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Original Article

The Use of Piperacillin/Tazobactam Among Neonates, Infants and Children**

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ABSTRACT

Beginning mid-1996, an increase in the incidence of gram negative bacteria resistant to third generation cephalosporins was observed in all pediatric wards (including the NICU and PICU) in the Philippine General Hospital. Several broad spectrum antibiotics, including Piperacillin/Tazobactam (PIP/TAZO) were used empirically in patients suspected to have these infections. Charts of 124 patients admitted to the pediatric wards who were treated with 129 courses PIP/TAZO for at least four days from the period of August to November 1996 were reviewed to determine clinical efficacy and adverse effects of this drug. All patients were also given an aminoglycoside. Ages ranged from 0 months to 16 years, and 84% were neonates. All patients were categorized as follows: Category 1 (n=57) – patients with positive isolates (blood, urine, ETA, peritoneal fluid, CSF) sensitive to PIP/TAZO, Category 2 (n=57) – patients with poor response to third generation cephalosporins with (–) cultures; Category 3 (n=15) – received PIP/TAZO but isolates were later found to be resistant. Only Categories 1 and 2 patients were evaluated for clinical efficacy while patients in all categories were evaluated for adverse effects.

Majority of the isolates were gram negative organisms including *Enterobacter, Klebsiella, H. alvei, Pseudomonas* and *Acinetobacter*. Indications for treatment included early onset neonatal sepsis, nosocomial sepsis, nosocomial pneumonia, febrile neutropenia, peritonitis and nosocomial UTI. The following clinical responses were observed: Category 1, 66% cured, 12% improved, 22% failed; Category 2, 70% cured, 7% improved and 23% failed. Thus clinically evaluable patients showed a favorable response of 78%.

Three (3) patients died while receiving PIP/TAZO. All the deaths were due to their underlying infections. Twenty-nine patients experienced 35 adverse events: vomiting or residuals (4%), rashes (1.6%), gastrointestinal bleeding (1.6%), thrombocytopenia (8.5%), and candidal infections (9.3%).

Conclusion: **Piperacillin/tazobactam may be used as definitive or empiric therapy in pediatric patients with known resistance or poor response to standard antimicrobial therapy.**

INTRODUCTION

An alarming increase in the incidence of *Klebsiella, Enterobacter* and other gram negative bacteria resistant to third generation cephalosporins has been observed in the pediatric wards of the Philippine General Hospital (PGH), especially in the Neonatal Intensive Care Unit in the last 2 years. In a survey done by Valmores (1997)[1] 84.7% of *Klebsiella* spp. isolated in the nursery in the PGH in 1996 were resistant to Ceftazidime. In the same year 37.6% of *Enterobacter* spp. and 43.75% of *Pseudomonas* spp. were also resistant to Ceftazidime. Unfortunately this seems to be the trend in many parts of the world, because over the last decade the number of infections caused by penicillin and cephalosporin resistant bacteria in the United States has increased dramatically, reducing the clinical utilities of these safe and previously effective drugs. [17] Because of this development, new broad spectrum antibiotics to which in vitro studies showed sensitivity were used empirically in patients suspected to have these infections to minimize morbidity and mortality. A newly introduced antibiotic – PIPERACILLIN/TAZOBACTAM (PIP/TAZO) was used quite extensively at this time to address this problem.

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PIP/TAZO is an antibacterial combination which consists of a broad spectrum anti-pseudomonal penicillin-piperacillin sodium, and a beta lactamase inhibitor – tazobactam. Piperacillin is a more potent beta lactam antibiotic than are the carboxypenicillins, and it has a broader antimicrobial spectrum than aminopenicllins.[3] Tazobactam is a more potent inhibitor of plasmid-mediated beta lactamases than sulbactam and a more potent inhibitor of chromosomally mediated beta lactamases than is clavulanic acid.[3] This combination has extended the spectrum of piperacillin's activity against beta lactamase producing strains of *Staphylococcus aureus, Staphylococcus epidermidis, Hemophilus influenzae, Enterobacteriacae* and *Bacteroides* species lowering the minimum inhibitory concentration values from the resistant to the susceptible or moderately susceptible range.[2] It is the newest beta lactam-beta lactamase inhibitor combination and it has been approved for the treatment of lower respiratory tract, skin and soft tissue, intraabdominal and gynecologic infections in adults.[3]

The clinical efficacy and safety of PIP/TAZO in adult patients have been well-documented and discussed in a large number of publications. [4, 6, 5, 7, 8, 9, 10, 11, 13, 15, 18] but among neonates infants and children, published data are very limited. One such study was the pharmacokinetics of PIP/TAZO being assessed after a single dose administration to 47 infants and children.[12] The pharmacokinetic behavior of tazobactam was very similar that observed for piperacillin supporting the use of these agents in a fixed dose combination. They concluded that with the data from this study with known in vitro susceptibilities of a broad range of pediatric pathogens that a dose of 100 mg of piperacillin and 12.5 mg of tazobactam per body weight every 6 to 8 hours would be appropriate to initiate clinical efficacy studies in infants and children for the treatment of systemic infections arising outside the central nervous system.

OBJECTIVE

Due to the paucity of clinical trials in children using PIP/TAZO, this study was conducted to report the clinical experience in our institution of the use of this drug among pediatric patients. Specifically, it aims to describe the clinical characteristics of the patients, the pathogens involved, the outcome of therapy and the observed adverse effects of these patients.

MATERIALS AND METHODS

The medical charts of patients admitted to the pediatric wards, Pediatric Intensive Care Unit and the Neonatal Intensive Care Unit who were treated with PIP/TAZO for at least four days from the period of August to November 1996 were reviewed. A total of 154 patients were identified but only 124 charts were recovered and included in the study.

The following **clinical data** were collected: date of birth, (in neonates, the pediatric age and weight were included), sex, age at first administration of PIP/TAZO, clinical diagnosis, indication for treatment, dose and duration of PIP/TAZO therapy, adverse effects during the treatment period.

The following **laboratory parameters** if performed were also noted. Hemoglobin, white blood cell count, differential count and platelet count, serum alkaline phosphatase, aspartate aminotransferase, serum urea and creatinine, organism isolated, sensitivity of the organism to PIP/TAZO, subsequent blood cultures.

All patients were categorized prior to evaluation of clinical efficacy. The categories are shown in Table 1.

Table 1. Categorization of patients

Category	Description
1	Patients with positive bacterial isolated and are sensitive to PIP/TAZO.
2	Patients with clinical signs and symptoms of infection, suspected to have organisms resistant to third generation cephalosporins due to poor or no response to therapy, but no organisms were isolated.
3	Patients empirically started on PIP/TAZO due to poor or no response to third generation cephalosporins, but organisms isolated were resistant to PIP/TAZO.

Only Categories 1 and 2 patients shall be evaluated for clinical efficacy, while patients in all categories shall be evaluated for adverse effects. Only Category 1 patients shall be assessed for bacteriological response.

Clinical cure is defined as the complete resolution of initial symptoms and there is no evidence of infection at the end of treatment; **clinical improvement** is defined as the partial resolution of symptoms, some symptoms still present, **clinical failure** is defined as no response with persistence of symptoms. **Documented eradication** of bacteria is defined as the absence of bacteria on repeat culture at least 4 days of therapy; **documented persistence** is defined as the presence of bacteria on repeat culture after at least 4 days of therapy. **Presumed eradication** is defined as patients with clinical improvement but cultures were not repeated.

RESULTS

Records of 124 patients with 129 courses of PIP/TAZO were retrieved. The majority of the patients were neonates as shown in Table 2 which comprised 85% of the patients. Of these neonates the majority were preterm and of low birth weight with the average gestational age of 33.8 ± 5.7 weeks and average birth weight of 1903 ± 757 gms (Table 2). PIP/TAZO was started in these patients because they are the subgroup of patients with the

highest risk of developing multidrug resistant *Enterobacter* and *Klebsiella* infections.[1]

An aminoglycoside (Netilmycin or Amikacin) was given to all the patients in combination with PIP/TAZO for synergy and to prevent the emergence of resistant strains. Combination therapy was also warranted in patients with severe infection.

Figure 2. Age distribution of 124 patients included

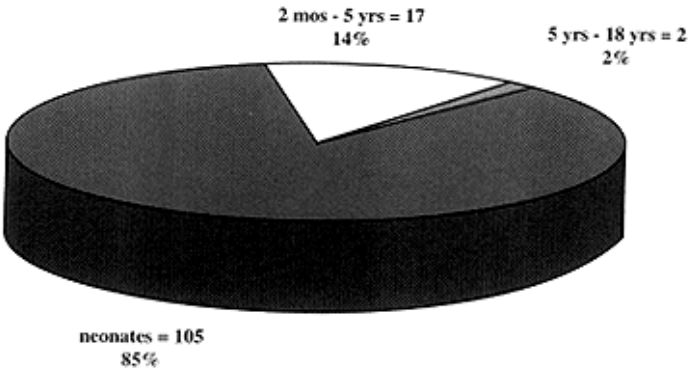

Table 2. Age, gestational age and birthweight of 105 neonates included treated with PIP/TAZO.

	Average	Range
AGE	7.25 ± 12.05 days	0 - 54 days
Gestational Age	33.8 ± 5.69 weeks	28 - 41 weeks
Birthweight	1903 ± 757 gms	800 - 3730 grams

DOSAGE AND DURATION OF TREATMENT

Neonates less than 7 days were given a dose of 50 mg/kg (based on the piperacillin sodium component) every 12 hours, then 50 mg/kg every 6 hours if they were more than 7 days old. Infants and children were treated at a dose of 200-250 mg/kg/day every 6 hours. Duration of treatment ranged from 4 to 21 days with a mean of 9.2 ± 4.2 days. Forty patients received PIP/TAZO for fourteen days or more.

Patients were classified into 3 categories as defined in the methods section. There were 57 patients in Category 1, 57 patients in Category 2 and 15 patients in Category 3.

Category 1

Indication for treatment of patients in Category 1 are listed in Table 3. Majority of the patients were neonates with early-onset sepsis (clinical signs of sepsis within the first 72 hours of life) or nosocomial sepsis. For the other pediatric wards including the ICU, the most common indications for treatment were nosocomial infections, specifically sepsis, pneumonia, ventriculitis, shunt infection and urinary tract infections. Majority of the nursery patients as well as all the pediatric intensive care unit patients required mechanical ventilation.

Table 3. Indications for usage of PIP/TAZO in Category 1 patients and outcome

Clinical indications	Number of patients (%)	Treatment failure (Died)
Nursery		
Early onset sepsis	22 (38.6)	5 (0)
Nosocomial sepsis	12 (22.8)	1 (0)
Nosocomial pneumonia	1 (1.75)	0 (0)
Soft tissue infection	2 (3.5)	0 (0)
Pediatric ICU		
Nosocomial pneumonia	4 (7.0)	1 (0)
Nosocomial sepsis	1 (1.7)	1 (0)
Pediatric wards		
Nosocomial UTI	3 (5.3)	1 (0)
Ventriculitis	3 (5.3)	1 (0)
Nosocomial pneumonia	5 (8.8)	0 (0)
Shunt infection	1 (1.75)	0 (0)
Peritonitis	1 (1.75)	0 (0)
Total	57 (100)	12 (0)

Table 4 lists the organisms isolated from patients in Category 1. Majority of the isolates were gram negative bacteria *(Enterobacter, Klebsiella, Haffnia alvei, Pseudomonas, Acinetobacter,* etc.) which reflects the predominant causes of bacterial nosocomial infection of our hospital. There were only 4 patients with gram positive bacteria isolated and considered to be clinically significant *(Staphylococcus, Streptococcus* and *Enterococcus).*

Table 4. Organisms isolated in Category 1 patients and their outcome

Organism	Number of isolates	Cured or improved	Failure
BLOOD			
Enterobacter spp.	12	11	1
Klebsiella spp.	13	10	3
Haffnia alvei	6	4	2
Pseudomonas	5	3	2
Acinetobacter	1	1	0
Serratia	2	2	0
S. epidermides	1	1	0
S. aureus	1	1	0
Group B strep	1	1	0
Enterococcus	1	1	0
URINE			
E. coli	1	1	0
Pseudomonas	2	1	1
WOUND DISCHARGE			
Haffnia alvei	1	1	0
Klebsiella	1	1	0
ENDOTRACHEAL ASPIRATE			
Klebsiella spp.	1	1	0
Acinetobacter	1	1	0
PERITONEAL FLUID			
Acinetobacter	1	1	0
CEREBROSPINAL FLUID			
Enterobacter	1	1	0
Klebsiella	2	0	2

Of the 57 patients included, 38 patients were cured and 7 patients improved. Thus 79% showed favorable responses to a combination of PIP/TAZO and an aminoglycoside. Bacterial eradication was difficult to assess because repeat cultures was performed in only half of the patients. In this group of patients bacterial eradication was achieved in 20 patients and presumed eradication occurred in 26 patients. All 4 patients with gram positive infections were cured. 10 patients with nosocomial pneumonia had good response with only 1 failure. Patients with sepsis also had good outcomes in 46 patients with 40 patients having a favorable response.

There were no patients who died while they were currently being given PIP/TAZO. There was a total of 12 clinical failures which was 21% of the patients. Failures included 2 patients with *Klebsiella* ventriculitis. Other patients with clinical failure had gram negative infections including *Pseudomonas, Enterobacter, Haffnia* and *Klebsiella* and their medications were shifted to Imipenem of which they were also sensitive. Despite the change of antibiotics there were 2 deaths within 5 days of changing the antibiotics due to their underlying infection.

Category 2

As with Category 1 patients, majority of the patients in Category 2 were neonates being treated empirically for early onset sepsis (see Table 4). In the other pediatric wards most patients were being treated for nosocomial infections non-responsive to third generation cephalosporins. Of 57 patients, 40 patients were cured and 4 patients improved. Thus favorable response was seen in 77% of patients while failure occurred in 22.8% of patients. In the 14 patients being treated for nosocomial pneumonia there were only 2 failures with an 85% favorable response. There was a 75% favorable response in patients being treated for sepsis with only 11 failures in 41 patients. Three patients died of their underlying infection while receiving PIP/TAZO. Of the 10 patients with clinical failure who were shifted to Imipenem empirically, there were 4 patients who died of their underlying infection. Majority of the failures were observed in neonates with early onset sepsis.

Table 4. Indications for treatment and outcome of Category 2 patients

Indications	No. of patients	Cured or improved	Failure	Died while on PIP/TAZO	Died of underlying infection*
Nursery					
Early onset sepsis	35	25	10	1	5
Nosocomial sepsis	5	4	1	1	1
Nosocomial pneumonia	6	6	0	0	0
Pediatric ICU					
Nosocomial pneumonia	4	3	1	1	1
Pediatric wards					
Febrile neutropenia	1	1	0	0	0
Suppurative lymphadenitis	1	1	0	0	0
Nosocomial sepsis	1	1	0	0	0
Nosocomial pneumonia	4	3	1	0	0
Total	57	44	13	3	7

**includes patients who died despite shifting PIP/TAZO to imipenem*

Category 3

Fifteen patients were empirically started on PIP/TAZO for nosocomial infections or for sepsis, but culture and sensitivity tests taken subsequently showed organism to be resistant to PIP/TAZO. These patients were shifted to other antibiotics depending on the sensitivity of the organism. Table 5 shows the organisms cultured in this category. Majority of the organisms were multi-drug resistant gram negative organisms mostly sensitive to imipenem. There was a high mortality rate of 33% in these patients all of whom died of their underlying infection.

Table 5. Organisms cultured in Category 3 patients*

Organisms	Number
Klebsiella spp.	11
Haffnia alvei	4
Pseudomonas spp.	1
Acinetobacter	1
Candida spp.	2
Total	19**

* organisms are resistant to PIP/TAZO
** a patient may have more than 1 culture

Adverse effects

There were 3 patients who died while receiving PIP/TAZO. In the patients who were shifted to another antibiotic either due to resistance or non-response, there were 12 patients who died. The cause of death for all these patients were attributed to their underlying infection.

Table 6. Clinical and laboratory adverse effects of pediatric patients receiving PIP/TAZO

Adverse effects	Number	% of total
Clinical		
Vomiting/residuals	5	3.96
Rashes	2	1.6
GI bleed	2	1.6
Laboratory		
Thrombocytopenia	11	8.5
Leukopenia	6	4.7
Eosinophilia	3	2.3
Elevated liver transaminase Levels	3	2.3
Superinfections		
Candidemia	9	7
Candiduria	2	1.5
UTI *(E. coli)*	1	0.8
Sepsis *(E. cloacae)*	1	0.8

Of the 129 courses of PIP/TAZO given, none of the patients were withdrawn from treatment due to drug-related adverse events. Twenty-nine patients experienced 35 adverse events during treatment. The clinical adverse events usually occurred within 5 days from the start of therapy. There were 5 patients wherein vomiting or residuals were experienced but these were mild and resolved within 1 to 2 days. There were 2 patients who developed rashes, one of which developed rashes during infusion of PIP/TAZO and recurred during the subsequent infusions. The only intervention done was to prolong the infusion time to 2 hours and the rashes did not recur. There was 1 patient who developed gastrointestinal bleeding which was moderate in severity but resolved after 2 days.

The most common laboratory parameter possibly altered by the treatment with PIP/TAZO was thrombocytopenia (platelet count of less than 100,000) but bleeding was not observed in any of the 11 patients. Other laboratory parameters which were deranged were minor alterations in blood count (leukopenia and eosinophilia). Hematologic adverse events were transient and reverted to normal without any intervention. Transient elevations in transaminase levels were seen in 3 patients.

Fourteen patients developed superinfections majority of which were due to Candida. One patient being treated for ventriculitis due to an unrepaired sacral myelomengocoele developed candida meningitis and had to be treated with Amphotericin B. Other superinfections included candidemia, candiduria, UTI and bacterial sepsis.

DISCUSSION

The changing epidemiology of nosocomial infections which include multiply resistant infections has forced clinicians to turn to new broad spectrum drugs. Unfortunately many of these drugs are either not available in our country, or are not yet approved for children less than 12 years old. But out of necessity, our institution has utilized these drugs on a compassionate basis and piperacillin/tazobactam was one of them.

Majority of the studies regarding the clinical efficacy of PIP/TAZO has been performed in adults. The US FDA has approved this drug for the treatment of adults and children over 12 years old for the following indications: intraabdominal infections, skin and skin-structure infections, postpartum endometritis or pelvic inflammatory disease and community acquired pneumonias.[2] Evidence is accumulating that this agent may also be useful in other clinical situations such as nosocomial pneumonias, complicated urinary tract infections, bacteremia, osteomyelitis and febrile episodes in neutropenic patients.[3] This remains to be seen in clinical trials in the pediatric age group.

The clinical response of the 114 clinically evaluable patients (Categories 1 and 2 combined) was 78%. This is a lower rate than that found in bacteremic adults which was 92% probably because of the high incidence of multiply resistant gram negative infections, and more immunocompromised patients (majority of patients were preterm neonates). Also the bacteria isolated in this group of patients are very difficult to treat. The MIC90 (the MIC at which 90% of the strains are inhibited) show very high values for *Enterobacter* (≥ 32 mg/li) and *Klebsiella* (16 mg/li). Even when these patients were shifted to imipenem, there was still a high mortality due to their underlying infection.

Patients with CNS infection such as ventriculitis had poor response. This probably reflects the poor penetration of tazobactam into the cerebrospinal fluid. PIP/TAZO should not be recommended when CNS infection is suspected.

Adverse effects which occurred were infrequent even in the neonatal age group. None of the patients had to discontinue treatment due to an adverse event. In adults, the most common adverse event was diarrhea (3.8%). This was not seen in our pediatric patients but another gastrointestinal manifestation, vomiting had roughly the same incidence (3.9%). Thus due to its efficacy and minimal side effects PIP/TAZO is still being used in the aforementioned indications in our institution as long as CNS infection is not suspected.

Candidal infections were the most common superinfection noted. The prevalence of candidemia in previous years was 3.3%.[14] The prevalence of candidemia in patients receiving PIP/TAZO was much higher at 9.3%. This is probably due to the broad spectrum of activity of PIP/TAZO altering the endogenous flora of the patients resulting in overgrowth of candida. Vigilance for such superinfections is needed in patients being given this drug.

CONCLUSIONS

1. There has been increase in the use of PIP/TAZO among neonates infants and children due to the increase in the number of multiply resistant gram negative bacteria.

2. Indications for using PIP/TAZO in this population include neonates with early onset and nosocomial sepsis, infants and children with nosocomial infections, a febrile neutropenic patient and ventriculitis.

3. Majority of the infections were due to gram negative organisms (*Enterobacter spp., Klebsiella spp., Haffnia alvei, Pseudomonas* spp, etc.) and only 4 patients were treated for gram positive organisms.

4. Of the 114 clinically evaluable patients, there was favorable response in 78% of the patients. Bacterial eradication was

difficult to assess because repeat cultures was performed in about half of the patients. Poor response was seen in patients with CNS infections.

5. The most common adverse event was vomiting/residuals in 3.9% of patients which resolved in 1 to 4 days. Hematologic abnormalities also occurred (thrombocytopenia, leukopenia and eosinophilia) which were transient. There was a 9.3% incidence of candidal infection.

RECOMMENDATIONS

Piperacillin/tazobactam may be used as definitive or empiric therapy in pediatric patients with known resistance or poor response to standard antimicrobial therapy. Patients should be monitored for the occurrence of candidal infections. This drug is not recommended for patients with suspected or definite CNS infections.

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