CHAPTER 1

INTRODUCTION

For almost 40 years, the most striking feature of gram negative bacteria has been their propensity to develope resistance to antimicrobial drugs. For each new drug, resistance and cross - resistance bacterial counterpart have emerge (1). Drug resistance can be transferred from one bacterial specie to another by the means of the extrachromosomal vectors such as plasmids and transposon (1).

The dissemination of multiple drug resistance has become a worldwide problem both in hospitals and in the communities. Antibiotic resistance has been demonstrated in all pathogenic organisms and virtually no known antibiotic is exempt. For example, the drastic decrease in the antimicrobial susceptibility of various gram negative bacteria isolated at Ramathibodi Hospital to gentamicin and cotrimoxazole from 1974 to 1975 (table 1).

Table 1 Antimicrobial susceptibitity patterns of various gram negative bacteria to gentamicin and cotrimoxazole during the years of 1974 and 1975 (2).

Organism	Percentage of susceptible			
	Gentamicin		Cotrimoxazole	
	1974	1975	1974	1975
E.coli	95	63	83	56
Enterobacter spp.	79	36	80	33
P. aeruginosa	59	24	-	-
Proteus spp.	88	61	47	14
Salmonella spp.	99	70	94	65
Shigella spp.	88	50	82	39
N. gonorrhoeae	82	47	69	31

Because there has been increased resistance of gram negative bacteria to existing compound (3,4), and an increased awareness of the toxic potential of other antimicrobial agents, particulary the aminoglycosides (5), the proliferation of new antimicrobial compounds, especially the beta-lactam antibiotics has contributed.

Aztreonam is the first monobactam, a new class of beta-lactam, with potent gram-negative activity but with a limited spectrum. Aztreonam has been raised for this research by the following concerns and properties (6) :-

1. Aztreonam is active only against aerobic and facultative gram-negative bacteria, notably the Enterobacteriaceae, P. aeruginosa, Haemophillus and Neisseria species.

2. From many reports, the in vitro activity of aztreonam to Enterobacteriaceae is excellent with the low MIC (less than 1.0 µg/ml) , except to Enterobacter spp.

3. It is highly resistant to virtually all plasmid-mediated and chromosomally mediated beta-lactamase.

4. Emergence of microbial resistance to the agent does not appear to be plasmid mediated ; hence, resistance to aztreonam will not become wide spread quickly.

5. Aztreonam is a poor inducer of beta-lactamase.

6. The absence of anti-gram positive and anti-anaerobic activity is a distinct asset in that little adverse effect on the normal, protective anaerobic microflora occurs.

7. Aztreonam appears to be as free from adverse side effect and toxicity as is any available beta-lactams. So, it may be used as a safe alternative to aminoglycosides.

8. It lacks of cross-allergenicity with penicillins and cephalosporins.

9. Its serum half-life is of sufficient duration (1.5 to 2 hours) to warrent dosage intervals of every 8 to 12 hours.

All of these mentioned data had motivated the researcher to handle the study of " Microbiological and Clinical Evaluation of Aztreonam in Treatment of Gram Negative Bacterial Infections"

Objective

The purposes of this research are to determine the followings : -

1. To study the in vitro efficacy of aztreonam to various strains of pathogenic gram negative bacteria.

2. To study the clinical and bacteriological efficacy of aztreonam against gram negative bacterial infections in children.

3. To determine the serum concentration of the drug at $\frac{1}{2}$ - 1 hour and at 6 or 8 hour after administration.

Materials and Methods

This thesis is divided into two parts, the in vitro study and the clinical study.

1. The In Vitro Study

This part is to determine the Minimal Inhibitory Concentration (MIC) of aztreonam to various strains of pathogenic gram negative bacteria.

The agar dilution method (7,8) was used with a multipoint inoculator apparatus.

Various strains of pathogenic gram negative bacteria were isolated from patients suspected specimens or cultures from various parts of Thailand. There were 351 isolates. This part of study would provide the

exact information of aztreonam susceptility of pathogenic gram negative bacteria in Thailand.

2. Clinical study

This part of the thesis is concerning the efficacy of aztreonam in treatment of the patients both clinically and bacteriologically. The determinations of drug sera levels were also included.

The drug was administered every 6-8 hours as multiple doses of 30 mg per kilogram body weight intravenously or intramusculary to the patients, suffered with gram negative bacterial infections. At least 10 children of age less than 15 years were studied for 5 days or until the symptoms had been releived. Patients were allowed to receive other antibiotics with activity against aerobic gram-positive or anaerobic bacteria, but not against the infecting aerobic gram-negative organisms. All patients were admitted in Ramathibodi Hospital.

2.1 Antimicrobial susceptibility test

Sample taken from the infected sites of all patients were cultured appropriately before initiation of therapy with aztreonam. The aztreonam susceptibilities of the organisms by disc diffusion method (7,9) using a 30 μg aztreonam disc were determined. Organisms were considered susceptible if the zone of inhibition was $\geq$ 22 mm.

22. Study for clinical efficacy of aztreonam

The following symptoms were observed daily for their improvements after drug administration :-

2.2.1 Fever

2.2.2 Other symptoms such as dysurea, lumbar or retropubic pain etc. in urinary tract infections, swelling at the infected sites in skin infection.

Clinical responses were assessed as follow :

Cure : signs and symptoms of the infection were subsided completely.

Improve : signs and symptoms were substantially improved without complete clinical resolution.

Failure : substantial improvement in signs and symptoms were absent.

2.3 Study for adverse effects

During drug administration, the adverse effects such as skin rash, nausea and vomitting, diarrhea etc. were recorded.

2.4 Study for bacteriological efficacy of aztreonam

The samples taken from all patients were cultured during and at the end of treatment. Culture were also repeated during the post-treatment follow-up period when clinically indicated and if specimens were available.

Microbiological responses were assessed as follow :

Elimination : The original causative microorganism was eradicated during therapy without any relapse in the follow-up period.

Relapse : The original causative organism was reappeared during the follow-up period, i.e. after completion of treatment.

Reinfection : The recurrence of infection due to a different organsim after completion of treatment was observed.

Failure : The causative organism had persisted during treatment.

Superinfection : The development infection due to an resistant organism, other than the original pathogen, was present during treatment with recurrence of signs and symptoms of infection.

Colonization : The new organism, which was not present in the original clinical specimens, was isolated from clinical material during/or after therapy but was not associated with signs or symptoms of infection.

These four parts (2.1 to 2.4) were studied and observed for 5 days or until the day of discharge from the hospital.

2.5 Determination of serum levels of aztreonam after administration

The sera were obtained from the blood drawn at $\frac{1}{2}$ - 1 hour after injection of aztreonam and immediately before the next dose. All samples were assayed immediately or frozen at -20° C and assay within 1 week. The microbiological assay of antibiotics by the plate method (10,11) were used. The details of materials and methods were described in chapter 3 page 41.

The serum levels of aztreonam were done to give the exact informations for Thai children in this study. These data may also be used to describe the results of aztreonam treatment.

Significance of the study

1. If aztreonam is found to be effective in treatment of gram negative bacterial infections, the advantage of this are :

1.1 To reduce the admission time. Due to the clinical symptoms especially fever were observed to be improved in a very short time in the pilot project.

1.2 It will mean medical progress in finding another new antimicrobial agent for the present and future use in the treatment of gram negative bacterial infections which have high rate of drug resistance.

1.3 Aztreonam may be used as a safe alternative to aminoglycosides, which would obviate the risks for nephrotoxicity and ototoxicity.

1.4 In the future, it may be used in patients with history of hypersensitivity to other beta-lactams.

2. The in vitro study of aztreonam efficacy to gram negative bacteria will give the exact information of drug susceptibility for the pathogenic gram negative bacteria which were isolated from Thai patients.