CHAPTER VI

DISCUSSION

A. IN VITRO RESULTS

1) The susceptibility results demonstrated that piperacillin has a broad spectrum of antibacterial activity against gram negative bacteria. Its activity is superior to other semi-synthetic penicillin (eq. ticarcillin) against all of the tested species (Table 2). A striking feature is its good inhibitory effect of 80.95% against *Ps. aeruginosa*, while the inhibitory effect of ticarcillin is only 68.25%. Comparable data was also reported by Baier and Puppel (1980) in that 55% of this strain was sensitive to ticarcillin and 96.3% was sensitive to piperacillin. It is more potent than gentamicin and amikacin against *Proteus mirabilis*, *Indole positive proteus* and *Citrobacter spp.* (Table 2). Piperacillin is less active than amikacin, cefsulodin and ceftazidime against *Ps. aeruginosa* (Table 2). Ceftazidime has the greatest potency against *Ps. aeruginosa* and *Enterobacteriaceae*. Same result was also reported by Richards and Brogden (1985).

There is the incidence of the same type of *Pseudomonas* resistant strains (Table 3). This resistance was the plasmid mediated β-lactamase which hydrolyzed piperacillin (Fu and Neu, 1978). The study further reveals a parallel resistance between piperacillin and ticarcillin ($\delta = 0.69$). Verbist (1978) also showed the parallel resistance between piperacillin and carbenicillin ($\delta = 0.92$). However,

piperacillin can inhibit the carbenicillin and ticarcillin isolated resistant strains which may due to its greater ease of entry into the receptor site (Neu *et al.*, 1982).

2) The piperacillin minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) confirmed the susceptibility results in that piperacillin has broad spectrum of activity against gram negative bacteria. It has the unusual relative high activity (in cumulative percentage) against most of *Enterobacteriaceae*, *Ps. aeruginosa* and *Ps. pseudomallii*. Its activity against *Ps. aeruginosa* was outstanding, about 80% of this isolated strains were inhibited by the MIC of 64 µg/ml compared to 6.3 µg/ml by Kwung and Harold (1978).

Piperacillin has high activity against *Proteus mirabilis*, *Indole positive proteus* and *Serratia spp.* (Table 4). Kwung and Harold (1978) reported the lower activity. Its activity in *Indole positive proteus* is extremely high, 80% of this species were inhibited at 1-2 µg/ml. Bodey and Le Blanc (1978) also reported the same susceptibility of *Proteus spp.* to piperacillin.

When the activity of piperacillin is determined in relative values of MICs and MBCs against all of the tested species, there is either marked difference or equal in these values (Fu and Neu, 1978; Verbist, 1978). For certain strains of *Ps. aeruginosa*, the ratio of MBC/MIC against 60% of this strains varied markedly, it was 4 in our study and 4-32 in the study of Winston (1977). The values of MIC_{90} and MBC_{90} of some species (*Acinetobacter spp.*, *Citrobacter spp.*, *E. coli*, *Enterobacter spp.*, and *Ps. aeruginosa*) were in the resistance

range (> 256 µg/ml). This revealed the large amount of β-lactamase in these isolated strains. Piperacillin activity against *Ps. aeruginosa* and *Ps. pseudomallii* was influenced by the inoculum size, espiacially the high inocula (10^6, 10^7 CFU/ml), which correlated with other studies (Fu and Neu, 1978; Verbist *et al.*, 1978; Winston, 1977).

There was no effect of antibiotic treatment to isolated *Pseudomonas* strains in three hospital centers studied, whereas the variation in drug uses were found.

B. IN VIVO STUDIES

1) The pharmacokinetic datas, after two doses (40 and 80 mg/kg/dose)(Table 8) demonstrated that the serum drug concentrations were approximately 2 folds in the higher doses. Piperacillin appeared to be rapidly distributed [average half lives for distribution $t_{\frac{1}{2}}\alpha$) were 0.25 and 0.23 h. respectively] within the extracellular fluid (V_1) and to some extent within the peripheral tissue compartment (V_2). The mean half lives were nearly equal (0.84 and 0.83 h.) at β-elimination phase ($t_{\frac{1}{2}}\beta$) and were longer than $t_{\frac{1}{2}}\alpha$. Thus, the $t_{\frac{1}{2}}$ was independent on doses. Piperacillin achieved a high distribution into tissues by its relatively high values of volume of distribution (Table 8). It underwent biotransformation or extrarenal excretion with renal clearance (Cl_R) approximately 20% lower than total clearance (Cl_{Tot})(Table 8). About 20% of piperacillin doses were excreted through biliary tract (Russo *et al.*, 1982). Piperacillin was highly excreted in an active form in the urine, about 80% of total doses were excreted in 24 h. Smaller percentage of excretion was seen with lower doses (Table 8).

Our pharmacokinetic values correlated well with those reported by Tjandra Maga *et al.*, (1978). There were some differences, especially the volume of distribution which may vary between subjects by sex, age, weight and body surface area (Gibaldi and Prescott, 1983).

The precise serum and tissue concentration needed to eradicate different type of infections were unknown. However the mean peak serum concentrations of piperacillin (Table 8) were several times nigher than its MICs (Table 4) for susceptible *Enterobacteriaceae* and *Ps. aeruginosa*. The relatively short half lives of piperacillin resulted in fast declining of drug levels which decreased to low concentration in about 6 hours (Figure 15). Maintenance dose of 200 mg/kg/d given every 4-6 hours should be recommended in order to maintain the MIC level which cover the dividing gram negative bacterial cell causing serious infections.

Determination of serum drug concentrations in patients at 0.5-1 h. was about 41 g/ml (Table 9) and was sufficient to inhibit 79% of *Ps. aeruginosa* 78% of *Enterobacteriaceae* and 100% of *Ps. pseudomallii* (Table 4). By 2-4 h, eventhough the serum drug level was decreased about ten times to 4 µg/ml, piperacillin can still inhibit 41% of *Ps. aeruginosa* and 67% of *Enterobacteriaceae* (Table 4).

According to the limitation of subjects in this study, the average values may not be the representative of the population. More subject should be selected in further study.

2) In non-comparative clinical study in patients with severe bacterial infections, piperacillin performed well both in efficacy

and patient tolerance. The clinical and bacteriological responses revealed more than 70% of improvement (Table 14,15). Serious clinical adverse effects were not observed. In 8 patients who received the combination of piperacillin and aminoglycosides showed satisfied responses (Table 9,10), although one case could not be evaluated. The other studies (Winston *et al.*, 1982; Wade *et al.*, 1981) also reported the same results in this combined therapy.

Piperacillin seemed to be particularly useful against *Pseudomonas* infections (Table 13), which correlated well with other studies (Tunn, 1980; Hasekawa and Kanda, 1977).

Piperacillin was beneficialy effective in severe nosocomial infections due to strains of gram negative bacteria especially *Ps. aeruginosa*, *Ps. pseudomallii* and *Proteus mirabilis* (Table 14). The overall responses according to infeciton sites (Table 16), piperacillin was effective in urinary and respiratory tract infections. Other studies (Kato *et al.*, 1977; Pancoast *et al.*, 1981) also reported this efficacy of piperacillin. All cephalosporins have no effect on enterococci and have less effect when compared to piperacillin on anaerobic bacteria (Holmes, 1984). Thus, in abdominal sepsis causing mainly by enterococci and bacteroid fragilis, piperacillin should be selectively used.

3) Adverse drug reactions (ADR_s) were minor, the common ADR was drug fever (33.7%). Allergic reactions occured in two patients (14.2%). All penicillins derived from penicillin nucleus may cross-react in sensitized individual (Stewat,1962). Mild allergic reaction primary transient skin rash and drug fever were observed(Clark,1980;

Gooding *et al.*, 1982; Humphreys, 1980). Gastrointestinal reaction with fever occured in one case. This reaction was mainly vomiting, nausea, loose stools and diarrhoea (Clark, 1980; Gooding *et al.*, 1982). At usual doses (200-300 mg/kg/d) hematological symptoms and nephrotoxicity were not found. Gribble *et al* (1983) and Winston *et al* (1980) found a few instances of raised serum creatinine levels and single report of Møller and Høiby (1981) showed renal toxicity.

Since piperacillin is monosodium salt, it shoud be likely to cause fluid and electrolyte disturbances. From our study, this effect was not found, although Wade *et al* (1980 and 1981) reported the hypokalemia, primarily occured only in severely ill patients.

CONCLUSION

Piperacillin when compared to other penicillin (carbenicillin ticarcillin), cephalosporin and aminoglycoside, should be drug of choice in the treatment of serious infections causing by gram negative bacteria especially *Ps. aeruginosa* and *Enterobacteriaceae* (excepted *Enterobacter* and *Acinetobacter spp.*). It can be used effectively and safely with recommended doses (200-300 mg/kg/d, 4-6 hourly) in paedriatic patients. Aminoglycoside should be added in the regimen to cover other gram negative bacteria. At present time, the third generation cephalosporin (ceftazidime) with higher efficacy is the latest choice for these infections. Nevertheless, it is the drug of choice in the physician consideration.

The differences in MICs and MBCs and inoculum effects of tested species should be considiered as the failure of teatment in some cases.