazidime were reported in 4% of patient, but larger series data available to the US manufacturer provide the incidence to be < 1%. The mild nervous system adverse events cause by ceftazidime such as headaches, transient parathesias and dizziness

occur in less than 1 to 2%*(5)*. In retrospective review from January 1980 to October 2002 reported 12 case of neurotoxicity induced by ceftazidime, 96% of patient were confusion with temporospatial disorientation, 33% of patient were myoclonus, and 13% of patient were seizure. These neurologic disorders frequently are encountered in uremic and elderly patient *(45)*. Haemologic events associated with ceftazidime are bleeding (≤ 0.05%), eosinophilia (7.4%), thrombocytosis (2%), leucopenia (1.1%), immune-mediated thrombocytopenia (rare), and nonimmunological positive Coombs' test (< 3%). Ceftazidime induces increasing in serum creatinine and blood urea nitrogen occurs in < 1% of patients but ceftazidime has not been associated with significant nephrotoxicity. There is no evidence suggest that ceftazidime potentiates nephrotoxicity associated with the aminoglycosides or loop diuretics *(1, 5, 6)*.

7. Determination in body fluid

There are two methods for determination of ceftazidime concentrations in biological fluid. The first method is microbiological assay *(46)* and another method is high performance liquid chromatography (HPLC). The HPLC assay for ceftazidime that was developed by Isla and colleagues was chosen for this study because it provides a sensitive and specific alternative with additional advantages of high precision, reproducible and rapid turn-around time *(47)*.

Review of amikacin and ceftazidime interaction

1. Pharmacokinetic interaction

Pharmacokinetic interactions of ceftazidime and amikacin in healthy volunteers were studied by Adamis et al. Six individuals were given 1 g of ceftazidime intravenous either alone or combined with 0.5 g of amikacin. The study revealed that co-administration of ceftazidime and amikacin resulted in higher C_{max} and AUC for amikacin than when administered alone. The tested interactions did not affect plasma half-life and clearance rate of any antimicrobial compared with its single administration *(48)*.

2. Pharmacodynamic interaction

Since 1982 until now many *in vitro* studies revealed the synergistic effect between ceftazidime and aminoglycosides including amikacin, tobramycin, and gentamycin against some strain of gram-positive and gram-negative organisms such as *Enterococcus*, *Enterobacteriaceae*, *Pseudomanas aeruginosa*, and *Klebsiella pneumoniae* that resisted to both drugs *(13, 17, 49-58)*. The mechanism of the synergistic effect was believed that inhibiting the cell wall synthesis by ceftazidime result in increasing the porosity of the bacterial cell and allowing more amikacin to penetrate *(59)*. The concurrent use of an aminoglycosides in combination with ceftazidime is recommended for treatment of gram-negative infection particularly *Pseudomanas aeruginosa* to prevent therapeutic failure *(60)*.

Review of correlation of pharmacokinetic parameters between aminoglycosides and other antibiotic

From 1993 to 1999, several studies were performed to explore the relationship of pharmacokinetic parameters between aminoglycosides and vancomycin. In 1993, Wragge et al. and Welch et al. reported the relationship between K_e of aminoglycosides and vancomycin which was superior to the relationship between K_e and Cl_{cr} and also suggested the linear regression equation to predict vancomycin elimination rate constant from aminoglycosides elimination rate constant. They revealed that their equation was less biased and more precise than those predicted by the monogram of Matzke et al. *(61, 62)*.

In 1998, Beringer et al. conducted the study to evaluate the precision of Wragge-Cooper method to predict vancomycin elimination rate constant. Their result not only confirmed the relationship between aminoglycosides and vancomycin pharmacokinetic parameter, but also presented a revised model by using Bayesian analysis that was more accurate *(63)*. Even though, a large portion of variability in vancomycin pharmacokinetics were reported, this relationship were also found in patients with hematological stem-cell transplantation *(64)*.

Until now, no further reports of the study of correlation of pharmacokinetic parameters between aminoglycosides and ceftazidime.

CHAPTER III

MATERIALS AND METHODS

Materials

1. Chemicals and reagents

1.1 Chemicals and reagents for analysis of ceftazidime

1) 78.62% Ceftazidime pentahydrate Buffered sterile
   (Siam Pharmaceutical (Thailand) Ltd.)
2) 92.94% Cephalexin monohydrate
   (Siam Pharmaceutical (Thailand) Ltd.)
3) Ammonium acetate (Fisher Scientific)
4) Dichloromethane (Fisher Scientific)
5) Acetonitrile (Lab-Scan analytical Science)

1.2 Chemicals and reagents for analysis of amikacin

Calibrators, controls, reagent pack and dilution buffer solution for analysis of amikacin were purchased from Abbott Laboratories.

1) No.9508-01, Amikacin calibrators (Lot.no.29349Q100 and 37018Q100)

   six vials of amikacin in 2.5 mL normal human serum at following concentrations:

CAL	Amikacin concentration (μg/mL)
A	0.0
B	3.0
C	10.0
D	20.0
E	35.0
F	50.0

Preservative: Sodium azide

2) No. 9508-10, Amikacin controls (Lot.no. 29348Q100 and 37017Q100)

Three vials of amikacin concentration in 2.5 mL normal human serum within the following range:

QC	Target conc.(μg/mL)	Range(μg/mL)
L	5.0	4.25 - 5.75
M	15.0	13.50 - 16.50
H	30.0	27.00 - 33.00

Preservative: Sodium azide

3) No.9508, Amikacin reagent pack (Lot.no.28668Q100 and 33573Q100)

The reagent pack consists of three vials as followed:

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

4) No. 9519, X SYSTEMS dilution buffer (Lot.no. 30656M102 and 33148M202)

Bovine gamma globulin in phosphate buffer containing sodium azide as a preservative is used as buffer solution.

2. Instruments

2.1 Instruments and chromatographic condition for analysis of ceftazidime

1) Instruments

High-Performance Liquid Chromatography (HPLC) system at clinical pharmacy department of Chulalongkorn University consisted of Dionex® P680 HPLC pump connected to Dionex® ASI-100 automated sample injection and Dionex® UVD 170U detector (Archemica International CO., LTD.).

2) Chromatographic condition

Column: HyperClone C_{18} 5 μm, 4.6 x 250 mm

Mobile Phase: 0.02 M Ammonium acetate buffer (pH 4.52): acetonitrile (93: 7 v/v)

Internal Standard: Cephalexin

Flow Rate: 1 mL/min

Detector: UV 257 nm

Injection volume: 50 μl

Temperature: Ambient temperature

2.2 Instruments for analysis of amikacin

Automated Fluorescence Polarization Analyzer (Diagnostic Division, Abbott Laboratories, Inc., TDx, U.S.A. Serial No. 18488).

Methods

1. Study design

This study was designed as an prospective observational pharmacokinetics study to investigate the relationship between pharmacokinetic parameters of amikacin and ceftazidime. The protocol was reviewed and approved by the ethical committee of Phramongkutklao Hospital. The flow chart of study was shown in Figure 5

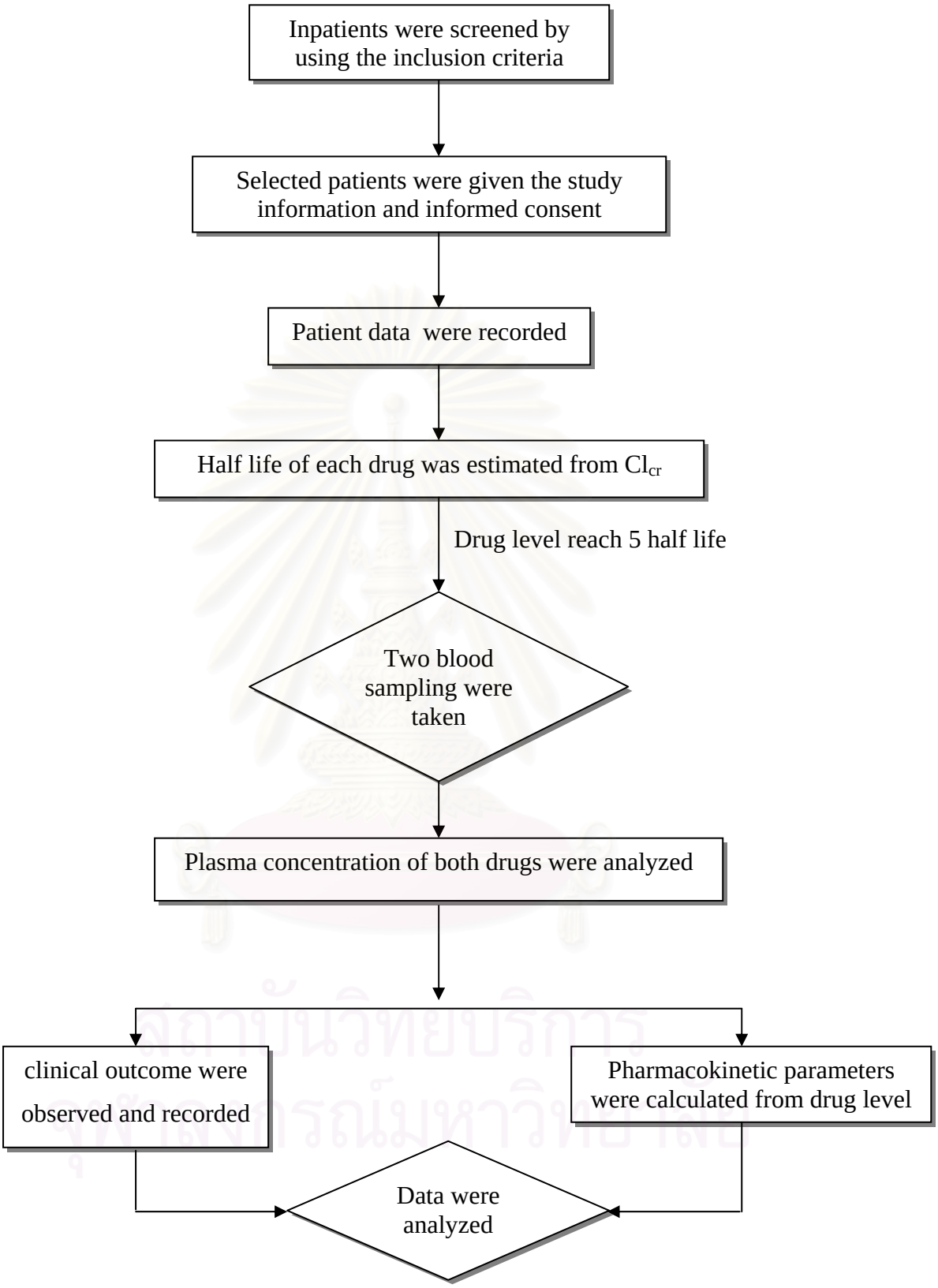

Figure 5 Flow chart of the study

2. Subjects

The study was conducted from February to May 2006 at Phramongkutklao Hospital, Bangkok, Thailand. Nineteen inpatients were recruited based on the following criteria:

2.1 Inclusion criteria

The inpatients who had all of these characteristics were enrolled in this study.

a. The patients over 18 years of age.
b. The patients who had been receiving amikacin combine with ceftazidime , and concentration of both drugs were in steady state based on the following criteria*:
    1) At least 24 hours for patients who had Cl_{cr} > 50 mL/min
    2) At least 48 hours for patients who had Cl_{cr} = 30-50 mL/min
    3) At least 72 hours for patients who had Cl_{cr} = 10-30 mL/min
c. The patients had stable serum creatinine concentration (< 20% interday fluctuation)
d. All patients consented to enroll in the study.

* : The criteria were derived from previous pharmacokinetic study of ceftazidime in patients with difference degree of renal function as showed in Table 4.

Table 4 The plasma $t_{1/2}$ of ceftazidime and approximated time to reach steady state in patients with various degree of renal function

Clcr (mL/min)	Half – life (hrs)	Time to reach steady state (5 $t_{1/2}$)	references
> 90	1.4 – 2.5	7 – 12.5	*(36, 38, 46, 65)*
50 - 89	1.3 -4.25	6.5 – 21.25	*(37, 38, 65)*
30 - 49	2.74 – 8.96	13.7 – 44.8	*(38, 46)*
10 - 29	3.6 - 10	18 -50	*(37, 46)*

2.2 Exclusion criteria

The inpatients who had either one of these characteristics were excluded from this study.

a. The patients had known hypersensitivity to amikacin or ceftazidime.
b. The patients were pregnancy or lactation.
c. The patients had the cystic fibrosis and ascites. The patient with end stage renal disease who were treated by renal replacement therapy were also excluded.
d. The patients were diagnosed by the physicians as the inappropriate subject to enroll in this study.

2.3 Sample Size Determination

One group sample size was estimated from the following criteria:

1) The sample size of correlation study was calculated from the following equation *(66)*:

$$n = \left(z_{\alpha} + z_{\beta}\right)^2 + 3z_F$$

When n = sample size

$Z_{\alpha,0.05}$ = 1.645

$Z_{\beta,0.1}$ = 1.282

Z_F = Fisher's Z Transformation

$Z_F = \frac{1}{2}\log_e \frac{1+r}{1-r}$

r = correlation coefficient

No study investigates the correlation between pharmacokinetic parameters of ceftazidime and aminoglycosides. However, Beringer et al. studied the correlation between the elimination rate constant of vancomycin and of aminoglycosides and reported that the correlation coefficient was 0.73 *(63)*. Because vancomycin is eliminated by renal as high proportion as ceftazidime, so using correlation coefficient from Beringer's study is reasonable.

$$Z_F = \frac{1}{2}\log_e \frac{1+(0.73)}{1-(0.73)} = 0.929$$

$$n = (1.645+1.282)^2 + 3(0.929) = 11.35 \approx 12$$

If 20% of patient dropped out, the sample size should be as followed:

$$n = \frac{12}{(1-0.2)} = 15$$

2) The sample size for regression analysis is dependent on amount of independent variables. The desired ratio of observations to independent variables is 15-20 to 1 *(67)*. Because this study has only one independent variable, so the sample size is 15-20.

The sample size from regression analysis was more than that from the correlation study. Thus 19 subjects were included in the study.

3. Drug administration and sampling

Nineteen infected patients who met the inclusion criteria were participated in this study. As the routine practice for patient care, without intervention, ceftazidime and amikacin dosage regimen were prescribed by physician. Creatinine clearance of each patient was calculated from serum creatinine by method of Cockcroft and Gault to estimate half-life of ceftazidime and amikacin.

After five times of estimated half-life of both drugs to ensure steady state, two to three blood samples were taken. Amikacin was given once daily while ceftazidime was given every eight or twelve hours. The schedule when amikacin was administered along with ceftazidime was chosen to collect blood sample. To avoid distribution phase, the first sample were taken at least 45 minutes after finished infusion of the second drug *(68)*. The second sample was taken at least one approximated half-life apart from the first sampling. To ensure measurable concentration of both drugs, three blood samples might be required in some patients who had short drug half-life and received amikacin and ceftazidime at separate time. The first and second samples were taken at least 45 minutes after finished infusion of each drug. The third sample was taken at least one approximated half-life apart from the second sampling.

6-mL of blood samples were collected in two 4-mL heparinized tubes and centrifuged at 3500 rpm for ten minutes. The plasma portion were separated and stored at -30 °C for not more than seven days, then transferred to store at -80 °C until analysis. The samples were analyzed within seven days for amikacin *(34, 69)* and one month for ceftazidime *(47)*.

4. Analysis method of ceftazidime and amikacin

4.1 Aanalysis of ceftazidime

The HPLC method, described by Isla et al.*(47)*, was chosen to determine the quantity of ceftazidime in plasma samples.

Validation of HPLC method including selectivity, linearity, precision, accuracy and stability was performed and the results were presented in appendix H. Plasma ceftazidime concentration was determined by adding 50 μl of internal standard (equivalence to cephalexin 50 μg) to 500 μl of plasma sample , then plasma sample was mixed with 500 μl of acetonitrile for 30 second and then centrifuged for 5 minute at 4000 rpm. Five milliliters of dichloromethane were added to the supernatant, shaken for 5 minute, centrifuged for 5 minute at 3500 rpm, and the upper aqueous phase was removed into 200 μl microvial. A volume of 50 μl was used for HPLC analysis.

4.2 Analysis method of amikacin

Amikacin plasma levels were determined by immunoassay method using TDx Analyzer system, Abbott Laboratories based on fluorescence polarization technique. Coefficient of variation is less than 5% at a concentration range between 5-30 μg/mL. Calibration and sample assay run were performed as mentioned in the TDx analyzer manual.

5. Clinical follow-up

The important information of each patient including medical history, physical examination, adverse drug reaction and laboratory value were followed and recorded. The clinical response and bacteriological response were observed and classified by definition of this study.

6. Pharmacokinetic parameter calculation

Pharmacokinetic parameters (K_e, $t_{1/2}$, V_d and Cl) of both drugs were calculated by using short infusion one compartment with first order elimination model. The following equations were used:

6.1 K_e and $t_{1/2}$ calculation

$$K_e = \frac{\ln\left(\frac{c_1}{c_2}\right)}{\Delta t} \qquad \text{(equation 1)}$$

$$t_{1/2} = \frac{0.693}{Ke} \qquad \text{(equation 2)}$$

6.2 V_d and Cl calculation

$$Cl = \frac{SF\left(Dose/t_{inf}\right)\left(1-e^{-Ket_{inf}}\right)\left(e^{-Ke\left(t-t_{inf}\right)}\right)}{c_t\left(1-e^{-Ke\tau}\right)} \qquad \text{(equation 3)}$$

$$V_d = \frac{Cl}{Ke} \qquad \text{(equation 4)}$$

when K_e = Elimination rate constant

c_1 = Concentration of drug at first sampling

c_2 = Concentration of drug at second sampling

$t_{1/2}$ = Half life of drug

Cl = Total clearance of drug

S = Chemical form factor

F = Bioavailability factor

t_{inf} = Time taken for infusion

c_t = Drug concentration at t

τ = Dosing interval

7. Estimated maximum and minimum concentrations of amikacin and ceftazidime

Maximum and minimum concentration of both drugs was calculated by using calculated pharmacokinetic parameter. The following equation was used:

$$C_{ss} = \frac{SF(Dose/t_{inf})(1-e^{-Ket_{inf}})(e^{-Ke(t-t_{inf})})}{Cl(1-e^{-Ke\tau})} \qquad \text{(equation 5)}$$

When calculate $C_{ss\ max}$, $t - t_{inf}$ is 0.5 hour, and t is dosing interval when calculate $C_{ss\ min}$.

8. Statistic analysis

The demographics of the subjects such as gender, age, weight, height, adverse drug reaction and laboratory data were recorded and analyzed using descriptive statistics.

The relationships of pharmacokinetic parameters between amikacin and ceftazidime were determined by simple linear regression.

9. Definitions

Cure: patient was considered to be cured if the following criteria were met:

1) Complete resolution of all the initial abnormal clinical sign and symptoms related to the initial infection.
2) If the site of infection and the pathogenic bacteria were determined, the causative bacteria should be eradicated from the site of infection.

Improvement: Improvement in one or more clinical signs and symptom of the initial abnormal clinical sign related to the initial infection without complete resolution including clinical improvement with death not related to an infection .

Failure: patient was considered to fail if one of the following criteria were met:

1) No change or worsening of clinical manifestations after 3-5 days of therapy.
2) Failure to eradicate the causative bacteria.
3) Death related to an infection

Elimination: A causative bacterium was eradicated.

Persistence: A causative bacterium was persistent.

Indeterminate: No source of infection ,or a follow up culture was not obtained.

Nephrotoxic: An increase in the serum creatinine level of ≥ 0.5 mg/dL during course of therapy *(70)*.

Ototoxicity : A hearing loss of 15 dB at two or more frequency verified by consecutive testing when a disturbance of vestibular function was suspected during or within 48 hours after amikacin therapy and diagnosed by physician *(70)*.

Unstable renal function : A change in the serum creatinine concentration of more than 20% over a period of 1 day *(71)*.

Creatinine clearance: Creatinine clearance of each patient was calculated using Cockcroft and Gault equation.

$$Cl_{cr}\ (mL/min) = \frac{[(140 - Age) \times IBW]}{Scr \times 72}$$

Where age is expressed in years, S_{cr} is the serum creatinine in mg/dL, and IBW is ideal body weight in kg. However in patients whose actual weight less than IBW, IBW in equation was replaced by actual weight. For females, the result was multiplied by 0.85 *(71)*.

Elimination rate constant (K_e): The fraction or percentage of the total amount of drug in the body removed per unit of time.

Half – life ($t_{1/2}$): The time required for the plasma drug concentration to be reduced to one-half of the original value.

Volume of distribution (V_d): The apparent volume required to account for all the drug in the body if it were present throughout the body in the same concentration.

Clearance (Cl): The intrinsic ability of the body or its organs of elimination to remove drug from the blood or plasma.

The susceptibility of pathogen: The susceptibility of pathogen were reported as susceptible, intermediate resistant and resistant according to the breakpoint of MIC which was determined by clinical and laboratory standards institute (CLSI)

CHAPTER IV

RESULTS

1. Study population

During February to May 2006, nineteen patients from general medicine or surgical ward at Phramongkutklao Hospital who met the inclusion criteria were enrolled in this study. All patients or their nearest relative signed their consent to participate in the study. All nineteen patients received concomitant therapy with ceftazidime and amikacin. Clinical outcome and adverse effect were continually observed until both drugs were discontinued.

1.1 Demographic data

This study enrolled nine patients from general medicine wards, eight patients from surgical ward and two patients from reverse isolated (RI) ward. There were six hematological malignancies, four malignancies in other organs, one pleural effusion and one spinal cord injury (SCI) patients. The general characteristic including gender, age, weight, body mass index (BMI), height, estimated creatinine clearance (Cl_{cr}), serum albumin, underlying disease, type of therapy, indication and duration of antimicrobial therapy, of nineteen patients were shown in Table 5.

Patients with age ranged from 19 to 83 years were enrolled in this study, Figure 6 showed frequency of patients in various range of ages. Table 6 presented frequency of patients with various range of creatinine clearance. Nine patients were not weighed because of unable to stand up, so approximated weights, which were recorded in patient chart, were use for calculating Cl_{cr} . However, IBW instead of approximated weight were used for calculating creatinine clearance for these patients, except only four patients who were emaciated and approximated weight were less than IBW. Mean serum albumin were 2.768 g/dL. Even though various underlying disease were reported, half of the patients had cancer and one/ third were diagnosed of febrile neutropenia. The average duration of amikacin therapy were shorter than ceftazidime therapy (10.32 ± 6.04 day and 12.32 ± 6.64 day, respectively).

Table 5 Demographic data of patients

Characteristics	Frequency, mean ± SD(range)	
Patients (n)	19	
males*	13 (68.4)	
females*	6 (31.6)	
Age (years)	51.68 ± 20.69	(19-83)
Weight (kg)	56.82 ± 10.80	(42-79)
BMI (kg/m^2)	21.23 ± 3.47	(16.40-28.54)
Height (cm)	163.42 ± 7.40	(153-185)
Cl_{cr} at starting of therapy (mL/min)	101.31 ± 41.07	(26-181)
Albumin (g/dL)	2.768 ± 0.982	(1.6 – 4.1)
Underlying disease* φ		
Cancer	10 (52.63)	
Diabetes	4 (21.05)	
Hypertension	3 (15.79)	
Dyslipidemia	2 (10.53)	
Chronic liver disease	1 (5.26)	
Deep vein thrombosis	1 (5.26)	
Asthma	1 (5.26)	
Hyperthyroid	1 (5.26)	
Pleural effusion	1 (5.26)	
Spinal cord injury	1 (5.26)	
Tuberculosis	1 (5.26)	
No Underlying disease	2 (10.53)	

* : Data are number (%) of total patients

φ : 6 patients had more than one underlying disease

Table 5 (Continued) Demographic data of patients

Characteristics	Frequency, mean ± SD(range)
Type of therapy *	
Empiric	16 (84.21)
Definitive	3 (15.79)
Duration of antimicrobial therapy (days)	
concomitant with amikacin and ceftazidime	9.58 ± 5.76 (3-21)
Indication *, ϕ	
Febrile neutropenia	6 (30.00)
Urinary tract infection	4 (20.00)
Wound infection	4 (20.00)
Fever with unknown origin	2 (10.00)
Pneumonia	2 (10.00)
Sepsis	1 (5.00)
Bile duct infection	1 (5.00)

* : Data are number (%) of total patients

ϕ : There is 1 patient who had 2 indications(pneumonia and urinary tract infection)

Table 6 Frequency of patients with various range of creatinine clearance

Creatinine clearance (mL/min)	Frequency (%)
<15	0
15-29	1
30-59	2
60-89	3
≥ 90	13

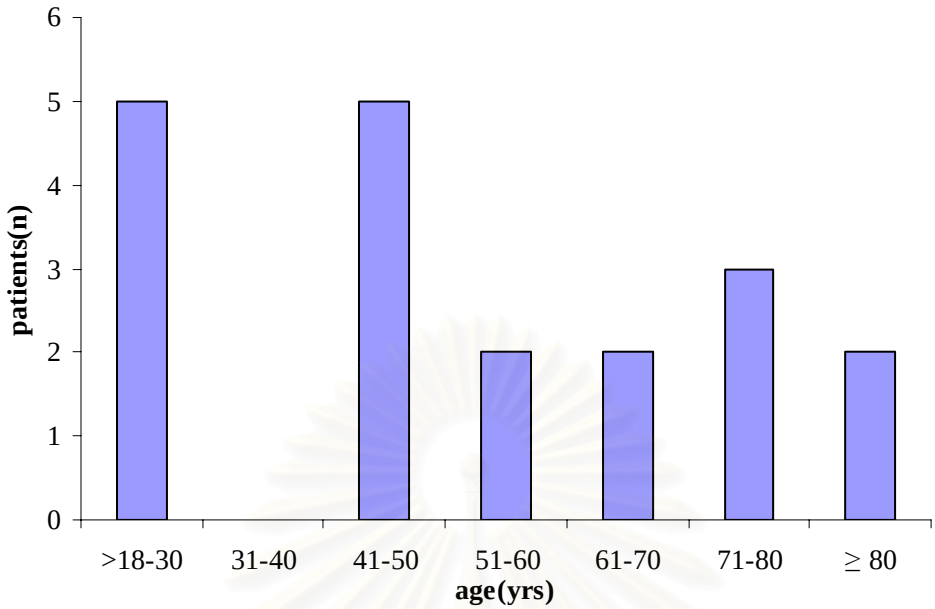

Figure 6 Frequency of patients with various range of ages

2. Characteristics of isolated pathogen

All nineteen patients were investigated for causative pathogen, twenty three gram-negative bacilli, two gram-positive cocci and one anaerobic bacteria were identified from thirteen patients. Six patients had mixed pathogens. The susceptibilities of isolated pathogens were presented in Table 7. *Pseudomonas aeruginosa* were the most frequently isolated and most of them were susceptible to amikacin and ceftazidime. Four pathogens were identified to be extended-spectrum ß-lactamase (ESBL)**,** while two pathogens were multi-drug resistance (MDR) and two pathogens were both ESBL and MDR. 73.08 %, 3.84 % and 23.08 % of the pathogens were susceptible, intermediate resistance and resistance to amikacin, respectively.

Table 7 Isolated pathogens and their susceptibility to amikacin and ceftazidime

Pathogens (*n*)	Susceptibility *	
	amikacin	ceftazidime
Acinetobacter baumanani (1)	R (1)	R (1)
Enterococcus faecium (1)	R (1)	R (1)
Escherichia coli (5)	R (1) , S (4)	R (3) , S (2)
Klebsiella pneumoniae (5)	I (1) , S (4)	R (3) , S (2)
Klebsiella oxytoca (1)	S (1)	S (1)
Proteus mirabilis (2)	S (2)	S (2)
Pseudomonas aeruginosa (8)	R (1) , S (7)	R (1) , S (6), N (1)$^{\varphi}$
Stenotrophomonas maltophilia (1)	R (1)	R (1)
Shewanella putrefaciens (1)	S (1)	S (1)
Viridans streptococci (1)	R (1)	R (1)

* : S = susceptible , I = intermediate resistant, R = resistant φ : Data not available

3. Plasma Drug Concentrations

3.1 Amikacin Plasma Concentrations

All of the patients received once daily amikacin infusion regimen. Mean and standard deviation of amikacin dosage in mg/kg/day were 11.74 and 2.4, respectively (Table 8). Since pharmacokinetic parameters would be calculated by using two drug levels, trough level of amikacin which is usually undetectable for once daily regimen was avoided. Table 9 presented starting time of administration, consuming time of infusion, collecting time of blood sample and plasma amikacin concentration of each patient.

3.2 Ceftazidime Plasma Concentrations

Ceftazidime was mostly given every 8 hours, only a few patients was administered as every 12 hours regimen. Unlike amikacin, trough level of ceftazidime is still within the detectable range; there the blood sample collecting time required only consideration on avoiding the distribution phase. Table 10 presented the starting time of administration, consuming time of infusion, collecting times of blood sample and plasma ceftazidime concentration of each patient.

Blood sampling for ceftazidime concentration of patient 6 were taken for peak and trough level of different dosing interval, however at steady state drug profile from every dose should be superimpose.

Table 8 Drug dosage regimen, drug clearance and estimated creatinine clearance

Subject No.	Dosage regimen				Clearance(mL/min)		
	Amikacin		Ceftazidime				
	Dose (mg) , (mg/kg)	τ (hrs)	Dose (g)	τ (hrs)	Creatinine	Amikacin	Ceftazidime
1	500 (9.61)	24	2	12	26.70	31.07	38.6322
2	500 (8.33)	24	1	12	54.77	44.71	46.8511
3	500 (11.09)	24	2	8	111.07	78.27	89.3575
4	750 (9.62)	24	2	8	145.65	137.81	139.777
5	750 (15.00)	24	2	8	98.21	109.51	115.846
6	500 (10.00)	24	2	8	69.14	79.85	69.9058
7	750 (14.15)	24	2	8	91.49	102.37	116.378
8	750 (13.64)	24	1	8	148.96	98.95	99.8483
9	750 (15.00)	24	2	8	166.67	79.81	101.704
10	750 (12.50)	24	2	8	180.96	116.63	106.421
11	750 (12.93)	24	2	8	148.38	94.38	95.0955
12	750 (10.14)	24	2	8	112.37	125.97	137.603
13	500 (10.00)	24	1	8	67.29	45.87	51.8084
14	750 (15.96)	24	2	8	91.00	101.91	175.834
15	750 (11.81)	24	2	8	98.09	109.54	107.103
16	750 (13.89)	24	2	8	96.00	67.11	65.8065
17	500 (8.06)	24	2	8	63.09	61.17	51.2995
18	500 (11.90)	24	1	8	51.24	53.92	60.5589
19	750 (9.49)	24	2	8	103.49	146.31	141.609

Table 9 Two plasma amikacin concentrations of each patient after once daily intravenous administration

Subject No.	Time			Amikacin level (μg/mL)
	t_0	t_{inf} (min)	Collecting time	
1	23.00	30	7.00	13.57
			11.00	9.6
2	11.00	30	14.02	20.05
			17.52	10.56
3	13.00	30	15.30	17.33
			18.30	3.87
4	12.55	40	15.15	16.41
			18.05	5.91
5	21.00	45	23.00	22.75
			2.00	8.63
6	17.18	66	19.35	15.15
			21.25	10.40
7	17.30	37	19.30	23.15
			21.30	11.95
8	17.10	37	18.50	27.37
			20.50	13.99
9	11.06	47	13.17	24.52
			15.15	15.30
10	17.37	25	19.02	25.24
			21.15	11.21
11	9.38	18	11.40	22.30
			14.20	10.32
12	17.16	39	19.05	20.99
			21.05	10.17
13	17.46	39	19.15	24.09
			21.30	17.01
14	9.45	35	11.08	30.82
			13.06	14.25
15	20.00	47	22.36	17.85
			1.07	8.23
16	9.39	17	11.32	29.87
			14.30	14.44
17	9.36	22	10.56	22.33
			13.55	12.03
18	17.16	42	19.05	19.15
			22.05	12.21
19	21.16	50	23.09	19.33
			1.01	8.96

Table 10 Two plasma ceftazidime concentrations of each patient after intermittent administration at least five estimated half-life of drug

Subject No.	Time			Ceftazidime level (μg/mL)
	t_0	t_{inf} (min)	Collecting time	
1	23.30	30	7.00	55.115
			11.00	32.570
2	11.30	30	14.02	50.725
			17.52	22.619
3	13.30	30	15.30	79.419
			18.30	17.659
4	13.35	40	15.15	57.253
			18.05	19.838
5	21.45	15	23.00	73.477
			02.00	24.733
6	13.00	30	19.35	29.029
	20.45	15	21.25	129.237
7	18.07	25	19.30	74.565
			21.30	32.723
8	13.30	8	14.40	42.654
			18.50	10.053
9	9.34	26	13.17	41.316
			15.15	29.263
10	16.50	45	19.00	61.167
			21.15	27.190
11	10.00	40	11.40	80.124
			14.20	33.688
12	13.10	40	16.05	36.79
			19.05	13.84
13	13.10	15	19.15	29.11
			21.30	21.39
14	5.55	15	11.08	11.43
			13.06	5.39
15	21.07	23	22.36	75.63
			1.07	29.54
16	9.58	16	11.32	106.12
			14.30	46.41
17	9.35	19	10.56	124.44
			13.55	63.73
18	17.02	12	19.05	44.47
			22.05	27.78
19	22.07	18	23.09	75.69
			1.01	30.39

4. Pharmacokinetic parameters of amikacin and ceftazidime

Pharmacokinetic parameters of both drugs were calculated by using short infusion one compartment with first order elimination model. Table 11 presented pharmacokinetic parameters of both drugs of each patient.

Creatinine clearances were calculated by using method of Cockcroft and Gault. Actual weights of patients were identified only in ten patients, so approximate weights were used in nine patients to calculate V_d per weight.

Maximum concentration ($C_{ss\ max}$) and minimum concentration ($C_{ss\ min}$) of both drugs were extrapolated from calculated pharmacokinetic parameters and presented in Table 12. Amikacin maximum concentration were more than 30 μg/mL in eight patients, in range of 20-30 μg/mL in ten patients and less than 20 μg/mL in one patient. Amikacin minimum concentrations were less than 1 μg/mL in eighteen patients and should be nondetectable because the lowest measurable concentration of amikacin by TDx analyzer was 0.8 μg/mL. Amikacin minimum concentration was 3.39 μg/mL in one patient who had renal impairment.

Concentrations of ceftazidime before administration of next dose (trough level) were more than 8 μg/mL in eight patients. In the same way as amikacin, the highest ceftazidime minimum concentration was found in patient who had renal impairment.

Table 11 The pharmacokinetic parameters of amikacin and ceftazidime

Subject No.	$K_e(hr^{-1})$		$t_{½}$(hr)		Cl(L/hr)		V_d(L)		V_d(L/kg)	
	amikacin	ceftazidime	amikacin	ceftazidime	amikacin	ceftazidime	amikacin	ceftazidime	amikacin	ceftazidime
1φ	0.0865	0.1315	8.0093	5.2697	1.8643	2.3179	21.5462	17.6259	0.4143	0.3380
2φ	0.1673	0.2107	4.1433	3.2889	2.6824	2.8111	16.0375	13.3411	0.2673	0.2224
3	0.4997	0.5012	1.3868	1.38276	4.6595	5.3614	9.3970	10.6978	0.2237	0.2547
4	0.3604	0.3741	1.9227	1.8523	8.2686	8.3866	22.9402	22.4169	0.2941	0.2874
5	0.3231	0.3630	2.1448	1.9094	6.5705	6.9507	20.3354	19.1508	0.4067	0.3830
6φ	0.2052	0.2489	3.3766	2.7844	4.7910	4.1943	23.3441	16.8523	0.4669	0.3370
7φ	0.3306	0.4118	2.0960	1.6829	6.1422	6.9827	18.5770	16.9565	0.3505	0.3199
8	0.3356	0.3468	2.0653	1.9981	5.9370	5.9909	17.6931	17.2734	0.3217	0.3141
9φ	0.2358	0.1725	2.9387	4.0185	4.7883	6.1022	20.3052	35.3848	0.4061	0.7077
10φ	0.3661	0.3659	1.8927	1.8942	6.9978	6.3852	19.1124	17.4528	0.3185	0.2909
11φ	0.2908	0.3270	2.3834	2.1196	5.6631	5.7057	19.4772	17.4510	0.3358	0.3009
12	0.3623	0.3258	1.9128	2.1268	7.5585	8.2562	20.8624	25.3380	0.2819*	0.3424*
13φ	0.1547	0.1369	4.4807	5.0628	2.7521	3.1085	17.7940	22.7097	0.3559	0.4542
14	0.3794	0.3699	1.8266	1.8736	6.1147	10.5500	16.1175	28.5238	0.3429	0.6069
15	0.3076	0.3736	2.2527	1.8552	6.5726	6.4262	21.3651	17.2030	0.3365	0.2709
16	0.2450	0.2787	2.8288	2.4863	4.0268	3.9484	16.4372	14.1658	0.3044	0.2623
17	0.2062	0.2230	3.3602	3.1072	3.6702	3.0780	17.7960	13.8008	0.2870	0.2226
18φ	0.1502	0.1569	4.6153	4.4183	3.2349	3.6335	21.5439	23.1662	0.5130**	0.5516**
19	0.4117	0.4889	1.6833	1.4176	8.7788	8.4965	21.3236	17.3807	0.2699	0.2094
								Mean ± S.D.	0.34 ± 0.07	0.35 ± 0.14

φ : using approximate weight in calculation Vd/weight * : Actual weigh is 28% more than ideal body weigh ** : Patient has edema

Table 12 Calculated $C_{ss\ max}$ and calculated $C_{ss\ min}$ of amikacin and ceftazidime

Subject No	Amikacin (μg/mL)		Ceftazidime (μg/mL)	
	$C_{ss\ max}$	$C_{ss\ min}$	$C_{ss\ max}$	$C_{ss\ min}$
1	24.87	3.3990	129.57	30.50
2	28.02	0.5980	69.58	6.85
3	36.67	0.0004	131.09	3.93
4	24.99	0.0063	69.03	5.03
5	28.99	0.0172	88.10	6.94
6	17.43	0.1553	114.12	19.99
7	31.00	0.0154	91.613	5.13
8	32.37	0.0144	50.732	4.48
9	30.08	0.1327	66.765	19.97
10	30.31	0.0067	88.187	6.81
11	31.92	0.0398	94.354	9.57
12	26.73	0.0065	65.08	6.65
13	25.36	0.7233	60.40	23.17
14	34.54	0.0056	57.83	4.34
15	26.76	0.0226	94.63	6.92
16	39.11	0.1397	132.63	18.85
17	24.58	0.2141	150.41	31.57
18	21.01	0.6646	54.96	18.33
19	24.24	0.0019	85.53	2.79
Mean ± S.D.	28.37 ± 5.31	0.3244 ± 0.78	89.19 ± 29.87	12.20 ± 9.32
Min	17.43	0.0004	50.73	2.79
Max	39.11	3.3990	150.41	31.57

$C_{ss\ max}$ **:** Concentration at 30 minute after the end of administration

$C_{ss\ min}$ **:** Concentration before administration of next dose

5. Correlation between ceftazidime and amikacin pharmacokinetic parameters

Scatterplot of amikacin pharmacokinetic parameters versus those of ceftazidime were performed and shown in Figure 7-13. Figure 14-16 showed scatterplot of total clearance of each drug versus creatinine clearance. The significance and high correlation were found between amikacin and ceftazidime for elimination constant (K_e), total body clearance (Cl) and elimination half-life ($t_{1/2}$). Figure 9 showed that there was an outlier which resulted from the extremely high value of ceftazidime clearance in patient no.14 while her amikacin clearance was within the average range. Regression analysis by excluding outlier showed significant correlation with better correlation coefficient (*r*). No correlation between appearance volume of distribution (V_d) of both drug in unit of liter (r = 0.359, p = 0.131), but fair correlation were found when corrected appearance volume of distribution data by weight to be the unit of liter per kilogram. The better correlation coefficient were found when analysis correlation of V_d (L/kg) by excluding patient no. 14 (r=0.671). .

Regression equations between pharmacokinetic parameters of both drugs were established and the predictive equations were shown in Table 13. Table 13 also showed regression equation between total clearance of each drug and creatinine clearance. Moderate correlation was found between drug clearance and creatinine clearance. Comparison of correlation coefficient showed that correlation between total clearances of both drugs was higher correlated than those between total clearance of each drug and creatinine clearance which estimated from the method of Cockcroft and Gault.

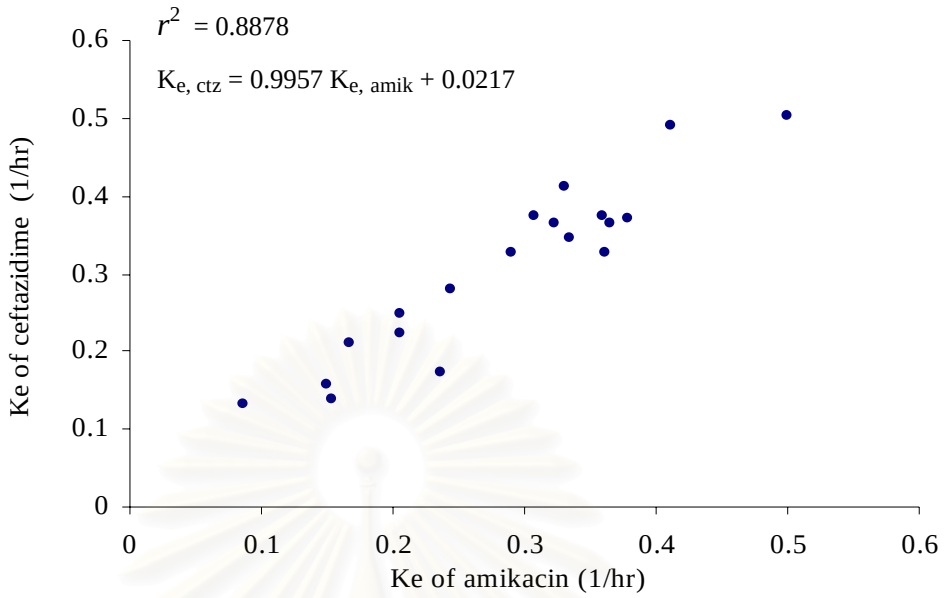

Figure 7 Scatterplot of elimination rate constant of ceftazidime versus elimination rate constant of amikacin (n = 19)

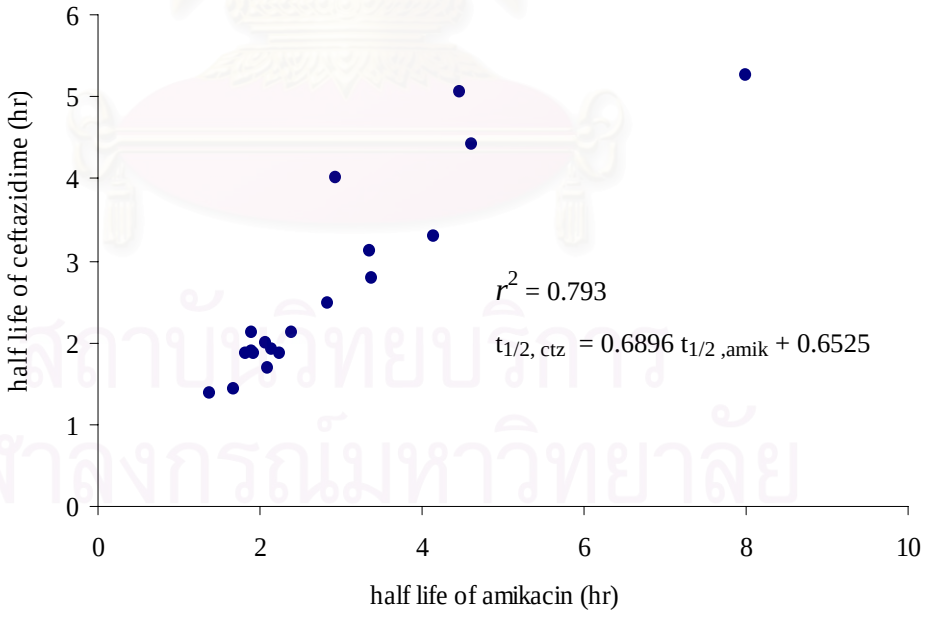

Figure 8 Scatterplot of elimination half-life of ceftazidime versus elimination half-life of amikacin (n = 19)

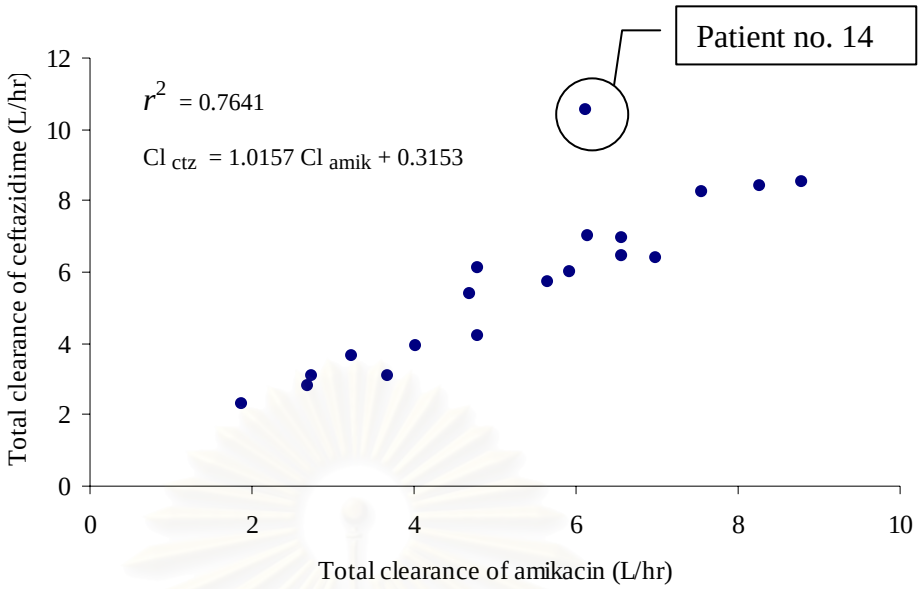

Figure 9 Scatterplot of total body clearance of ceftazidime versus total body clearance of amikacin (n = 19)

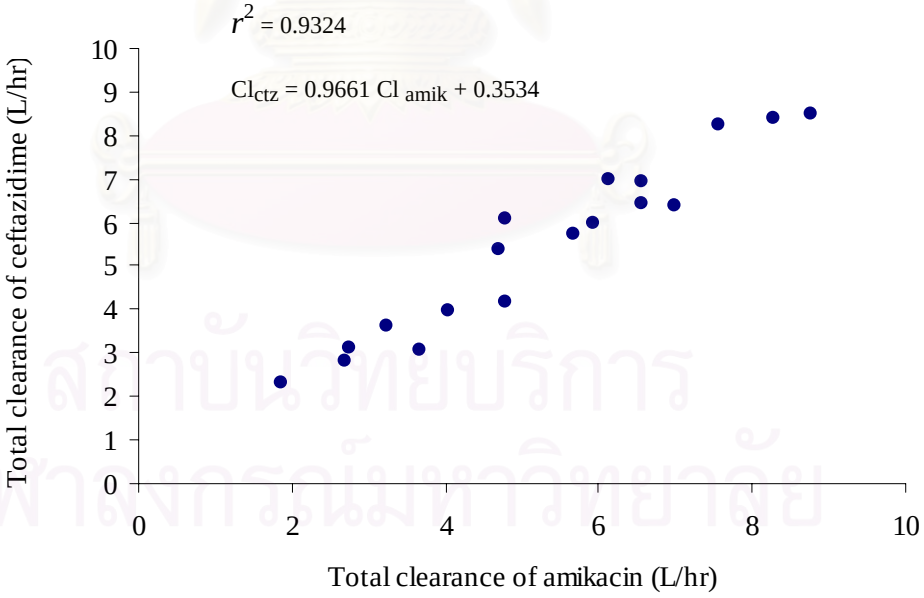

Figure 10 Scatterplot of total body clearance of ceftazidime versus total body clearance of amikacin (n = 18; exclude patient no. 14)

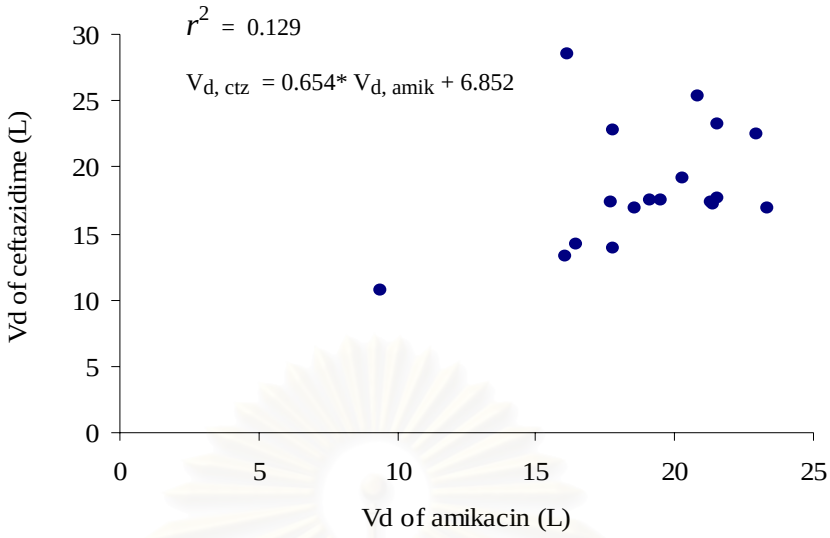

Figure 11 Scatterplot of appearance volume of distribution of ceftazidime and appearance volume of distribution of amikacin (n = 19)
*: p = 0.131

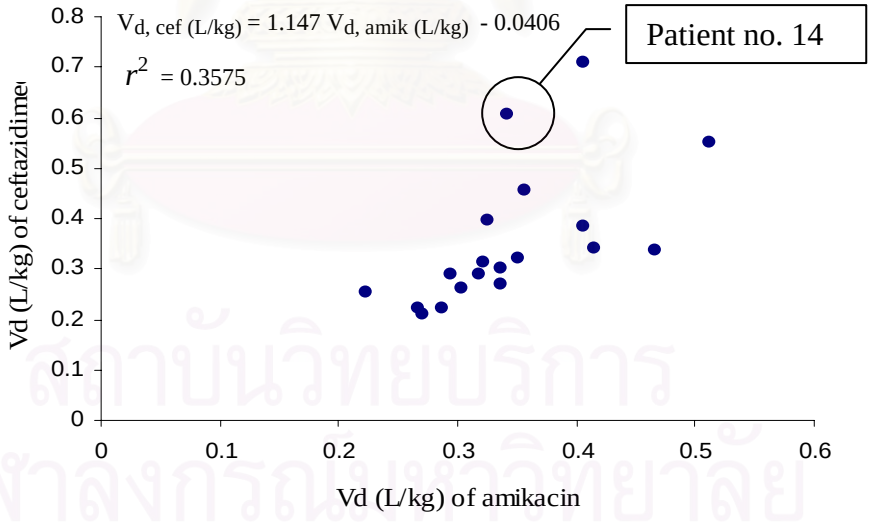

Figure 12 Scatterplot of appearance volume of distribution divide by weight (n = 19)

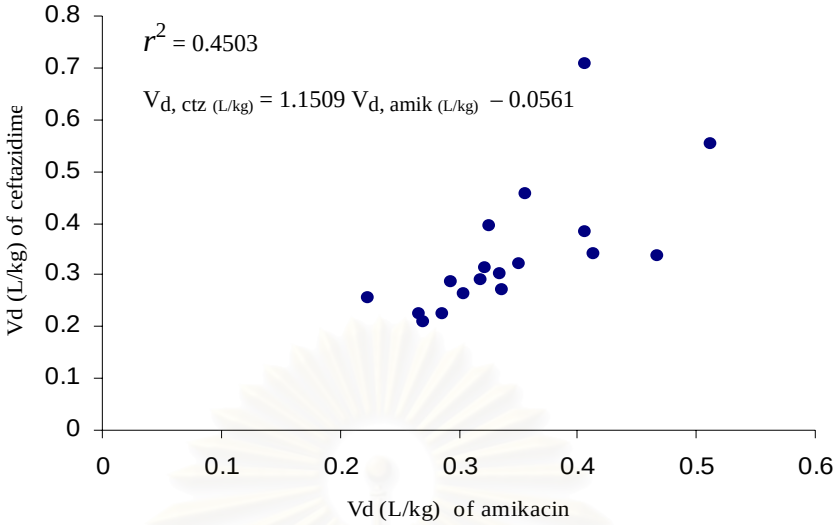

Figure 13 Scatterplot of appearance volume of distribution divide by weight (n = 18 ;exclude patient no. 14)

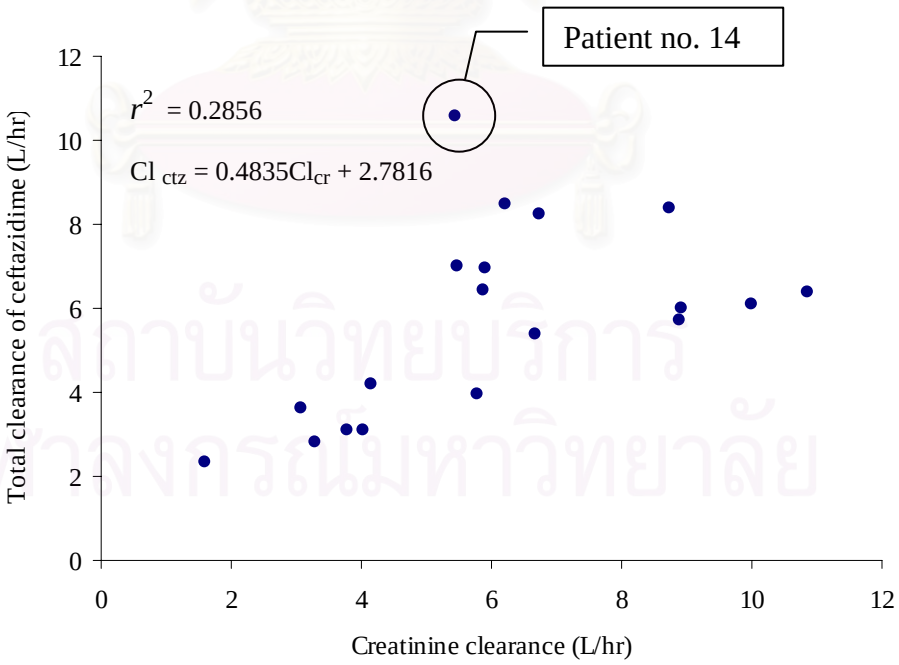

Figure 14 Scatterplot of ceftazidime clearance versus creatinine clearance (n = 19)

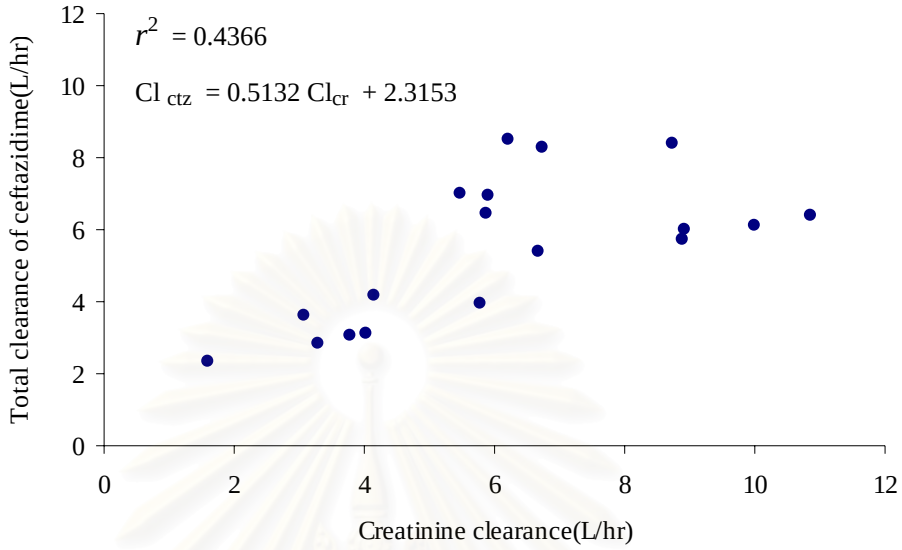

Figure 15 Scatterplot of ceftazidime clearance versus creatinine clearance (n = 18 ;exclude patient no. 14)

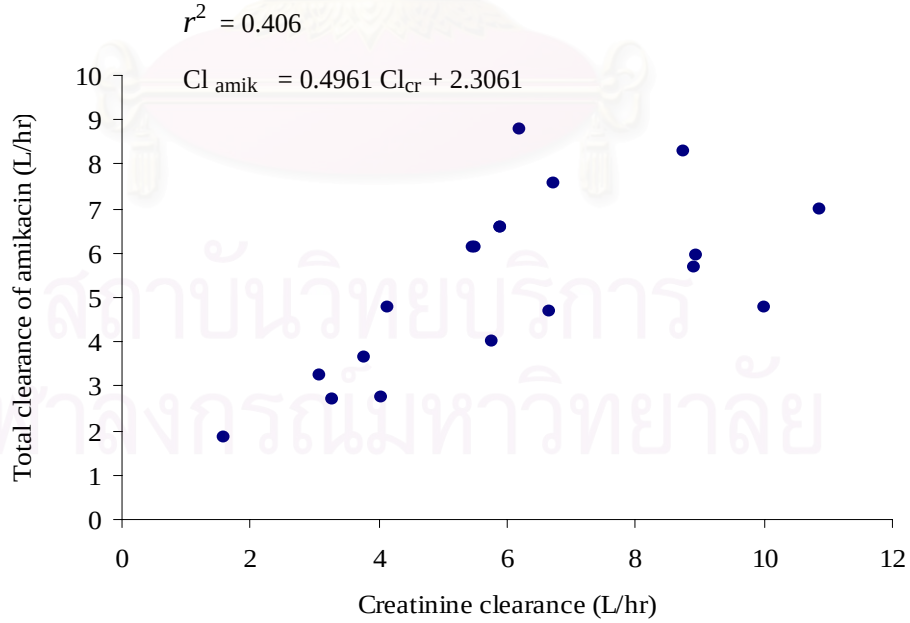

Figure 16 Scatterplot of amikacin clearance versus creatinine clearance (n = 19)

Table 13 Relationships between amikacin and ceftazidime pharmacokinetic parameters

Regression Equation $^{\varphi}$	r^{ϕ}	r^2	P value*
$K_{e,\ ctz}$ (hr^{-1}) = 0.9957 $K_{e,\ amik}$ + 0.0217	0.942	0.8878	< 0.0001
$K_{e,\ amik}$ (hr^{-1}) = 0.8916 $K_{e,\ ctz}$ + 0.0127			
$Cl_{\ ctz}$ (L/hr^{-1}) = 1.0157 $Cl_{\ amik}$ + 0.3253	0.874	0.7641^{λ}	< 0.0001
$Cl_{\ amik}$ (L/hr^{-1}) = 0.75231 $Cl_{\ ctz}$ + 1.0184			
$t_{1/2\ ,cef}$ (hr) = 0.6896 $t_{1/2\ ,amik}$ + 0.6525	0.891	0.7933	< 0.0001
$t_{1/2,\ amik}$(hr) = 1.1504 $t_{1/2,\ ctz}$ - 0.1489			
$V_{d,\ ctz}$ (L/kg) = 1.147 $V_{d,amik}$ – 0.0406	0.598	0.3575^{δ}	0.007
$V_{d,amik}$ (L/kg) = 0.3117 $V_{d,\ ctz}$ + 0.2338			
$Cl_{\ ctz}$(L/hr^{-1}) = 0.4835 $Cl_{\ cr}$ + 2.7816	0.5344	0.2856^{ε}	0.018
$Cl_{\ amik}$ (L/hr^{-1}) = 0.4961 $Cl_{\ cr}$ + 2.3061	0.637	0.4060	0.003

φ : K_e = elimination constant, amik = amikacin, ctz = ceftazidime, Cl = total body clearance, Cl_{cr} = creatinine clearance, $t_{1/2}$ = elimination half-life

* : from regression analysis

ϕ : from pearson correlation

λ : If exclude patient no. 14 (n = 18) , the equation will be following:

$Cl_{\ ctz}$ (L/hr^{-1}) = 0.9661 $Cl_{\ amik}$ + 0.3534 ; r = 0.966, r^2 = 0.9324, p < 0.0001

$Cl_{\ amik}$ (L/hr^{-1}) = 0.9651 $Cl_{\ ctz}$ + 0.0156

δ : If exclude patient no. 14 (n = 18) , the equation will be following:

$V_{d,\ ctz}$ (L/kg) = 1.1509 $V_{d,amik}$ - 0.0561 ; r = 0.671, r^2 = 0.4503, p = 0.002

$V_{d,amik}$(L/kg) = 0.3913 $V_{d,\ ctz}$ – 0.2112

ε : If exclude patient no. 14 (n = 18) , the equation will be following:

$Cl_{\ ctz}$(L/hr^{-1}) = 0.5132 $Cl_{\ cr}$ + 2.3153 ; r = 0.661, r^2 = 0.4366, p = 0.003

6. Therapeutic outcome

Outcome of therapy including clinical outcome, microbiological outcome and adverse drug reaction were observed and presented in Table 14. 68.42% of patients responded to therapy (cure and improve). All pathogens in patient whose clinical sign and symptom were improved, were susceptible to amikacin and ceftazidime exept for only one pathogen which resisted to ceftazidime. Among the five patients who were cured, three were infected with only one pathogen and two had fever without source of infection. Six patients with therapeutic failure, four had multi-pathogen infections which included ESBL and/or MDR pathogens and two had fever without source of infection. All persistent pathogens were resisted to ceftazidime and half of them were resisted to amikacin. Two/third of eliminated pathogens were susceptible to ceftazidime and amikacin (The data were shown in appendix C). Stepped up to higher potency antimicrobial agent were performed in nonresponsive patients. Tazocin® (piperacillin + tazobactam), Tienam® (Imipenem + cilastatin) and Invanz® (Ertapenem) administrated as single or combination therapy with ciprofloxacin were prescribed in five nonresponsive patients. One nonresponsive patient died without step up therapy. Mild adverse reaction occurred in only one patient who had itching rash in the first day of ceftazidime administration and resolved later. No serious adverse drug reaction occurred in any patient during therapy.

Table 14 Data of therapeutic outcome

Outcome	Value (n) , (%)
Clinical outcome	
cure	5 (26.32)
improvement	8 (42.10)
failure	6 (31.58)
Microbiological outcome*	
elimination	6 (23.08)
persistence	7 (26.92)
indeterminate	13 (50.00)
Adverse drug reaction	
Amikacin	
nephrotoxicity	-
ototoxicity	-
Ceftazidime	
rash and itching	1 (5.26)

* : number of pathogen

CHAPTER V

DISCUSSION

This study showed high correlation between total drug clearance (Cl), elimination rate constant (K_e) and elimination half-life ($t_{1/2}$) of ceftazidime and amikacin (r = 0.966, 0.942, 0.891 for Cl, K_e, and $t_{1/2}$ respectively). Even though K_e ,Cl and $t_{1/2}$ correlation were analyzed by include data of patients such as hematological malignancies patients, spinal cord injury patients and patients with edema who had different pharmacokinetic parameters (volume of distribution and total drug clearance) from general patient were reported *(9-11, 72-76)*. This may due to similar physical properties of both drugs. The slopes of regression equation for predicting K_e from each other were nearly 1.0, these results supported the similar properties of both drugs.

The relationships of pharmacokinetic parameters between these two drugs were stronger than the relationships between aminoglycosides and vancomycin pharmacokinetic parameters previously reported *(61-64)*. The difference could be due to the chemical properties which are more different between aminoglycosides and vancomycin than aminoglycosides and ceftazidime (V_d of vancomycin = 0.5 – 1 L/kg, 10% - 50% of total vancomycin bind with plasma protein and its mean serum half-life is 4 to 6 hours in patient with normal renal function) *(77-79)*.

The V_d obtained in this study was estimated from two drug concentrations at elimination phase which was subjected to several confounding factors. Analysis by exclusion of patient 14 whose V_d value was altered by her treatment, fair correlation of V_d (L/kg) was found (r = 0.671). Furthermore, there were nine patients whose exact weights were unknown and the approximated weights had to be used in place and these might contribute some effect.

It has been reported that patients with hypoalbuminemia have significantly greater V_d value of aminoglycoside *(80)*. In this study, only three patients had serum albumin in the normal range, this could contribute to average large V_d of both drugs (V_d = 0.34 ± 0.07 L/kg and 0.35 ± 0.14 L/kg for amikacin and ceftazidime, respectively). The lowest serum albumin (1.6 g/dL) was found in patient 9 who had

spinal cord injury which altered V_d and Cl had been reported. Hence, his large V_d may resulted from both interference. Percentage of CV of the estimated value of amikacin V_d was less than those of ceftazidime V_d (20.58% and 40% respectively), this indicated that interpatient variation was larger for ceftazidime V_d.

Patient 9 had spinal cord injury (SCI) which had been indicated to have larger weight-adjusted V_d for aminoglycosides than those of able-bodied patients *(81, 82)*. His V_d of both drugs were obviously larger than others, particularly the V_d of ceftazidime. This result indicated that not only amikacin but also ceftazidime dosage should be adjusted individually in SCI patient. Patient 14 had biliary obstruction, percutaneous transhepatic biliary drainage (PTBD) was done to relieve the obstruction. Although ceftazidime and amikacin distribute to bile and the gallbladder, they do not penetrate into obstructed bile. However ceftazidime penetrates quickly once the obstruction is relieved *(5, 29)*. Non renal drug clearance in this patient might affected ceftazidime and amikacin concentrations and in turn might altere the estimated V_d and Cl of both antibiotics in unpredicted proportion. This study did not measured the concentration of ceftazidime and amikacin in bile, so two predictive models were presented and uncleared which one was better. For patient 18 with edema, high V_d were found for both drugs.

The correlation between amikacin clearance and ceftazidime clearance was better than the correlation between either drug clearance and creatinine clearance. This result indicated that ceftazidime clearance could be more accurately predicted from amikacin clearance than from creatinine clearance estimated from the method of Cockcroft & Gault.

The method of estimating creatinine clearance plays an important role, in this study, creatinine clearance from serum creatinine was calculated using the equation of Cockcroft & Gault. The equation was reported to give an over estimated result in patient with impair renal function and was limited to be accurately estimated in only normal muscle mass patient *(71)*. This may contribute to fair correlation between ceftazidime clearance and creatinine clearance.

Pea and colleagues studied ceftazidime pharmacokinetics in twenty acute myeloid leukemia patients with febrile neutropenia and showed fair correlation between clearances of creatinine and ceftazidime (r = 0.52) *(11)*. The medium correlation might be due in part to the large variation of ceftazidime V_d (%CV = 41.44%) which appeared also in our study (%CV = 40.9%). Correlation between ceftazidime clearance and creatinine clearance was studied by Angus and colleagues in twenty one septicemia meliodosis patients and showed better correlation (r = 0.71) *(40)*. Creatinine clearances in both mentioned studies were determined by the method of Cockcroft & Gault.

Studies in critical ill patients were controversial. In fifteen edematous critical ill patients, Gomez and coworkers reported significant correlation only between ceftazidime K_e and creatinine clearance (r = 0.67) but not between creatinine clearance and ceftazidime clearance *(10)*. In contrast, Young and colleagues studied in ten critical ill patients with normal renal function and reported excellent correlation (r = 0.89) between creatinine clearance and ceftazidime clearance *(12)*. The last study was performed in pneumonia without edema patients only, this may result in lower variation in ceftazidime V_d (%CV = 13%). Creatinine clearances were determined from 8-hours urine collection in both studies.

The studies of Ackerman and colleagues in eleven subjects with creatinine clearances ranging from 6 to 113 mL/min and Welage and colleagues in fourteen volunteers with different degrees of renal function (Cl_{cr} = 4.5 – 122.3 mL/min) showed excellent correlation (r = 0.99 and 0.95 respectively) between creatinine clearance and ceftazidime clearance *(37, 38)*. Creatinine clearances were determined with 24-hours urine collection in both studies. Wide range of creatinine crearance and accurate method of estimating creatinine clearance in these two studies may participate in more correlation between creatinine clearance and ceftazidime clearance than our study (Cl_{cr} = 26 – 181 mL/min).

The correlation coefficient (r) between amikacin clearance and creatinine clearance was 0.647 (p = 0.003). This weak correlation indicated that predicted amikacin clearance by estimating from creatinine clearance (using the method of

Cockcroft & Gault) might be less accurate than those predicted from ceftazidime clearance (r = 0.966). However, inconvenience in measurement of ceftazidime concentration may be an obstacle of using ceftazidime pharmacokinetic parameters to predict amikacin pharmacokinetic parameters.

Previous studies by Zarowitz and coworkers suggested that aminoglycoside clearance which estimated from two point drug concentrations could be used as an estimate of GFR in critically ill patients *(83)*. From our study, it was indicated that, in infectious patients who were treated with antibiotics, the aminoglycoside clearance or ceftazidime clearance might be a better estimator of the GFR or the clearances of other drugs which were primary excreted by GFR. Ceftazidime might be slightly better than aminoglycosides since it was primarily eliminated by GFR only, while aminoglycosides, besides GFR , was partially tubular reabsorbed *(26)*. Further studies to prove this suggestion are required.

If more convenient method to determine ceftazidime concentration is available, appropriate drug dosage regimen will then be easily designed, whether an intermittent or a continuous intravenous administration should be used in order to get optimum therapeutic level for each patient. This will not only maximize the therapeutic efficacy but also minimize the development of resistant bacterial strains *(84)*.

This study did not design to evaluate the relationship between clinical outcomes and drug levels. The outcome reported in Table 14 came from clinical observation only and could not be treated as an absolute outcome. Approximately 70% of the patients were cure or improved while the less showed non responsive which might relate in part to plasma concentrations of both drugs, therefore, the calculated $C_{ss\ max}$ and $C_{ss\ min}$ of both drugs should be taken into consideration.

For amikacin, $C_{ss\ max}$ which is ten times higher than the MIC of the pathogen is recommended for good efficacy. In this study the average calculated $C_{ss\ max}$ was 28.37 mg/L, which indicated that it might be effective only to high susceptible pathogen which their MIC were less than 3 mg/L. However, previous study in Phramongkutklao Hospital reported the MIC of *Pseudomonas aeruginosa* to amikacin

was 3 mg/L *(85)*, so maximum concentration of at least 30 mg/L or higher should be optimized for the efficacy, therefore, higher dosage should be recommended. Majority of the patients had a long drug-free interval (less than 0.8 μg/mL around 10 hours) which might be longer than the duration of its PAE effect particularly in neutropenic patients. Anaizi recommended the dosing interval to be shorter than 24 hrs in patients with high clearance (e.g., young adults, etc) to allow a drug-free interval of not longer than 3 - 5 hours *(86)*. Calculated amikacin C_{min} of eighteen patients were less than 1 μg/mL indicated that amikacin was completely eliminated within 24 hours in most patients, these might be the reason for not observing nephotoxicity in any patient. One patient whose amikacin C_{min} was 3.4 μg/mL had renal impairment from the beginning and amikacin was used for a short period of time.

For ceftazidime, the time above MIC has been reported to give the best prediction of the therapeutic efficacy. Concentrations which were four to five times above MIC in optimum duration are desired to maintain efficacy, therefore, the $C_{ss\ min}$ which is an important parameter for comparison with MIC should be taken into consideration. Eleven patients had calculated $C_{ss\ min}$ of ceftazidime which were less than 8 mg/L (the clinical and laboratory standards institute (CLSI) breakpoint for susceptibility to ceftazidime) and among these patients, nine had already been administered with maximum dose of ceftazidime (2 g every 8 hours). This indicated that ,even for susceptible pathogen, ceftazidime continuous infusion method of administration should be considered in these patients to optimize the efficacy. The dermatological adverse effect of ceftazidime which found in one patient was not related to drug concentration. Continued therapy was allowed since the symptom was better after later dose of administration.

There are many factors which influence the outcome of therapy such as host factor, type of microorganism and the antimicrobial susceptibility of pathogen. This study did not determined the MIC of pathogen to ceftazidime and amikacin. The susceptibility of pathogens were roughly reported as susceptible, intermediated resistant and resistant using CLSI breakpoint and half of the cases, pathogens had not been followed after treatment. However, majority of patients whose clinical sign and symptom were improved or cured, were infected with pathogens which were susceptible to ceftazidime and amikacin. These pathogens may required low level of

both drugs to achieve their pharmacodynamic index. For therapeutic failure patients, all pathogens were ESBL and/or MDR. Even though, *in vitro* synergistic effect from ceftazidime and aminoglycosides had been reported and lower MIC of pathogens were recorded when compare with single drug exposure *(55, 87)*, the exact MIC of ESBL and/or MDR pathogens in our patients had not been determined. Requirement of high level of amikacin and ceftazidime to achieve the pharmacodynamic index may take part in the therapeutic failure.

Most pharmacokinetic/pharmacodynamic studies were conducted to predict the therapeutic efficacy of single-antimicrobial regimen. In combination antimicrobial therapy, specific pharmacodynamic parameters should be considered. Several *in vitro* studies propose new pharmacodynamic parameter for prediction of the efficacy in combination therapy; however, clinical studies are desired to prove this proposition. *(87, 88)*.

CHAPTER VI

CONCLUSION

Correlations between ceftazidime and amikacin pharmacokinetic parameters were examined in nineteen infectious patients at Phramongkutklo Hospital during February to May 2006. Ratio of men : women was 2.2 : 1, age ranged from 19 to 83 years, estimated Cl_{cr} ranged from 26 to 181 mL/min, mean of serum albumin was 2.77 g/dL, half of them had cancer and most of them were prescribed for febrile neutropenia. *Pseudomonas aeruginosa* were most frequently isolated from patients and most of them were still susceptible to ceftazidime and amikacin.

Pharmacokinetic parameters were calculated from two plasma drug concentrations by using short infusion one compartment with first order elimination model. Regression analysis showed significant linear with high correlation between total drug clearance (Cl), elimination rate constant (K_e) and elimination half-life ($t_{1/2}$) of ceftazidime and amikacin (equation showed in Table 13). The correlation between amikacin clearance and ceftazidime clearance was better than the correlation between either drug clearance and creatinine clearance. Fair correlation was found between V_d of both drugs.

This result indicated that Cl, K_e and $t_{1/2}$ of ceftazidime could be more accurately predicted from those of amikacin clearance than from estimated creatinine clearance. This will help the physician to design an appropriated dosage regimen of ceftazidime for each patient. If more convenient method of measuring ceftazidime concentration shall be developed, pharmacokinetic parameters (Cl, K_e and $t_{1/2}$) of amikacin may be quite accurately predicted from those of ceftazidime. Furthermore, ceftazidime clearance might be used as an estimator of GFR in individual patient.

The limitations of this study include the following:

1) The equations for predicting pharmacokinetic parameters of ceftazidime from amikacin in this study were conducted in patients who had Cl_{cr} in range of 26 – 181 mL/min. Hence, extrapolation to patient who has Cl_{cr} below 26 mL/min or over 181 mL/min should be done with caution.
2) This study obtained exact weight from ten patients. Estimated weight from nine patient were used for correcting V_d to be the unit of liter per kilogram. This may result in fair correlation between V_d of ceftazidime and amikacin. Even though Cl_{cr} of four patients were calculated from estimated weight, the relationship between drug clearance and creatinine clearance may be affected.

Considerations for further studies:

1) The predictive equations from this study should be further evaluate to determine the accuracy and precision.
2) Further study to investigate the benefit of individualized pharmacokinetic dosing of ceftazidime from predicting method over the standard dosing which are recommended from reference will be verify the clinical significant of the predictive method.
3) The relationship of pharmacokinetic parameters between ceftazidime and other aminoglycosides are expected because the pharmacokinetic properties of all aminoglycosides are the same. However, further studies to confirm this assumption are desired.
4) Further study to investigate the correlation of pharmacokinetic parameters between ceftazidime and amikacin in patients with cystic fibrosis and ascites may provide the new method of dosage modification for ceftazidime.

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APPENDICES

APPENDIX A

แบบฟอร์มบันทึกข้อมูลผู้ป่วย

<u>ส่วนที่ 1</u>

ชื่อ-สกุล.....HN……..AN……..เพศ.....

หอผู้ป่วย.....วันที่เข้ารับการรักษา.....วันที่จำหน่าย.....

จำนวนวันที่รักษาในโรงพยาบาลรวม.....วัน สิทธิในการรักษาพยาบาล.....

อายุ.....ปี น้ำหนัก.....กิโลกรัม ส่วนสูง.....เซนติเมตร CL_{cr}…….....mL/min

ประวัติการแพ้ยา☐ ไม่แพ้ยา ☐ แพ้ยา.....

โรคประจำตัว ☐ โรคหัวใจและหลอดเลือด ☐ โรคเบาหวาน ☐ โรคความดันโลหิตสูง

☐ โรคไต ☐ โรคตับ ☐ โรคอื่นๆ.....

โรคที่ทำให้ผู้ป่วยต้องเข้ารับการรักษาในโรงพยาบาลในครั้งนี้

……

สาเหตุที่ต้องใช้ยา ceftazidime ร่วมกับ amikacin

.....

ยาที่ได้รับในปัจจุบัน

รายการยา													

ผลการตรวจทางห้องปฏิบัติการ

วันที่																			

U/A

วันที่																			

ผลการเพาะเชื้อและทดสอบความไวของเชื้อ

ว/ด/ป	specimen	เชื้อ	ไวต่อยา	ดื้อยา

รูปแบบการสั่งใช้ยา

☐ empirical therapy ☐ definitive therapy

ยา	เริ่มต้น			สุดท้าย	
	regimen	วันที่	เวลา	วันที่	เวลา
ceftazidime					
amikacin					

<u>ส่วนที่ 2</u>

ระดับยา

วันที่เจาะเลือด	ceftazidime		amikacin	
	เวลาที่เจาะเลือด	ระดับยา	เวลาที่เจาะเลือด	ระดับยา

ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์

ค่าพารามิเตอร์	ceftazidime	amikacin
Cl		
Ke		
Vd		
$t_{1/2}$		
$C_{ss\ max}$		
$C_{ss\ min}$		

ผลการรักษา

☐ ตอบสนองต่อการรักษา

☐ อาการดีขึ้นหลังได้รับยา ☐ หายจากโรค ☐ ระบุไม่ได้

☐ การรักษาล้มเหลว

☐ อาการไม่ดีขึ้นต้องเปลี่ยนชนิดยาปฏิชีวนะ ☐ เสียชีวิต

☐ เปลี่ยนชนิดยาปฏิชีวนะตามผลการทดสอบความไวของเชื้อ

☐ เกิดอาการไม่พึงประสงค์ ☐ <u>ไม่</u>เกิดอาการไม่พึงประสงค์

☐ เกิดอาการไม่พึงประสงค์ต่อไต ☐ เกิดอาการไม่พึงประสงค์ต่อหู ☐ อื่นๆ.....

APPENDIX B

เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัย
(Research Subject Information Sheet)

ชื่อโครงการวิจัย

ความสัมพันธ์ระหว่างค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาเซฟเทซิดิมและยาอะมิเคซิน

วันที่ชี้แจง

.....

ชื่อและสถานที่ทำงานของผู้วิจัย

นางสาวสำอางค์ เกียรติเจริญสิน ภาควิชาเภสัชกรรม(คลินิก) คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-1864-7631

ชื่ออาจารย์ที่ปรึกษาและอาจารย์ที่ปรึกษาร่วม

รศ.ดร.ดวงจิต พนมวัน ณ อยุธยา ภาควิชาเภสัชกรรม(คลินิก) คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-2218-8405 และ พ.อ. ธนะพันธ์ พิบูลย์บรรณกิจ แผนกโรคติดเชื้อ กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า

ผู้ให้ทุนวิจัย

บัณฑิตวิทยาลัย จุฬาลงกรณ์มหาวิทยาลัย

ท่านได้รับการเชิญชวนให้เข้าร่วมการวิจัยเรื่องนี้ แต่ก่อนที่ท่านจะตกลงใจเข้าร่วมโครงการวิจัยหรือไม่ โปรดอ่านข้อความในเอกสารนี้ทั้งหมด เพื่อให้ทราบว่า เหตุใดท่านจึงได้รับการเชิญให้เข้าร่วมโครงการวิจัยนี้ โครงการวิจัยนี้ทำเพื่ออะไร หากท่านเข้าร่วมโครงการวิจัยนี้ท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจจะเกิดขึ้นในระหว่างโครงการวิจัยนี้

ในเอกสารนี้ อาจมีข้อความที่ท่านอ่านแล้วไม่เข้าใจ โปรดสอบถามหัวหน้าโครงการหรือผู้ช่วยที่ทำโครงการวิจัยนี้ให้ช่วยอธิบายจนกว่าจะเข้าใจตลอด ท่านอาจขอเอกสารนี้กลับไปอ่านที่บ้านเพื่อปรึกษาหารือกับญาติพี่น้อง เพื่อน หรือแพทย์ที่ท่านรู้จัก ให้ช่วยคิดว่าควรจะเข้าร่วมโครงการวิจัยครั้งนี้หรือไม่ การเข้าร่วมโครงการวิจัยครั้งนี้จะต้องเป็นความสมัครใจของท่าน ไม่มีการบังคับหรือชักจูง ถึงแม้ท่านจะไม่เข้าร่วมในโครงการวิจัยท่านก็จะได้รับการรักษาพยาบาลตามปกติ การไม่เข้าร่วมหรือถอนตัวจากโครงการวิจัยนี้จะไม่มีผลกระทบต่อการได้รับบริการ การรักษาพยาบาล หรือผลประโยชน์ที่พึงจะได้รับของท่านแต่อย่างใด

โปรดอย่าลงลายมือชื่อของท่านในเอกสารนี้ จนกว่าท่านจะแน่ใจว่ามีความประสงค์จะเข้าร่วมโครงการวิจัยนี้จริง คำว่า “ท่าน” ในเอกสารนี้ หมายถึงผู้เข้าร่วมโครงการวิจัยในฐานะเป็น

อาสาสมัครในโครงการวิจัยนี้ หากท่านเป็นผู้แทนโดยชอบธรรมตามกฎหมายของผู้ที่จะเข้าร่วมโครงการวิจัย และจะลงนามแทนในเอกสารนี้ โปรดเข้าใจว่า “ท่าน” ในเอกสารนี้ หมายถึงผู้เข้าร่วมโครงการวิจัยเท่านั้น

โครงการวิจัยนี้มีที่มาอย่างไร และวัตถุประสงค์ของโครงการ

เซฟเทซิดิม(ceftazidime)เป็นยาปฏิชีวนะที่มีคุณสมบัติในการกำจัดเชื้อแบคทีเรียได้อย่างกว้างขวาง การใช้ยาเซฟเทซิดิมเพื่อกำจัดเชื้อแบคทีเรีย ซูโดโมแนส แอรูจิโนซา(*Pseudomonas aeruginosa*) นิยมใช้ร่วมกับยาในกลุ่มอะมิโนไกลโคไซด์(aminoglycoside) โดยเฉพาะยาอะมิเคซิน(amikacin) เพื่อเพิ่มประสิทธิผลในการกำจัดเชื้อและลดอัตราการดื้อยา ขนาดยาเซฟเทซิดิมที่แนะนำโดยทั่วไปคือ 0.5 – 2 กรัม ทุก 8 ชั่วโมง ในผู้ป่วยที่ภาวะการทำงานของไตปกติ และสำหรับผู้ป่วยที่ภาวะการทำงานของไตบกพร่อง จะต้องปรับระยะห่างระหว่างการให้ยาให้เหมาะสมกับค่าการทำงานของไต เนื่องจากยาเซฟเทซิดิม มีคุณสมบัติละลายน้ำได้ดี จับกับโปรตีนในซีรั่มได้น้อย ยาส่วนใหญ่จะกระจายอยู่นอกเซลล์ การขจัดยาพบว่ายาไม่ถูกเมตาบอไลซ์ และขจัดออกทางไตในรูปเดิมถึง 80 – 90% ดังนั้นการปรับขนาดยาในผู้ป่วยที่มีการทำงานของไตบกพร่องจึงมีความสำคัญ เพราะหากขนาดยาต่ำเกินไป และ/หรือ ระยะห่างระหว่างการให้ยานานเกินไปจะมีผลต่อการรักษาและต่ออัตราการดื้อยา แต่หากขนาดยาสูงเกินไปและ/หรือระยะห่างระหว่างการให้ยาสั้นเกินไปจะทำให้มีการสะสมยาจนอาจเกิดอาการไม่พึงประสงค์ได้ ซึ่งแม้จะพบได้น้อยแต่ก็มีรายงานในผู้สูงอายุและผู้ป่วยที่การทำงานของไตบกพร่อง และเมื่อพิจารณาข้อแนะนำในการปรับระยะห่างการให้ยาเซฟเทซิดิม ในผู้ป่วยที่มีการทำงานของไตบกพร่องจากตำราวิชาการที่ใช้อ้างอิงต่างๆพบว่าค่าการขจัดครีเอตินิน(creatinine clearance) ที่แนะนำให้ปรับระยะห่างการให้ยาและระยะห่างการให้ยาที่แนะนำมีความแตกต่างกัน ซึ่งความแตกต่างจะเห็นได้ชัดในผู้ป่วยที่มีค่าการขจัดครีเอตินินต่ำ ซึ่งเป็นผู้ป่วยที่มีภาวะการทำงานของไตบกพร่องรุนแรง จากปัญหาการขาดเครื่องมือที่แม่นยำในการปรับขนาดยาเซฟเทซิดิม ประกอบกับการวัดระดับยาเซฟเทซิดิมในเลือด ต้องใช้เครื่องมือราคาแพงและต้องอาศัยความชำนาญในการวัด ในขณะที่การวัดระดับยาอะมิเคซิน สามารถทำได้สะดวกกว่า เนื่องจากมีการพัฒนาชุดตรวจให้ง่ายต่อการใช้และราคาถูก อีกทั้งยาอะมิเคซิน ก็มีการขจัดออกทางไตเป็นหลักเช่นเดียวกัน ดังนั้นงานวิจัยนี้จึงมุ่งศึกษาความเป็นไปได้ที่จะนำค่าพารามิเตอร์ทางเภสัชจลนศาสตร์(Ke ,Cl ,Vd)ของยาอะมิเคซิน มาใช้ทำนายค่าพารามิเตอร์ทางเภสัชจลนศาสตร์(Ke ,Cl ,Vd) ของยาเซฟเทซิดิม ซึ่งข้อมูลที่ได้จากการวัดระดับยาอะมิเคซินไม่เพียงจะเป็นประโยชน์ต่อการปรับขนาดยาอะมิเคซินให้เหมาะสม เพื่อลดการเกิดอาการไม่พึงประสงค์ต่อไตและหูแล้ว ยังสามารถนำมาใช้ประโยชน์ต่อการปรับขนาดยาเซฟเทซิดิมให้เหมาะสมด้วย นอกจากนี้ในอนาคตหากมีการพัฒนาวิธีการตรวจวัดระดับยาเซฟเทซิดิมให้ง่ายและสะดวกต่อการใช้เช่นเดียวกับการตรวจวัดระดับยาอะมิเคซินแล้ว การติดตามวัดระดับยา

เซฟเทซิดิมก็จะทำได้สะดวกขึ้นดังนั้น ผู้วิจัยจึงศึกษาถึงความเป็นไปได้ในการนำค่าพารามิเตอร์ทางเภสัชจลนศาสตร์(Ke ,Cl ,Vd)ของ ยาเซฟเทซิดิมมาใช้ทำนายค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ (Ke ,Cl ,Vd)ของยาอะมิเคซินด้วย ซึ่งวิธีการนี้จะช่วยให้ประหยัดค่าใช้จ่ายในการตรวจวัดระดับยา

ท่านได้รับเชิญให้เข้าร่วมโครงการวิจัยนี้เพราะคุณสมบัติที่เหมาะสมดังต่อไปนี้

1. ได้รับยาอะมิเคซิน ร่วมกับ เซฟเทซิดิมในรอบการบริหารยา 24 ชั่วโมง
2. อายุไม่น้อยกว่า 18 ปี
3. มีคุณสมบัติเข้าตามเกณฑ์การคัดเลือกกลุ่มตัวอย่าง

ท่านไม่สามารถเข้าร่วมโครงการวิจัยได้หากท่านมีคุณสมบัติดังต่อไปนี้

1. แพ้ยาอะมิเคซิน และ/หรือ ยาเซฟเทซิดิม
2. ผู้ป่วยหญิงที่อยู่ในระหว่างการตั้งครรภ์และให้นมบุตร
3. ได้รับยาอื่นใดที่มีผลต่อการขจัดยาอะมิเคซิน และ/หรือ ยาเซฟเทซิดิม
4. ผู้ป่วยที่มีระดับซีรั่มครีเอคินิน ระหว่างวันแกว่งมากกว่า 20%
5. ผู้ป่วยโรค ซีสทิคไฟโบรซิส(Cystic fibrosis) ผู้ป่วยท้องมาน(Ascites) ผู้ป่วยฟอกเลือดด้วยเครื่องไตเทียม และผู้ป่วยล้างไตทางช่องท้อง
6. ผู้ป่วยอื่นที่แพทย์เห็นว่าไม่เหมาะสมที่จะเข้าร่วมการวิจัย

สถานที่ทำโครงการวิจัย และจำนวนผู้เข้าร่วมโครงการวิจัย

สถานที่ทำโครงการวิจัยนี้คือ แผนกอายุรกรรมและศัลยกรรมผู้ป่วยใน โรงพยาบาลพระมงกุฎเกล้า โดยมีจำนวนผู้เข้าร่วมโครงการวิจัยทั้งสิ้น 20 คน

ระยะเวลาที่ท่านจะต้องร่วมโครงการวิจัยและจำนวนครั้งที่นัด

ระยะเวลาที่ท่านจะต้องเข้าร่วมโครงการวิจัย คือตลอดช่วงเวลาที่ท่านได้รับยาอะมิเคซินร่วมกับ เซฟเทซิดิม ในรอบการบริหารยา 24 ชั่วโมง และการวิจัยจะสิ้นสุดลงเมื่อท่านหยุดใช้ยาทั้ง 2 ชนิดร่วมกัน

หากท่านเข้าร่วมโครงการวิจัยครั้งนี้ ท่านจะต้องปฏิบัติตามขั้นตอน หรือได้รับการปฏิบัติอย่างไรบ้าง

เมื่อท่านเข้าร่วมโครงการวิจัยท่านจะได้รับตรวจระดับซีรั่มครีเอตินินเพื่อประเมินภาวะการทำงานของไต และกำหนดเวลาที่เหมาะสมในการตรวจวัดระดับยาในเลือด ผู้ป่วยจะถูกเจาะเลือดเพื่อตรวจวัดระดับยาอะมิเคซิน และยาเซฟเทซิดิม 2 ครั้ง โดย 1) ผู้ป่วยที่มีค่าการขจัดครีเอตินินมากกว่า 30 มิลลิลิตร/นาที จะถูกเจาะเลือดในวันที่ 3 ของการได้รับยาอะมิเคซิน ร่วมกับยาเซฟเทซิดิม 2)ผู้ป่วยที่มีค่าการขจัดครีเอตินินเท่ากับ10 - 30 มิลลิลิตร/นาที จะถูกเจาะเลือดในวันที่ 4 ของการได้รับยาอะมิเคซินร่วมกับยาเซฟเทซิดิม 3) ผู้ป่วยที่มีค่าการขจัดครีเอตินินน้อยกว่า 10 มิลลิลิตร/นาที

จะถูกเจาะเลือดในวันที่ 6 ของการได้รับยาอะมิเคซินร่วมกับยาเซฟเทซิดิม ผู้วิจัยจะติดตามบันทึกผลการรักษา และประเมินอาการไม่พึงประสงค์จากยาทั้ง 2 ชนิดที่อาจเกิดกับผู้ป่วย

ความไม่สุขสบาย หรือความเสี่ยงต่ออันตรายที่อาจจะได้รับจากกรรมวิธีการวิจัย และวิธีการป้องกัน/แก้ไขที่หัวหน้าโครงการวิจัยเตรียมไว้หากมีเหตุการณ์ดังกล่าวเกิดขึ้น

ความไม่สุขสบาย หรือความเสี่ยงต่ออันตรายที่ท่านอาจจะได้รับคือ การเจ็บปวดเล็กน้อยระหว่างการเจาะเลือดโดยวิธีการปราศจากเชื้อ ซึ่งอาการดังกล่าวจะหายเป็นปกติเองภายหลังเจาะเลือดเสร็จ

ประโยชน์ที่อาจจะได้รับจากการวิจัย

ประโยชน์ที่ผู้เข้าร่วมโครงการวิจัยจะได้รับจากการวิจัย คือ ได้รู้ระดับยาทั้ง 2 ชนิดที่ผู้ป่วยได้รับว่าอยู่ในช่วงการรักษาหรือไม่ โดยไม่เสียค่าใช้จ่ายในการตรวจวัด

ประโยชน์ที่อาจจะได้รับจากการวิจัยต่อส่วนรวมคือ สามารถนำข้อมูลที่ได้มาหาความสัมพันธ์ระหว่างค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาทั้ง 2 ชนิดเพื่อหาสมการทำนายค่าพารามิเตอร์ทางเภสัชจลนศาสตร์(Ke ,Cl ,Vd)ของยาเซฟเทซิดิม จากค่าค่าพารามิเตอร์ทางเภสัชจลนศาสตร์(Ke ,Cl ,Vd)ของยาอะมิเคซิน ซึ่งสมการที่ได้จะเป็นประโยชน์ต่อการพิจารณาปรับขนาดยาเซฟเทซิดิมให้เหมาะสมกับผู้ป่วยแต่ละรายที่ได้รับยาเซฟเทซิดิมร่วมกับยาอะมิเคซิน

ค่าใช้จ่ายที่ท่านจะต้องรับผิดชอบระหว่างโครงการวิจัย

ค่าใช้จ่ายที่ท่านจะต้องรับผิดชอบระหว่างโครงการวิจัยคือ ค่าใช้จ่ายด้านยา และการรักษาอื่นๆที่ไม่เกี่ยวข้องกับโครงการวิจัย ส่วนที่ท่านจะได้รับจากโครงการวิจัยโดยไม่เสียค่าใช้จ่ายคือ การตรวจระดับยาเซฟเทซิดิม และยาอะมิเคซินในเลือด

ค่าตอบแทนที่จะได้รับเมื่อเข้าร่วมโครงการวิจัย

งานวิจัยนี้ไม่มีค่าตอบแทนสำหรับผู้เข้าร่วมโครงการวิจัย

หากท่านไม่เข้าร่วมโครงการวิจัยนี้ท่านมีทางเลือกอื่นอย่างไรบ้าง

หากท่านไม่เข้าร่วมโครงการวิจัยนี้ท่านมีทางเลือกอื่นคือ แพทย์จะพิจารณาปรับขนาดยาทั้ง 2 ชนิดตามผลการประเมินภาวะการทำงานของไต

หากมีอันตรายที่เกี่ยวข้องกับโครงการวิจัยนี้เกิดขึ้นจะติดต่อกับใคร และจะได้รับการปฏิบัติอย่างไร

หากมีอันตรายที่เกี่ยวข้องกับโครงการวิจัยนี้เกิดขึ้นท่านสามารถติดต่อกับพันเอกนายแพทย์ธนะพันธ์ พิบูลย์บรรณกิจ แผนกโรคติดเชื้อ กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า โทร. 0-6041-8151 หรือ นางสาวสำอางค์ เกียรติเจริญสิน ภาควิชาเภสัชกรรม(คลินิก) คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-1864-7631 ตลอด 24 ชั่วโมง

หากท่านมีคำถามที่เกี่ยวข้องกับโครงการวิจัย จะสอบถามได้จากใคร

1. นางสาวสำอางค์ เกียรติเจริญสิน ภาควิชาเภสัชกรรม(คลินิก) คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 0-1864-7631 ผู้วิจัย
2. พันโทนายแพทย์ธนะพันธ์ พิบูลย์บรรณกิจ แผนกโรคติดเชื้อ กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า โทร. 0-6041-8151 อาจารย์ที่ปรึกษางานวิจัย

หากท่านรู้สึกว่าได้รับการปฏิบัติอย่างไม่เป็นธรรมในระหว่างโครงการวิจัยนี้ ท่านอาจแจ้งเรื่องได้ที่

สำนักงานพิจารณาโครงการวิจัย พบ. โทร. 0-2354-7600 ต่อ 93681

ข้อมูลส่วนตัวของท่านที่ได้จากโครงการวิจัยครั้งนี้จะถูกนำไปใช้ดังต่อไปนี้

ผู้วิจัยจะนำเสนอข้อมูลจากโครงการวิจัยนี้ในรูปที่เป็นสรุปผลการวิจัยโดยรวม เพื่อประโยชน์ทางวิชาการ โดยไม่เปิดเผย ชื่อ นามสกุล ที่อยู่ ของผู้เข้าร่วมโครงการวิจัยเป็นรายบุคคล และมีมาตรการในการเก็บรักษาข้อมูลทั้งส่วนตัวและข้อมูลที่ได้จากโครงการวิจัย โดยการเปิดเผยข้อมูลต่อหน่วยงานต่างๆที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ท่านจะถอนตัวออกจากโครงการวิจัยหลังจากได้ลงนามเข้าร่วมโครงการวิจัยแล้วได้หรือไม่

ท่านสามารถถอนตัวออกจากโครงการวิจัยได้ตลอดเวลา โดยไม่เกิดผลเสียใดๆตามมา และท่านอาจถูกขอให้ออกจากโครงการวิจัยโดยหัวหน้าโครงการวิจัย ในกรณีที่แพทย์ประเมินแล้วว่าท่านอยู่ในภาวะที่ไม่เหมาะจะเข้าร่วมการวิจัย

หากมีข้อมูลใหม่ที่เกี่ยวข้องกับโครงการวิจัย ท่านจะได้รับแจ้งข้อมูลนั้นโดยหัวหน้าโครงการวิจัยหรือผู้ร่วมวิจัยทันที

หากผู้วิจัยมีข้อมูลเพิ่มเติมทั้งด้านประโยชน์และโทษที่เกี่ยวข้องกับการวิจัยนี้ ผู้วิจัยจะแจ้งให้ท่านทราบทันทีโดยไม่ปิดบัง

APPENDIX C

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย (Consent form)

รับรองโดยคณะอนุกรรมการพิจารณาโครงการวิจัย พบ.

ชื่อโครงการวิจัย ความสัมพันธ์ระหว่างค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาเซฟเทซิดิมและยาอะมิเคซิน

วันที่ลงนาม.....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตราย หรืออาการที่อาจเกิดขึ้นจากการวิจัย หรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆที่ข้าพเจ้าสงสัยด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ และเข้าร่วมโครงการวิจัยนี้โดยสมัครใจ และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ผู้วิจัยรับรองว่าหากเกิดอันตรายใดๆจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลตามความเหมาะสม

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงชื่อ.....ผู้เข้าร่วมโครงการวิจัย

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....ผู้ดำเนินการโครงการวิจัย

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ในกรณีที่ผู้เข้าร่วมโครงการวิจัยไม่สามารถลงลายมือชื่อด้วยตนเองได้ ให้ผู้แทนโดยชอบตามกฎหมายซึ่งมีส่วนเกี่ยวข้องเป็น.....ของผู้เข้าร่วมโครงการวิจัย เป็นผู้ลงนามแทน

ลงชื่อ.....ผู้แทนโดยชอบธรรม

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ.....พยาน

(.....ชื่อ-นามสกุล ตัวบรรจง)

APPENDIX D

Table 1 Demographic data of the individual patients

Subject No.	Gender	Age (year)	Weigh (kg)	High (cm)	BMI (kg/m^2)	albumin$^{\delta}$ (g/dL)	Ceftazidime regimen	Amikacin regimen	Clcr (mL/min)	Indication	Empric/ Definite
1	F	81	52$^{\Psi}$	153	22.21	3	2 g q 12 hr	500 mg q 24 hr	26.70	Febrile neutropenia	Empiric
2	F	78	60$^{\Psi}$	160	23.43	3.4	1 g q 12 hr	500 mg q 24 hr	54.77	Febrile neutropenia	Empiric
3	F	28	42	160	16.40	2.7	2 g q 8 hr	500 mg q 24 hr	111.07	Febrile neutropenia	Empiric
4	M	19	78	185	22.79	-	2 g q 8 hr	750 mg q 24 hr	145.65	Wound infection	Definite
5	M	41	50	164	18.59	4.1	2 g q 8 hr	750 mg q 24 hr	98.21	Sepsis	Definite
6	M	71	50$^{\Psi}$	153	21.36	3.1	2 g q 8 hr	500 mg q 24 hr	69.14	HAP	Empiric
7	M	53	53$^{\Psi}$	159	20.90	2.6	2 g q 8 hr	750 mg q 24 hr	91.49$^{\varphi}$	Fever*	Empiric
8	M	62	55	170	19.03	2.3	1 g q 8 hr	750 mg q 24 hr	148.96	HAP,UTI	Empiric
9	M	44	50$^{\Psi}$	170	17.30	1.6	2 g q 8 hr	750 mg q 24 hr	166.67$^{\varphi}$	Wound infection	Empiric
10	M	29	60$^{\Psi}$	162	22.86	2.1	2 g q 8 hr	750 mg q 24 hr	180.96	Fever*	Empiric
11	M	49	58$^{\Psi}$	162	22.10	2.2	2 g q 8 hr	750 mg q 24 hr	148.38	Wound infection	Empiric
12	M	28	74	161	28.54	4.1	2 g q 8 hr	750 mg q 24 hr	112.37	Wound infection	Definite
13	F	83	50$^{\Psi}$	170	17.30	2.4	1 g q 8 hr	500 mg q 24 hr	67.29$^{\varphi}$	UTI	Empiric
14	F	58	47	158	18.83	3	2 g q 8 hr	750 mg q 24 hr	91.00	Bile duct infection	Empiric
15	M	48	63.5	165	23.32	3.2	2 g q 8 hr	750 mg q 24 hr	98.09	Febrile neutropenia	Empiric
16	M	63	54	165	19.84	3.4	2 g q 8 hr	750 mg q 24 hr	96.25	UTI	Empiric
17	M	41	62	158	24.84	3.2	2 g q 8 hr	500 mg q 24 hr	63.09	Febrile neutropenia	Empiric
18	F	78	42$^{\Psi}$	160	16.40	2.1	1 g q 8 hr	500 mg q 24 hr	51.24$^{\varphi}$	UTI	Empiric
19	M	27	79	170	27.33	4.1	2 g q 8 hr	750 mg q 24 hr	103.49	Febrile neutropenia	Empiric

* : Fever of unknown origin Ψ**:** approximate weight φ**:** calculation from approximate weight δ: value obtained within 7 day of the study day

(continue)Demographic data of the individual patients

Subject No.	Underlying disease
1	Diabetes, Hypertension, Dyslipidemia ,Breast cancer
2	Diabetes, Hypertension, Asthma, Hyperthyroidism
3	Haematologic Cancer (NHL)
4	-
5	Haematologic Cancer (CML)
6	Amyotrophic lateral scerosis (ALS)
7	Subarrachnoid hemorrhage, Chronic liver disease
8	Liver cancer
9	Spinal cord injury
10	Haematologic Cancer (NHL)
11	Empyema thoracic with esophageal fistula ,Pleural effusion
12	-
13	Deep vein thrombosis
14	Diabetes, Hilar cholelithiasis cancer
15	Tuberculosis, Haematologic Cancer (AML)
16	Tuberculosis, Brain tumor
17	Haematologic Cancer (ANLL), CHF
18	Diabetes, Hypertension, Dyslipidemia
19	Haematologic Cancer (Acute leukemia)

Table 2 Infection data and clinical outcome of the individual patients

Subject No	Site of Infection	Culture result	Susceptibility		ADR	Outcome	
			Cef	Amik		clinic	bacterial
1	urinary tract	*Ps. aeruginosa*	S	S		F	In
		K. pneumoniae (ESBL)	R	S		F	In
2	unidentified	-	-	-		C	-
3	unidentified	-	-	-		Im	-
4	wound	*Ps. aeruginosa*	S	S	√	Im	E
5	blood	*Ps. aeruginosa*	S	S		Im	In
6	sputum	*Ps. aeruginosa*	S	S		F	In
	urinary tract	*E. coli* (ESBL)	R	S		F	P
7	unidentified	-	-	-		C	-
8	urinary tract	*P. mirabilis*	S	S		Im	In
	sputum	*E. coli*	S	S		Im	In
		K. pneumoniae	S	S		Im	In
9	wound	*P. milabilis* (ESBL)	R	S		F	P
		A. baumananii (MDR)	R	R		F	P
		Ps. Aeruginosa (MDR)	R	R		F	P
		E. faecium	R	R		F	P
10	unidentified	-	-	-		Im	-
11	chest pus	*V. streptococci*	R	R		F	P
		K. oxytoca	S	S		F	E
		Ps. aeruginosa	S	S		F	E
	Pleural fluid	*K. pneumoniae(ESBL)*	R	S		F	P
		Stenotrophomonas maltophilia (MDR)	R	R		F	In
12	wound	*Ps. aeruginosa*	-	S		Im	In
13	urinary tract	*E. coli*	S	S		C	E
14	bile	*K. pneumoniae*	S	S		Im	In
		Ps. aeruginosa	S	S		Im	In
		Shewanella putrefaciens	S	S		Im	In
15	unidentified	-	-	-		F	-
16	urinary tract	*E. coli* (ESBL,MDR)	R	R		C	E
17	blood	*E. coli (ESBL)*	R	S		Im	In
18	urinary tract	*K. pneumoniae* (ESBL,MDR)	R	I		C	E
19	unidentified	-	-	-		F	-

Amik: Amikacin , C: Cure , Cef: Ceftazidime , E: Elimination , ESBL: Extended-spectrum ß-lactamase , F: Fail , I: Intermediate , Im: Improvement , In: Indeterminate resistant, MDR: Multi-drug resistant , R: Resistant , S: Susceptible.

Table 3 Duration of antimicrobial therapy

Subject No.	Duration of antimicrobial therapy (day)		
	Amikacin	Ceftazidime	Co-administration
1	4	4	4
2	7	7	7
3	4	10	4
4	9	22	9
5	10	14	10
6	11	11	11
7	18	18	18
8	4	4	4
9	13	13	13
10	15	21	15
11	17	24	17
12	12	12	12
13	3	4	3
14	3	15	3
15	21	21	21
16	14	13	13
17	8	3	3
18	3	6	3
19	20	12	12
Mean ± S.D.	10.32 ± 6.04	12.32 ± 6.64	9.58 ± 5.76

APPENDIX E

Calculation of pharmacokinetic parameters

Using two plasma amikacin concentrations to calculate pharmacokinetic parameters of amikacin.

Example

Patient no. 19: He received amikacin 750 mg once daily at 9.16 p.m. and finished at 10.06 p.m. Blood was taken at 11.09 p.m. and 1.01 a.m., the concentration were 19.325 μg/mL and 8.96 μg/mL, respectively. From this data, the values which will use in calculation are:

drug	dose	Start infusion	Finish infusion	Infusion time (t_{inf})
Amikacin	750 mg/day	9.16 p.m	10.06 p.m.	50 min(0.833 hrs)

drug	finish	Blood sampling(t)	t - tinf	Drug level
Amikacin	10.06 p.m.	11.09 p.m	1hr 3 min(1.05hr)	19.325 μg/mL
		1.01 a.m.	2 hr 55 min(2.92hr)	8.96 μg/mL

Δt = 1.01 a.m. – 11.09 p.m. = 1.867 hrs

1) Calculate K_e from two plasma amikacin concentrations:

$$K_e = \frac{\ln\left(\frac{c_1}{c_2}\right)}{\Delta t} = \frac{\ln\left(\frac{19.325}{8.96}\right)}{1.86hr}$$

$$= 0.4117 \ hr^{-1}$$

2) Calculate $t_{1/2}$ from K_e :

$$t_{1/2} = \frac{0.693}{Ke} = \frac{0.693}{0.4117} \ hr$$

$$= 1.6833 \ hr$$

3) Calculate total Cl of amikacin from concentration at 11.09 p.m.:

$$\text{Cl} = \frac{SF\left(Dose / t_{\text{inf}}\right)\left(1 - e^{-Ket_{\text{inf}}}\right)\left(e^{-Ke\left(t - t_{\text{inf}}\right)}\right)}{c_t\left(1 - e^{-Ke\tau}\right)}$$

$$= \frac{\left(750mg / 0.833hr\right)\left(1 - e^{-0.4117(0.833)}\right)\left(e^{-0.4117(1.05)}\right)}{19.325mg / L\left(1 - e^{-0.4117(24)}\right)}$$

$$= 8.778 \text{ L/hr}$$

4) Calculate V_d from K_e and Cl

$$V_d = \frac{Cl}{Ke} = \frac{8.778L / hr}{0.4117hr^{-1}}$$

$$= 21.3221 \text{ L}$$

His weigh is 79 kg. Hence V_d in unit of L/kg is :

$$= \frac{21.3221L}{79kg} = 0.27 \text{ L/kg}$$

APPENDIX F

Dosage regimen design

Using the amikacin pharmacokinetic parameters of the patients to design the appropriate dosage regimens for both amikacin and ceftazidime

Example

Patient no. 19: His amikacin pharmacokinetic parameters were as follow:

$K_{e\ amik}$ = 0.4117 hr^{-1}, $t_{½\ amik}$ = 1.68 hr, Cl_{amik} = 8.78 L/hr, $V_{d\ amik}$ = 0.27 L/kg and weight = 79 kg. His calculated amikacin maximum concentration was 24.24 mg/L

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1) Calculate the dosage of amikacin to give the maximum concentration of 30 mg/L. Using short infusion model, assuming $C_{ss\ max}$ appear at t = 1 hour:

$$C_{ss\ max} = \frac{SF(Dose/t_{inf})(1-e^{-Ket_{inf}})(e^{-Ke(t-t_{inf})})}{Cl(1-e^{-Ke\tau})} \ ;\ t-t_{inf} = 0.5 \text{ hour}$$

$$30 \text{ mg/L} = \frac{(Dose/0.5hr)(1-e^{-0.4117(0.5hr)})(e^{-0.4117(0.5hr)})}{8.7788L/hr(1-e^{-0.4117(24hr)})}$$

Dose = 869.74 mg

For convenience, the dosage of amikacin should be rounded up to 900 mg which will result in calculated amikacin maximum concentration that is equaled to 31.04 mg/L. Since $t_{½\ amik}$ is 1.68 hrs, therefore, amikacin concentration will be less than 1 mg/L after 8.5 hours (5 $t_{½}$). Therefore the recommended dosage of amikacin for patient no.19 is 900 mg every 12 hours which is expected to give maximum amikacin concentration of 31.04 mg/L and allow the drug free interval of approximately 3 hours.

2) Calculate the dosage of ceftazidime to give the minimum concentration of more than 8 mg/L (base on the assumption that the MIC of pathogen to ceftazidime is less than 2 mg/L)

2.1) Pharmacokinetic parameters of ceftazidime were calculated using the equation obtained from our study:

Ke ctz = 0.9957 (0.4117) + 0.0217 = 0.4316 hr^{-1}

Cl ctz = 0.9661 (8.7788) + 0.3534 = 8.8346 L/hr

2.2) Calculate the dosage of ceftazidime when the dosing interval is 8 hours

A. Using short infusion model:

$$C_{ss\,min} = \frac{SF(Dose/t_{inf})(1-e^{-Ket_{inf}})(e^{-Ke(t-t_{inf})})}{Cl(1-e^{-Ke\tau})} \; ; \; t-t_{inf} = 7.5 \text{ hour}$$

$$8 \text{ mg/L} = \frac{(Dose/0.5hr)(1-e^{-0.4316(0.5hr)})(e^{-0.4316(7.5hr)})}{8.8346L/hr(1-e^{-0.4316(8hr)})}$$

Dose = 4,488.27 mg

This calculated dose is higher than the maximum recommend dose (6 g/day).

B. Using continuous infusion model:

$$C_{ss} = \frac{SF(Dose/\tau)}{Cl}$$

$$\frac{Dose}{24hr} = \frac{C_{ss} \times Cl}{SF} = 8mg/L \times 8.8346L/hr$$

Dose = 1,696.24 mg/day

Calculation of the loading dose

$$\text{Loading Dose} = \frac{(Vd)(C)}{(SF)}$$

$$= \frac{(20.47)(8)}{(1)}$$

$$= 163.76 \text{ mg}$$

For convenience, ceftazidime loading dose should be rounded up to 200 mg then maintenance dose of 2000 mg/day of ceftazidime should be continuously infused 24 hours to provide ceftazidime concentration above 8 mg/L throughout the course of therapy. If ceftazidime 6 g/day is continuously infused, the predictive ceftazidime level at steady state will be 28.30 mg/L.

APPENDIX G

Bioanalysis of amikacin

Analytical Method

Amikacin plasma levels were determines by immunoassay method using TDx Analyzer system, Abbott Laboratories based on fluorescence polarization technique. The equipments consisted of carousel, cuvettes, sample catridges, reagent pack, calibrators and controls.

1. Calibration.

Calibrations were performed following the operation manual of TDx analyzer. An acceptable amikacin assay calibration curve should meet the following criteria:

a) Polarization Error (PERR) -3.00 to +3.00 for all calibrations.
b) Root Mean Squared Error (RMSE) less than or equal to 2.00.
c) All controls are within the acceptable ranges.

The following amikacin calibrator solution was measured for their amikacin concentrations to make a calibration curve.

CAL	Amikacin concentration (μg/mL)	PERR
A	0.0	0.00
B	3.0	0.47
C	10.0	0.23
D	20.0	0.09
E	35.0	0.53
F	50.0	0.37
RMSE	0.30	

The following three levels of amikacin control solution (L, M and H) were measured for their amikacin concentration and compared with the standard range of amikacin control concentration.

Control	Amikacin concentration (μg/mL)	
	Standard	Study
L	4.25 – 5.75	4.75
M	13.50 – 16.50	14.95
H	27.00 – 33.00	29.22

2. Sensitivity

According to the manufacturer, sensitivity is defined as the lowest measurable concentration which can be distinguished from zero with 95% confidence and was determined to be 0.8 μg/mL.

3. Precision

According to the manufacturer, precision was determined as described in National Committee for Clinical Laboratory Standard (NCCLS) protocol EP5-T using human serum with 5.0, 15.0, and 30.0 μg/mL of amikacin added. Results from these studies typically yielded CV's of less than 5%.

4. Accuracy by recovery

According to the manufacturer, recovery was determined by adding amikacin to human serum at clinically relevant concentrations and assaying in replicates of five. Recoveries were found to be quantitative. The average recoveries are 100.1 ± 2.6%.

APPENDIX H

Bioanalysis of ceftazidime

Analytical Method

The concentration of ceftazidime in plasma samples were determined by using High-Performance Liquid Chromatography.

1. Calibration curve and linearity

The linearity was determined from six levels of calibration curve between concentrations of 3 to 200 μg/mL for ceftazidime. The representative calibration curve was shown in Figure 1. The heteroscedastic data were observed and weighting is needed. The value of power maximizing log-likelihood function was selected using SPSS version 11.5. The weighted (1/concentration squared) least squares linear regression equation was

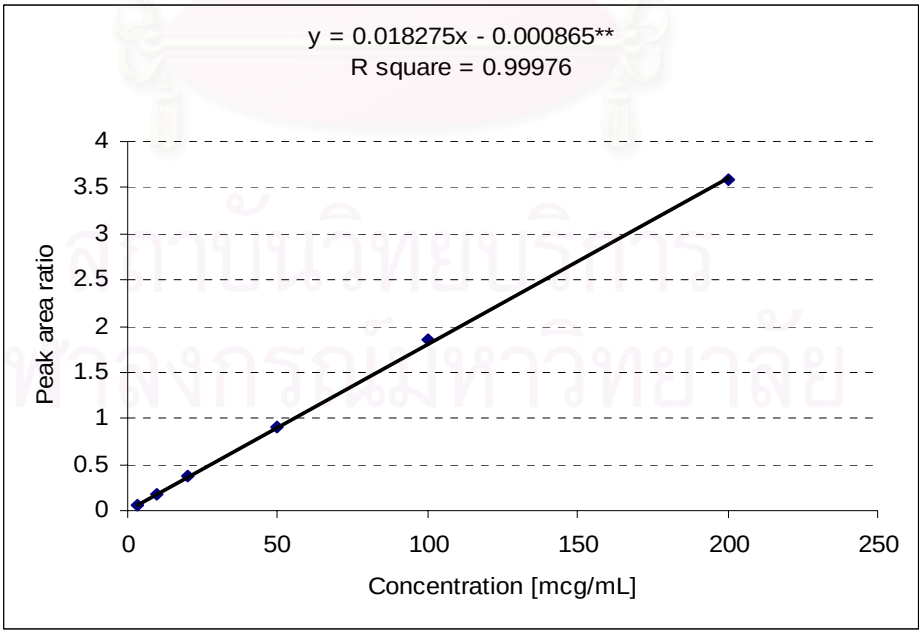
$$y = 0.018275x - 0.000865 \text{ , R square} = 0.99976$$

Where

x = Plasma drug concentration

y = Peak area ratio of drug to internal standard (IS)

R square = Coefficient of determination

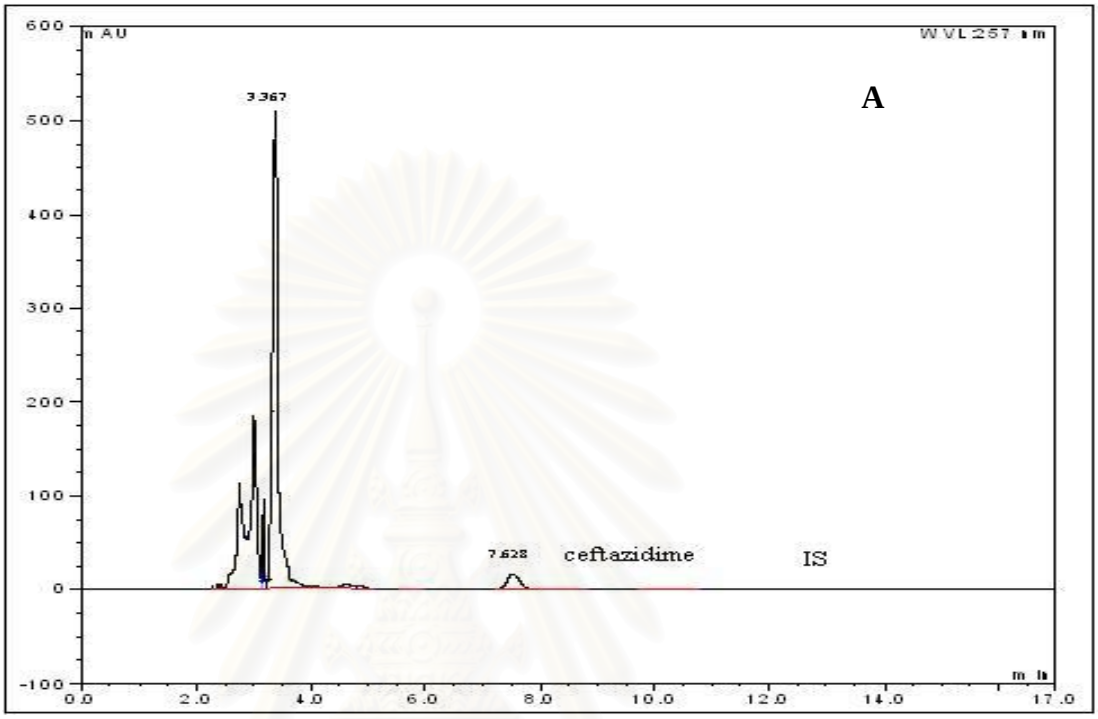


** weighted (1/concentration squared) least squares linear regression equation

Figure 1 Calibration curve of ceftazidime

2. Specificity and selectivity

Chromatograms of drug-free plasma and spiked plasma are demonstrated in Figure 2. No interference from endogenous substances in plasma was observed.



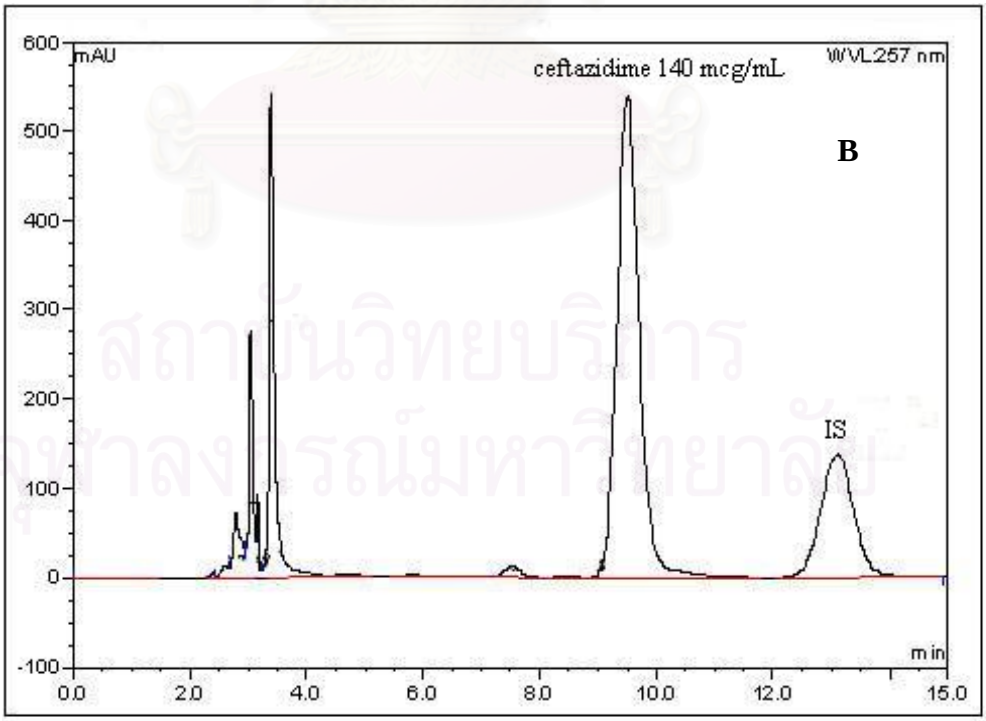


Figure 2 Chromatogram of A: Drug – free plasma .
B: Spike plasma of IS (cephalexin), ceftazidime at 140 μg/mL.

3. Limit of quantification

The lowest concentration on the calibration curve which was linearity correlated with peak area of each drug and had acceptable in range ± 20% accuracy (% RD; percent deviation from the nominal concentration = 3.12 %) and in range ± 20% precision (% CV; coefficient of variation = 2.47 %) as showed in Table 1. Chromatogram of spiked plasma for 3 μg/mL (limit of quantification) was demonstrated in Figure 3.

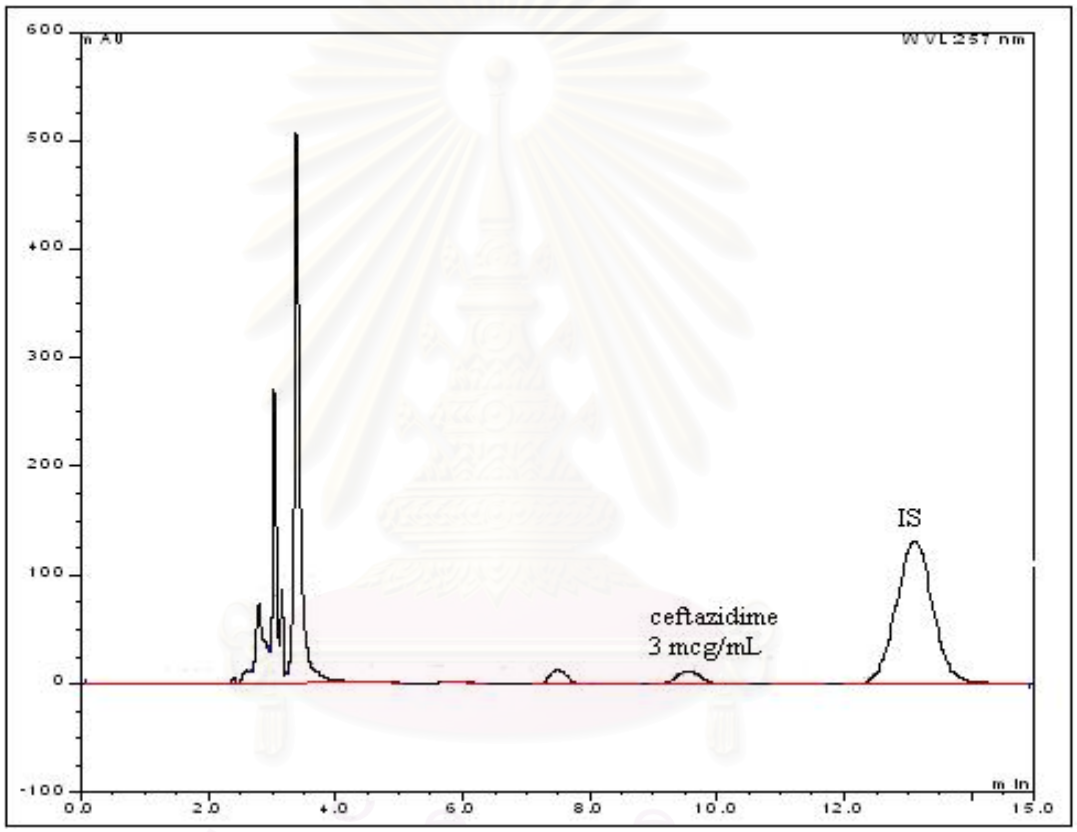


Figure 3 Chromatogram of spike plasma of IS (cephalexin) and ceftazidime at 3 μg/mL.

4. Accuracy, precision and recovery

The precision and accuracy of the assay procedure were evaluated from %CV and %RD, respectively. As showed in Table 1 , the intra-day and inter-day precision/ accuracy were in ranged of acceptable at all concentration levels (acceptable range should be within ±15 %, except at LLOQ should be within ±20 %). Extraction of ceftazidime resulted in percentage recovery of approximately 110 %.

Table 1 Accuracy , precision and recovery of spiked plasma of ceftazidime

QCs	Acceptable limit(±%)	Conc (µg/mL)	Intraday(n=5)		Interday (n=15)		Recovery of drug* (%)	Recovery of IS** (%)
			Precision (%)	Accuracy deviation (%)	Precision (%)	Accuracy deviation (%)		
LLOQ	20	3	2.47	3.12	2.84	0.35	-	-
QCL	15	7	0.94	1.73	1.83	-0.03	107.494	109.731
QCM	15	40	1.29	-2.27	3.13	-0.73	109.089	108.949
QCH	15	140	2.09	0.36	2.55	-1.5	105.067	109.731

* : compare with ceftazidime solution , ** : compare with cephalexin solution

5. Stability of spiked plasmas and extracts

The stability of plasma samples and extracts left at various conditions was checked and shown in Table 2. Sample were considered stable when the area of ceftazidime peak were at least 85% of freshly prepare sample. The stability of ceftazidime at QCL and QCH were always higher than 85%, a value comprised within the assay variability, indicating that the plasma samples appear to be stable through out the study.

Table 2 Stability of ceftazidime in plasma samples and final extracts

Condition	Stability (%)	
	QCL	QCH
Long -term stability*	98.34	91.46
3 cycles of freeze/thaw	103.79	108.60
Short – term stability		
- 2 hr at room temperature	96.77	97.70
Final extract stability		
- in autosampler for 2 hr	93.20	90.78
- 4 °C for 10 hr	91.77	90.53

* : Long – term stability were tested at 2 months.

VITAE

Miss Sam-ang Kiatjaroensin was born on the 29th of December in 1972 at Bangkok. She graduated with Bachelor degree in Pharmacy in 1995 from Faculty of Pharmacy, Chulalongkorn University. Her current position is a pharmacist at Rayong Hospital.