http:// ijp.mums.ac.ir
Review Article (Pages: 4803-4819)

Clinical Pharmacology of Ceftazidime in Neonates: Effects and Pharmacokinetics

*Gian Maria Pacifici[1], Giovanna Marchini[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Ceftazidime is a valuable third-generation bactericidal cephalosporin. Ceftazidime inhibits the biosynthesis of bacterial cell peptidoglycan, causing inhibition of bacterial growth or cell lyses and death. Common nosocomial gram-negative organisms susceptible to ceftazidime include Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris, and Providencia stuartii. Good activity remains against other gram-negative species including Salmonella, Shigella, and Neisseria species. Ceftazidime is widely distributed in most body tissues and fluids including respiratory secretion, ascitic fluid and cerebrospinal fluid. Ceftazidime is administered parenterally, is completely absorbed after intramuscular injection, and peak drug concentrations generally occur within 3 hours of intramuscular injection. Ceftazidime is not absorbed when taken by mouth.

Ceftazidime half-life is 4 to 10 hours at birth, but half this in infants more than a week old. In premature infants, the distribution volume and the clearance of ceftazidime range from 292±44 to 366±130 ml/kg and from 27.8±5.8 to 60.8±8.3 ml/h/kg, respectively. Ceftazidime binds to plasma proteins at 10% to 17%. No ceftazidime metabolites have been identified and this drug is excreted by renal elimination. The dose of ceftazidime is 25 mg/kg once-daily in the first week of life. Ceftazidime crosses the placenta freely, but there is no evidence of teratogenicity. As empirical ceftazidime monotherapy may not be appropriate for the treatment of neonatal sepsis, the addition of ampicillin, to cover against enterococci and Listeria monocytogenes, seems prudent in these neonatal patients. The aim of this study is to review the effects of ceftazidime in neonates.

Key Words: Ceftazidime, Effects, Neonate, Pharmacokinetics.

Archive of SID

*Please cite this article as: Maria Pacifici G, Marchini G. Clinical Pharmacology of Ceftazidime in Neonates: Effects and Pharmacokinetics. Int J Pediatr 2017; 5(5): 4803-19. DOI: **10.22038/ijp.2017.22928.1920**

Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

Received date: Mar.02, 2017; Accepted date: Mar.22, 2017

www.SID.ir

1-INTRODUCTION

Ceftazidime is a valuable third-generation bactericidal cephalosporin. It is resistant to most β-lactamase enzymes and has good activity in vitro against a wide range of gram-negative bacteria, including Pseudomonas aeruginosa. It is reasonably active against group A and group B streptococci and against Streptococcus pneumoniae, but only has limited efficacy with most other gram-positive organisms. Ceftazidime is not effective against enterococci, Listeria, Helicobacter or Bacteroides fragilis group (1). Ceftazidime is widely distributed in most body tissues and fluids including respiratory secretion, ascitic fluid and cerebrospinal fluid, although cerebrospinal fluid penetration is rather variable unless the meningitis are inflamed.

Overall, ceftazidime remains an effective agent for the treatment of serious infections, particularly those due to major nosocomial pathogens, and respiratory infections in patients with cystic fibrosis. Ceftazidime-containing regimens also remain an important option for the empirical therapy of febrile episodes in neutropenic patients. The tolerability profile of ceftazidime makes the drug a useful option in seriously ill patients who are at risk of developing adverse events with other antibacterial agents. Although patterns of bacterial resistance have changed in the ensuing years since ceftazidime introduction, judicious use of this important agent will help maintain its present clinical utility (2). Like other cephalosporin antibacterial agents, ceftazidime inhibits the biosynthesis of bacterial cell peptidoglycan, causing inhibition of bacterial growth or cell lyses and death. Ceftazidime remains active in vitro against most major aerobic nosocomial bacterial pathogens. Common nosocomial gram-negative organisms susceptible to ceftazidime are Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris and Providencia stuartii. Good activity remains against other gram-negative species including Salmonella, Shigella and Neisseria. Ceftazidime is completely absorbed after intramuscular injection, is widely distributed in body tissues and fluids, and exhibits low plasma protein binding (10% to 17%). Peak drug concentrations generally occur within 3 hours of intramuscular administration. No ceftazidime metabolites have been identified and the drug is excreted almost entirely (> 95%) by renal elimination.

Ceftazidime crosses the placenta freely, but there is no evidence of teratogenicity. The drug is not absorbed when taken by mouth and is excreted unchanged in the urine. The half-life is 4 to 10 hours at birth, but half this in infants more than a week old. In premature infants, the half-life of ceftazidime ranges from 3.85 ± 0.40 and 9.39 ± 3.15 hours. Hypersensitive reactions are occasionally seen in older infants (sometimes overlapping with hypersensitivity to penicillins). The dose of ceftazidime is 25 mg/kg once-daily in the first week of life, and once every 12 hours in infants 1 to 3 weeks of life and every 8 hours in infants older than this (1). A very high blood level, is usually seen in infants with renal failure and a reduction in dose frequency is recommended. High blood levels of ceftazidime can cause central nervous system toxicity as is true for all the β-lactam antibiotics. Rashes, phlebitis and leucopenia have all been reported. As empirical ceftazidime monotherapy may not be appropriate for the treatment of neonatal sepsis, the addition of ampicillin, to cover against enterococci and Listeria monocytogenes, seems prudent in these neonatal patients.

Some 5% of infants given a cephalosporin develop a transient positive Coombs test (and this can interfere with the crosshatching of blood), but frank

Archive of SID

www.SID.ir

hemolytic anemia is extremely uncommon. Tests may wrongly suggest that there is glucose in the urine because of interference with the alkaline copper reduction test, and interference with the Jaffé reaction may affect the measurement of creatinine (giving a false reading that can be particularly misleading when renal failure is a concern) (1).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; January 2017 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "pharmacokinetics ceftazidime neonate", and "effects ceftazidime neonate" were used. In addition, the books Neonatal Formulary (1) and NEOFAX by Young and Mangum (3) were consulted.

3-RESULTS

3-1. Dose and administration

Give 25 mg/kg of ceftazidime intravenously or deep intramuscular injection once-daily in the first week of life, twice-daily in infants 1-3 weeks old, and once every 8 hours in infants older than this. Doses of 50 mg/kg should be used in the treatment of suspected or proven meningitis (3). The dosage interval should be increased in infants with renal failure (1). The dosing interval chart is shown in **Table.1**.

3-2. Uses of ceftazidime

Ceftazidime is useful in the treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms such as Escherichia coli, Haemophilus influenzae, Neisseria, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris and Providencia stuartii. Good activity remains against other gram-negative species including Salmonella, Shigella and Neisseria species. Ceftazidime is resistant among strains of Serratia and Enterobacteriaceae family (3).

3-3. Incompatibility

Amiodarone, azithromycin, erythromycin lactobionate, fluconazole, midazolam, nicardipine, phenytoin, and vancomycin (3).

3-4. Treating neonates with ceftazidime

The clinical efficacy and safety of ceftazidime was assessed in infants and children with pseudomonas infection (4). Eleven children with cystic fibrosis and with acute pulmonary exacerbation, received ceftazidime intravenously three times a day, at a total daily dose of 150 mg/kg for 14 days. Clinical and radiological amelioration was obtained in 12 out of 13 treatment courses. Eradication of pseudomonas from the sputum was obtained in 3 cases. Fourteen patients were treated for urinary tract infections. They received the drug at a mean dose of 78 mg/kg twice-daily for 10 to 18 days.

Eradication of bacteria was obtained promptly in 9 cases, while in 6 cases this took 4 to 8 days. Relapse occurred in 3 cases, but they were definitely cured with a further course of ceftazidime. Pharmacokinetic studies were performed in children with cystic fibrosis. A group of neonates with cystic fibrosis received a single intravenous dose of 50 mg/kg ceftazidime. The results indicate that cystic fibrosis in children eliminate ceftazidime at higher rates than normal adults and this necessitates using higher doses of the drug. Sputum levels exceeding 2 mg/kg were achieved in these patients, but the minimal inhibitory concentration (MIC_{90}) for

Archive of SID

www.SID.ir

Pseudomonas aeruginosa was never exceeded. Serum ceftazidime concentrations decreased slowly in neonates, and the mean half-life was 4.7±1.5 hours. Neonates also had a higher distribution volume of the drug. Ceftazidime was well tolerated and only minor and transient adverse effects were noticed. The elevated in vitro activity of ceftazidime against pseudomonas is clinically confirmed in children with serious infections caused by this pathogen.

High serum ceftazidime concentrations, well exceeding the MIC_{90} for most common neonatal pathogens were obtained and maintained throughout treatment. Penetration into the cerebrospinal fluid was excellent in eight of the nine cases studied. Ceftazidime has a theoretical role as a broad spectrum antibiotic suitable for neonatal use with no evident side effects. In the study by Low et al. (5) however, it was only appropriate for gram-negative infections, and was ineffective against gram-positive organisms. Ceftazidime cannot therefore be recommended as monotherapy before the results of bacteriological culture are known.

3-5. Effects of ceftazidime in neonates

Ninety-one neonates received 108 courses of intravenous ceftazidime (25 mg/kg, 12 hourly) over a study of 15 months (5). Fourteen had clinically and bacteriologically proven infection. Only one of these had resistant organism. Four (two with group B β-hemolytic streptococcal infection, one with Escherichia coli infection, and one with Staphylococcal aureus septicemia) failed to respond despite adequate treatment. Bacteriological eradication or clinical improvement, or both, were obtained in the remaining nine neonates. Routine biochemical and hematological values were monitored and there was no side effects.

3-6. Efficacy of ceftazidime in neonatal infection

The efficacy of ceftazidime in the treatment of infections in compromised children was evaluated in 80 such episodes occurring in 64 patients with various underlying diseases (6). Among the patients treated, 9 were newborns with severe neonatal distress, 21 were children with cancer and neutropenia, 8 were surgical patients, 22 had cystic fibrosis and 4 were suffering from meningitis. The following types of infections were treated: 19 bacteriologically documented and 8 possible septicemias (the latter only in newborns and neutropenic cancer patients); 2 severe upper respiratory tract infections in cancer patients; 8 soft tissue or skin infections; 1 cholangitis; 1 pneumonia; 1 osteomyelitis; 1 Mediastinitis; 35 infections exacerbations of underlying pulmonary disease in cystic fibrosis patients; and 4 meningitis infections. In almost all cases, ceftazidime was administered intravenously in combination with an aminoglycoside. In 2 cases it was also given intrathecally or intraventricularly. Bacteriological documentation was achieved in 70 out of 80 episodes. A successful outcome was obtained in 79% of cases with slight and statistically non-significant differences between groups of patients with different etiological patterns in terms of prevalence of gram-positive microorganisms. Tolerance of the treatment was uniformly good, only one patient showed a mild, transient transaminase elevation.

The pharmacokinetics and safety of ceftazidime (25 mg/kg twice-daily intravenously or intramuscularly) were determined in 41 young, premature neonates who were clinically infected and would otherwise have received gentamicin plus penicillin (7). The pharmacokinetic parameters of ceftazidime after intravenous and intramuscular administrations are summarized in **Table.2**

Archive of SID

www.SID.ir

and the ceftazidime serum concentrations after intravenous and intramuscular administrations are shown in **Table.3**. Ceftazidime was assayed in 46 series of blood samples. Blood was collected before, during and after treatment for analysis of biochemical and hematological factors. Fecal specimens were examined for the presence of Clostridium difficile and its toxin. Although, the peak concentration was higher (77±8 mg/l) than that following intramuscular injection (56±7 mg/l), satisfactory serum levels were maintained throughout the dosage interval using either route. Mean pharmacokinetic profiles following the dosage interval using either route were performed. Postnatal age was the most important factor governing total body clearance (P = 0.001) and serum half-life (P = 0.001). The biochemical and hematological status of the majority of neonates remained unaffected by therapy and there was no increase in the incidence of Clostridium difficile isolation from stools. Ceftazidime is a safe and well tolerated drug for use in the treatment of neonates. Twenty-five mg/kg ceftazidime administered twice-daily resulted in adequate serum levels in neonates during the first two weeks of life.

3-7. Resistance of ceftazidime in neonates

Since the introduction of ceftazidime in the early 1980s, it has retained a broad spectrum in vitro antimicrobial activity and clinical utility in serious infections (2). However, increasing resistance to ceftazidime and other third-generation cephalosporins, particularly Enterobacteriaceae, due to the emergence of plasmid-mediated β-lactamases and the class I chromosomally mediated β-lactamases, is of concern. There is now a wealth of information on the pharmacokinetics of the drug, enabling ceftazidime to be used predictably, and with a low potential for adverse effects, in a diversity of patient populations. Overall, ceftazidime remains an effective agent for the treatment of serious infections, particularly those due to major nosocomial pathogens, and respiratory infections in patients with cystic fibrosis. Ceftazidime-containing regimens also remain an important option for the empirical therapy of febrile episodes in neutropenic patients. The tolerability profile of ceftazidime makes the drug a useful option in seriously ill patients who are at risk of developing adverse events with other antibacterial agents. Although patterns of bacterial resistance have changed in the ensuing years since its introduction, judicious use of this important agent will help maintain its present clinical utility.

3-8. Pharmacokinetics of ceftazidime in neonates

Ceftazidime pharmacokinetics in 28 preterm infants (gestational ages, 25.6 to 31.9 weeks) were studied on day 3 of life. Patients with suspected septicemia were randomized on day 1 of life in two groups (8). One group (n=13) was administered 25 mg/kg of ceftazidime once-daily, and the other group (n=15) was given 25 mg/kg twice-daily. Both groups also received 25 mg/kg amoxicillin twice-daily. Blood samples were collected on day 3 of life by an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 hours after an intravenous bolus injection. An additional blood sample was taken at 24 hours from the group dosed once-daily. The pharmacokinetics of ceftazidime are best described by using a one compartment model.

The pharmacokinetic parameters of ceftazidime are summarized in **Table.4**. The glomerular filtration rate was studied simultaneously by means of 24-hour continuous inulin infusion technique. The ceftazidime inulin clearance ratio was 0.72 for both groups. However, trough concentrations in serum for the twice-daily group were significantly (P < 0.001)

Archive of SID

www.SID.ir

higher (42.0±13.4 mg/l) than those for the once-daily group (13.1±4.7 mg/l). The latter concentrations were all still substantially higher than the MIC_{90} of ceftazidime for major neonatal pathogens. The currently recommended dosage of 25 mg/kg of ceftazidime twice-daily for preterm infants with gestational ages below 32 weeks may be adjusted during the first days of life to once-daily dose at 25 mg/kg, provided that for the empirical treatment of septicemia, amoxicillin at 25 mg/kg is also given twice-daily. Dosage reduction from twice-daily to once-daily results in a significant ($P < 0.001$) reduction in mean serum trough concentrations. However, the individual trough concentrations (8.1 to 25.6 mg/l) are still well above the MICs of ceftazidime for such major neonatal pathogens as Streptococcus agalactiae and Escherichia coli (9, 10); van den Anker et al. (11) showed that ceftazidime has such a prolonged half-life in preterm infants that once-daily administration of a low dose results in concentrations (8.1 to 25.6 mg/l) during the complete 24-hours dosing interval. These authors conclude that the recommended twice-daily administration of ceftazidime in preterm infants with gestational ages below 32 weeks may be adjusted to once-daily dosing in the first days of life. Alternatively, twice-daily dosing with doses lower than 25 mg/kg might even lead to an increased therapeutic effect compared with that of once-daily dosing at 25 mg/kg (12, 13).

3-9. Effects of postnatal exposure to indomethacin on ceftazidime pharmacokinetics in neonates

The effects of postnatal age and postnatal exposure to indomethacin and the pharmacokinetic parameters of ceftazidime were investigated in 23 preterm infants with a gestational age of 28.7±1.7 weeks and a body weight of 1,086±311 grams on day 3 and day 10 after birth (14). Ceftazidime (25 mg/kg once-daily) was administered by intravenous bolus injection. Blood samples were drawn from an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 hours after the dose. Ceftazidime pharmacokinetics followed a one compartment open model. The glomerular filtration rate of all infants was studied by means of the 24 hours continuous inulin infusion technique. The kinetic parameters of ceftazidime are summarized in **Table.4**.

In infants with postnatal exposure to indomethacin the changes in ceftazidime pharmacokinetics were markedly reduced. These results indicate that the dosage regimen of ceftazidime should be adjusted after the first week of life except in infants who were postnatally exposed to indomethacin. The glomerular filtration rate values in preterm infants with gestational ages of less than 32 weeks, and without postnatal exposure to indomethacin increase significantly between days 3 and 10 of life. In infants who are not exposed postnatally to indomethacin, the glomerular filtration rate increased by a mean of 0.19 ml/min during the day period between days 3 and 10 after birth. The postnatal increase of the glomerular filtration rate in the first days of life is 5.4 times higher in comparison with the intrauterine increase.

3-10. Effects of postnatal age on ceftazidime pharmacokinetics in neonates

Postnatal age seems to be associated with an acceleration of the development of the glomerular filtration rate. The positive relationship ($r = 0.81$, $P < 0.001$) between the glomerular filtration rate and the clearance of ceftazidime indicates the important role of the glomerular filtration rate in the clearance of ceftazidime. The distribution volume of ceftazidime decreased significantly between day 3 and day 10 of life in control infants. During the first week of life a significant decrease of the extracellular water volume was

Archive of SID

www.SID.ir

observed (15). This may have caused the decrease of the distribution volume of ceftazidime into the extracellular water compartment. Both the postnatal age increase in the clearance of ceftazidime and the decrease in serum half-life between days 3 and 10 was were shown in the study by van den Anker et al. (14).

3-11. Effects of gestational age on ceftazidime pharmacokinetics in preterm infants

van den Anker et al. (16) determined the effects of gestational age on ceftazidime pharmacokinetics in preterm infants and related these effects to changes in glomerular filtration rate, and established appropriate dosage recommendations for preterm infants on day 3 of life. Multiple-dose pharmacokinetics of ceftazidime (administrate twice-daily in a 25 or 50 mg/kg intravenous dose) were evaluated in 136 preterm infants on day 3 of life. Blood samples were collected from an arterial catheter 0, 0.5, 1, 2, 4, 8, and 12 hours after the intravenous dose.

The glomerular filtration rate was studied simultaneously by means of 24-hour continuous inulin infusion technique. The pharmacokinetic parameters of ceftazidime are summarized in table 2. The mean $\pm$ standard deviation (SD) peak and trough levels of ceftazidime were 114.9$\pm$39.4 and 33.9$\pm$17.8 mg/l, respectively. All infants had a serum trough level above 5 mg/l. The clearance and distribution volume of ceftazidime and the glomerular filtration rate increased significantly with increasing gestational age. Ceftazidime clearance increased significantly with an increase the glomerular filtration rate. Prenatal exposure to indomethacin resulted in significantly lower glomerular filtration rate values and ceftazidime clearances (**Table.4**). Dosage recommendations for ceftazidime administration in preterm infants during the first week of life should be based on gestational age and glomerular filtration rate. Additional adjustment in dosage is indicated in preterm infants who are exposed prenatally to indomethacin. Preterm infants with gestational ages of less than 34 weeks were given ceftazidime 25 mg/kg intravenously every 12 hours and amoxicillin 25 mg/kg intravenously every 12 hours. Preterm infants with gestational ages between 34 and 37 weeks were assigned to receive ceftazidime 50 mg/kg intravenously every 12 hours and amoxicillin 50 mg/kg intravenously every 12 hours. Patients with documented invasive bacterial infections received at least 10 days of therapy. Patients with sterile blood cultures and only a suspicion of infection received a total of 72 hours of therapy.

3-12. Effects of exposed prenatally to betamethasone or indomethacin in neonates

Eighty-four infants (group A) were not exposed prenatally to betamethasone or indomethacin. Twenty-five infants were exposed prenatally to indomethacin but not to betamethasone (group B). Only six infants were exposed prenatally to betamethasone but not to indomethacin (group C). Twenty-one infants were exposed prenatally to both betamethasone and indomethacin (group D) (16). Betamethasone was administered in two intravenous doses of 12 mg/kg each in 2 consecutive days. This dose was repeated every week until delivery or until the thirty-second week of gestation. Indomethacin was administered in suppositories of 100 mg each, which were given repeatedly in the presence of preterm uterine concentrations. The glomerular filtration rate was measured by the continuous inulin infusion on day 3 after birth. Prenatal exposure to indomethacin resulted in significantly lower glomerular filtration rate values (-0.15$\pm$0.03 ml/min; $P < 0.001$) at day 3 after birth. Prenatal administration of betamethasone and indomethacin

Archive of SID

www.SID.ir

significantly (P < 0.001) increased the glomerular filtration rate in comparison with exposure to indomethacin alone to levels not different than those seen in patients who were not prenatally exposed to betamethasone or indomethacin. Six infants who were prenatally exposed to betamethasone had a clearance of 34.5±7.2 ml/h/kg which was lower (41.0±12.2 ml/h/kg) than that of infants who were not exposed to betamethasone and indomethacin. Glomerular filtration rate measurements were repeated in 40 preterm infants on day 10 after birth. During this 7-day period, a significant increase in glomerular filtration rate values (0.17±0.03 ml/min; P < 0.001) was detected. This postnatal increase in glomerular filtration rate values was independent of gestational age and was not influenced by prenatal exposure to betamethasone or indomethacin. These authors (16) conclude that prenatal exposure to betamethasone or indomethacin exerts significant effects on the renal function of preterm infants in the first days of life.

3-13. Effects of gestational age on the pharmacokinetics of ceftazidime in neonates

The clearance of ceftazidime (r = 0.83; P < 0.001) and the distribution volume of ceftazidime (r = 0.74; P < 0.001) increased significantly with increasing gestation age. The clearance of ceftazidime (r = 0.88; P < 0.001) and the distribution volume (r = 0.84; P < 0.001), also increased significantly with the body weight. The half-life of ceftazidime decreased significantly with gestational age (r = -0.54; P < 0.001) as well as with the body weight (r = -0.50; P < 0.001). The clearance of inulin (as a parameter of the glomerular filtration rate) increased significantly with increasing gestational age (r = 0.63; P < 0.001). The clearance of ceftazidime increased significantly with inulin clearance (r = 0.73; P < 0.001) whereas the half-life of ceftazidime decreased significantly with inulin clearance (r = -70; P < 0.001). The present results indicate that twice-daily administration of 25 mg/kg to infants with gestational ages of less than 34 weeks and 50 mg/kg to infants with gestational ages of more than 34 weeks results in high serum levels during the entire dosing interval. The values for the half-life decreased markedly in the less mature preterm infants and showed a gestational age dependent decrease. The positive relationship (r = 0.73; P < 0.001) between the glomerular filtration rate and the clearance of ceftazidime indicates that the glomerular filtration has an important effect on the clearance of ceftazidime.

3-14. Effects of asphyxia on ceftazidime pharmacokinetics in neonates

The multiple-dose pharmacokinetics of ceftazidime were studied after intravenous administration twice-daily at a 50 mg/kg dose. Ten severely asphyxiated term infants with suspected septicemia and 9 term infants with suspected septicemia, but without asphyxia were enrolled (17). Blood samples were collected from an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 hours after intravenous bolus injection. Ceftazidime pharmacokinetics followed a one compartment open model.

The glomerular filtration rates were simultaneously studied by means of the 24-hour continuous inulin infusion technique. Serum trough concentrations (46±14 versus 23±7 mg/l) of ceftazidime were significantly (P < 0.001) increased in the asphyxiated newborns. The glomerular filtration rate expressed in ml/min (3.14±0.43 versus 4.73±0.89) significantly (P < 0.001) decreased in the asphyxiated newborns. The positive relationship (r = 0.87; P <0.001) between the glomerular filtration rate and the ceftazidime clearance indicates the important role of

Archive of SID

www.SID.ir

the glomerular filtration rate in the clearance of ceftazidime. The decrease in the glomerular filtration rate results in a significant decrease in the clearance of ceftazidime and a concomitant decrease of the half-life of ceftazidime and serum trough levels (46±14 mg/l) in asphyxiated infants. Asphyxia of neonates is associated with impaired renal function, which will result in high serum levels of ceftazidime. Twice-daily administration of 50 mg/kg of ceftazidime given to asphyxiated term newborns in the first days of life results in significantly higher serum trough levels in comparison with control infants.

3-15. Optimal dose regimen of ceftazidime in neonates

The optimal dose regimen should result in a high clinical efficacy and a minimal change of toxicity. To ensure clinical efficacy, serum concentrations of ceftazidime should be above the minimal inhibitory concentration of ceftazidime for major neonatal pathogens such as Streptococcus agalactiae (MIC_{90} < 0.25 mg/l) and Escherichia coli (MIC_{90} < 0.25 mg/l) (9, 10). In preterm infants, serum concentrations of ceftazidime were sufficiently high to obtain maximal clinical efficacy. In adults, ceftazidime has been reported to cause encephalopathy, hallucinations, confusions and neuromuscular excitability (18-23).

In addition to these potential neurotoxic side effects, high concentrations of ceftazidime may also result in inhibition of cell proliferation in cultured human myeloid precursor and lymphoid cells (13). This may lead to neutropenia and impairment of cellular and humeral immune responses. The presence of high serum trough concentrations and a prolonged half-life suggests that dosage adjustments are needed in preterm infants. The dose recommendations of ceftazidime in preterm infants should be based primarily on gestational age. There is a strong correlation between ceftazidime clearance and gestational age (r = 0.83). To calculate dosage recommendations, infants are stratified into three groups: gestational age less than 28 weeks, 28 to 32 weeks and 32 to 37 weeks. The dosage recommendations are calculated according to a fixed dosing interval of 12 hours. Alternatively, appropriate dosing may also be achieved by prolonging the dosing interval to 24 hours in infants with gestational ages of less than 32 weeks. The recommended dosage of ceftazidime for infants with gestational ages of less than 28 weeks should be adjusted to 7.5 mg/kg every 12 hours, and for infants with gestational ages between 28 and 32 weeks this should be adjusted to 10 mg/kg every 12 hours.

3-16. Peak and trough serum concentrations of ceftazidime in neonates

McCracken et al. (24) studied the pharmacokinetics of ceftazidime in 31 infants whose gestational age ranged from ≤ 32 and ≥ 38 weeks. The kinetic parameters are summarized in **Table.5**. Ceftazidime was administered as 15 to 20 minutes intravenous infusion to 29 infants for 3 to 5 days. Three of these infants and 2 additional infants were given a single dose of ceftazidime intramuscularly. The dosage used was 50 mg/kg of ceftazidime given every 12 hours in week 1 of life and every 8 hours thereafter. There was considerable variation in serum concentrations of ceftazidime. The peak values occurred at 0.5 hour after the dose (**Table.6**).

The peak concentrations of ceftazidime were observed after multiple doses; these serum values correlated with smaller distribution volume. The pre-dose plasma concentrations after multiple doses were smaller in term infants (≥ 38 weeks of gestation) than in premature infants (< 38 weeks of gestation). The elimination half-

Archive of SID

www.SID.ir

life values after one or two doses ranged from 6.7±2.6 hours in the most premature infants (≤ 32 weeks) to 4.2±1.2 hours in term infants; after multiple doses, the values ranged from 2.9±1.3 to 3.7±1.3 hours in the three study groups. The clearance of ceftazidime from plasma was higher after multiple doses; the mean ± SD values ranged from 59±14 to 108±15 ml.h/kg. The mean ± SD of ceftazidime peak concentration after intramuscular administration in five infants was 108±18 mg/l, and the mean ± SD area under the curve (AUC) value was 528±161 µg.h/ml. The mean plasma half-life was 2.9±1.4 hours, and the mean ± SD of clearance was 101±26 ml/kg/h. These pharmacokinetic values were similar to those observed in the group of 33 to 37-week gestational age infants who received multiple doses (**Table.5**).

The gestational ages of the five infants who received ceftazidime intramuscularly ranged from 34 to 42 weeks (mean 38 weeks). Bactericidal titers were determined in 48 peak and 25 trough serum samples. Mean (range) titers against Escherichia coli and group B streptococcus were 1:256 (1:64 to ≥ 1:1,024) and 1:512 (1:32 to ≥ 1:1,024), respectively, in peak specimens, and 1:128 (1:16 to 1:512 and 1:256 (1:32 to ≥ 1,024), respectively, in trough specimens. The highest serum concentrations exceeded the MIC_{90} of most gram-negative enteric bacilli and Pseudomonas aeruginosa by at least 25 to 50-fold and trough (12-hours or pre-dose) concentrations were equal to or several-fold greater (25-26). Against group B streptococci, the principal bacterial pathogen of neonates, peak and trough serum levels exceeded the $MICs_{90}$ by circa 200 and 20-fold, respectively. The peak and trough bactericidal titers against Escherichia coli and group B streptococcus strain were at least 1:16 and 1:32, respectively, and frequently exceeded 1:512. Single and multiple doses of ceftazidime were well tolerated, and there were no adverse effects observed in the 31 infants.

3-17. Intravenous versus intramuscular administration of ceftazidime in neonates

The pharmacokinetics and safety of ceftazidime (25 mg/kg twice-daily intravenously (n=32), or intramuscularly (n=8) were determined in 41 young, premature neonates who were clinically infected and would otherwise have received gentamicin plus penicillin (7). Blood samples were collected before, during and after treatment for analysis of biochemical and hematological factors. Fecal species were examined for the presence of Clostridium difficile and its toxin. Although the peak concentration following intravenous administration was higher (77±8 mg/l) than following intramuscularly injection (56±7 mg/l; $t = 2.45$; $P < 0.02$), there were no other differences in pharmacokinetics variables between the two routes of administration. Tmax following intramuscular administration was 1.5 hours, but ceftazidime concentrations > 20 mg/l were recorded within 15 minutes of the injection.

Peak concentration increased with increasing serum protein concentration ($r=0.491$; $P < 0.005$). The lowest trough concentration (3 mg/l) was recorded in an infant 27 day old. The serum concentrations of ceftazidime are summarized in **Table.4**. The peak serum concentrations ranged between x100 and x1,000 the MIC_{90} for Escherichia coli and Streptococcus agalactiae, respectively, and between x5 and x30 MIC_{90} for Pseudomonas aeruginosa and Staphylococcus aureus, respectively.

3-18. Pharmacokinetics of ceftazidime after single and multiple administration

Archive of SID

www.SID.ir

The mean concentration/time data are summarized in **Table.4** (7). Serum concentrations were higher in the first hour after dosage following multiple injection, but no accumulation occurred. This was because infants who had received multiple injections were significantly older and rate of clearance increased with increasing postnatal age ($r = 0.703$; $P < 0.001$).

It was possible to compare assay data taken after the first injection (at age one to two days) and after multiple injections (at age 4 to 5 days) in seven neonates. There was a steep reduction in half-life from 9.9±4.3 to 5.7±2.2 hours and increase in clearance from 0.52±0.15 to 1.04±0.48 ml/min/kg between first and multiple injections. Half-life decreased with increasing postnatal age ($r = 0.495$; $P < 0.001$) and serum creatinine concentration ($r = 0.387$; $P < 0.02$).

The half-life was not related to gestational age or birth weight. Urine ceftazidime concentrations were measured in 23 neonates and varied from 192 to 6,028 mg/l during the 12 hours interval. Six oropharyngeal aspirates contained 4.7 to 45 mg/l of ceftazidime.

Table-1: Dosing interval chart of ceftazidime in neonates, by Young and Mangum (3).

Postmenstrual age (weeks)	Postnatal age (days)	Interval (hours)
≤ 29	0 to 28	12
	> 28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥ 45	All	8

Table-2: Pharmacokinetics of ceftazidime in neonates after intravenous or intramuscular administrations (7).

Route of administration		
	Intravenous (n=32)	Intramuscular (n=8)
Peak concentration (mg/l)	77±8 (35-269)*	56±7 (43-63)*
Trough serum concentration (mg/l)	16±8 (3-16)	20±14 (9-53)
Half-life (hours)	7.3±0.7 (2.9-20.1)	14.2±54 (3.5-43)
Clearance (ml/min/kg)	0.84±0.08 (0.17-2.1)	0.63±0.1 (0.13-1.2)
Distribution volume (ml/kg)	464±31 (235-1,188)	399±25 (317-507)
Tmax (hours)	-----	1.45±0.24 (0.78-2.7)

The figures are the mean ± standard error of mean (SEM) and range, by Mulhall and de Louvois; *P<0.02. Ceftazidime was administered either intravenously or intramuscularly at a dosage of 25 mg/kg every 12 hours.

Archive of SID

www.SID.ir

Table-3: Pharmacokinetic parameters of ceftazidime in neonates.

Gestational age (weeks)	Postnatal age (days)	Body weight (grams)	Number of cases	Clearance (ml/h/kg)	Distribution volume (ml/kg)	Half-life (hours)	Reference
$29^{1/7}$±2.0 [A]	3	1,168±309	12/1 [C]	27.8±5.8	323±62	8.15+1.18	8
$29^{4/7}$±$2^{1/2}$ [B]	3	1,141±400	12/3 [D]	30.8±7.5	305±57	7.09±1.66	
28.4±1.7 [E]	3	1,024±319	12	30.7±5.9	363±59*	8.7±2.8	14
29.1±1.1 [F]	10	1154±301	11	41.6±9.0	292±44*	5.0±0.9	
28.4+1.7 [G]	3	1,024+319	12	31.1+6.0	327+71**	7.4+1.3**	
29.1±1.1 [H]	10	1,154±301	11	39.9±20.4	317±37**	6.8±1.8**	
31.5±2.8 I	3	1,579±597	84	41.0±12.2	356±94	6.32±1.72	16
28.9±2.3 [L]	3	1,133±33	25	28.2±9.5	366±130	9.39±3.15	
30.4±2.0 [M]	3	1,093±266	6	34.5±7.2	294±38	6.05±1.0	
29.2±1.3 [N]	3	1,174±265	21	34.0±6.2	326±53	6.83±1.57	
$39^{2/7}$±$1^{4/7}$ [O]	3	3,05±371	10	40.9±6.1***	344±79	5.86±1.13***	17
$39^{5/7}$±$39^{2/7}$ [P]	3	3,367±531	9	60.8±8.3***	336±46	3.85±0.40***	

The figures are the mean± standard deviation; [A] Appropriate size for gestational age. [B] Small for gestational age. [C] Treated once-daily. [D] Treated twice-daily. [E,F] Not exposed to indomethacin. [G,H] Postnatal exposure to indomethacin. [I] Group A: not exposed to indomethacin and betamethasone. [L] Group B: postnatal exposure to indomethacin but not to betamethasone. [M] Group C: postnatal exposed to betamethasone but not to indomethacin. [N] Group D: postnatal exposure to indomethacin and betamethasone. The gestational age of group A was significantly ($p < 0.005$) different from the gestational ages from groups B and D. The clearance of ceftazidime in group B was significantly ($p < 0.005$) different from those of group A, C and D. [O] Asphyxiated. [P] Controls. *P < 0.05; **P < 0.005, ***P < 0.001; Daily doses (mg/kg of body weight): [C] 25 mg/kg once-daily. [D] 25 mg/kg twice-daily. [E-H] 25 mg/kg once-daily. [I-N] 25 or 50 mg/kg twice-daily. [O-P] 50 mg/kg twice-daily.

Table-4: Mean± Standard error of mean ceftazidime serum concentrations (mg/l) after intravenous or intramuscular administration of 25 mg/kg ceftazidime every 12 hours, by Mulhall and de Louvols (7).

		Time following administration (hours)					
Route	Injection	0.25	0.5	1	3	5	12
Intravenous	Single (n=17)	71.6±5.9	65.9±3.1	57.9±2.6	46.0±2.3	38.5±1.8	20.6±2.8
Intravenous	Multiple (n=14)	81.7±4.0	70.0±4.5	69.0±3.3	50.0±3.5	39.5±3.0	16.1±2.6
Intramuscular	Single (n=4)	27.0±3.5	34.8±5.9	43.2±3.9	51.7±2.0	45.2±1.5	19.8±2.0
Intramuscular	Multiple (n=4)	41.0±4.6	54.0±5.5	63.5±7.4	53.8±8.4	40.0±11.4	21.7±10.7

Archive of SID

www.SID.ir

Table-5: Serum concentrations after infusion of 50 mg/kg of ceftazidime every 12 hours in the first week of life and every 8 hours thereafter in newborn infants, by McCracken et al. (24).

Serum concentrations (mg/l ± SD) at designed times (hours).									
Gestational age (weeks)	Number of previous Doses [A]	Number of cases	Pre[B]	0[B]	0.5	1	2	4	8
≤ 32	0-1	7	ND	98±37	109±15	94±25	76±16	59±13	41±8
≤ 32	≥ 5	5	19±5	ND	121±19	118±23	ND	64±15	ND
33-37	0-1	14	ND	135±39	109±18	98±21	75±18	54±12	31±9
33-37	≥ 5	13	16±5	ND	101±19	117±41	ND	53±14	ND
≥ 38	0-1	8	ND	98±27	95±18	98±17	66±9	50±10	29±8
≥ 38	≥ 5	5	14.1±1	ND	95±34	85±15	ND	46±6	ND

The figures are the mean± standard deviation (SD); [A] Serum concentrations were determined after zero or one (0-1) or multiple (≥ 5) previous doses of ceftazidime; [B] Serum samples were obtained immediately before the dose (Pre) and at the completion of the 15- to 20- minutes infusion (0); ND: not done.

4-DISCUSSION

Ceftazidime inhibits the biosynthesis of bacterial cell peptidoglycan causing inhibition of bacterial growth or cell lyses and death. Common nosocomial gram-negative organisms susceptible to ceftazidime include Escherichia coli, Haemophilus influenzae, Neisseria, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Salmonella, Shigella and Neisseria species (2).

Children with cystic fibrosis and with acute pulmonary exacerbation were treated with 50 mg/kg ceftazidime three times a day. Clinical and radiological amelioration was obtained in 12 out of 13 treatment courses. Ceftazidime was found to eradicate bacterial infection in the urinary tract. Ceftazidime was found an effective agent to treat cystic fibrosis (4). Penetration of ceftazidime into the cerebrospinal fluid was excellent in eight of nine cases studied (5). Ceftazidime is an appropriate treatment for gram-negative infections, and is ineffective against gram-positive organisms (5). Ceftazidime was administered at the dosage of 25 mg/kg twice-daily intravenously or intramuscularly to 41 preterm infants infected by Clostridium difficile (7). Although the peak concentration of intravenous ceftazidime was higher (77±8 mg/l) than that following intramuscular injection (56±7 mg/l), satisfactory serum levels were maintained throughout the dosage interval using either route. Postnatal age was the most important factor governing total body clearance (P = 0.001) and serum half-life (P = 0.001). Ceftazidime is a safe and well tolerated drug for use in the treatment of neonates. Twenty-five mg/kg ceftazidime administered twice-daily result in adequate serum levels in neonates during the first two weeks of life (7).

Ceftazidime has a broad spectrum in vitro antimicrobial activity and clinical utility in serious infections. This antibiotic remains an important option for the empirical

Archive of SID

www.SID.ir

therapy of febrile episodes in neutropenic infants (2). Ceftazidime is not absorbed following oral administration and is usually administered by intravenous bolus or short infusion, or intramuscular injection. The absorption is complete from intramuscular injection sites (2). In common with most cephalosporins, ceftazidime is excreted by the kidney, almost exclusively by glomerular filtration (25, 26). A group of preterm infants received ceftazidime at the dosage of 25 mg/kg once-daily and another group of preterm infants received 25 mg/kg ceftazidime twice-daily. The trough serum concentration was 13±4.7 mg/l after once-daily and 42.0±13.4 mg/kg after twice-daily ceftazidime ($P < 0.001$). After once-daily administration of ceftazidime, the trough concentrations of ceftazidime were substantially higher than the MIC_{90} of ceftazidime for major neonatal infections (8); van den Anker et al. (8), conclude that ceftazidime 25 mg/kg once-daily is appropriate for infants with gestational age below 32 weeks of gestation. After once-daily 25 mg/kg ceftazidime, the trough concentrations ranged from 8.1 to 25.6 mg/l and are well above the MICs for major neonatal pathogens as Streptococcus agalactiae and Escherichia coli (11). Ceftazidime has such a prolonged half-life in preterm infants that once-daily administration is recommended in preterm infants with a gestational age below 32 weeks.

The glomerular filtration rate values in preterm infants with gestational ages less than 32 weeks increase significantly between days 3 and 10 of life (8). The glomerular filtration rate increases by a mean of 19 ml/min during the day period between days 3 and 10 after birth. The postnatal increase of the glomerular filtration rate in the first days of life is 5.4 times higher in comparison with the intrauterine increase. The positive relationship ($r = 0.81$; $P < 0.001$) between the glomerular filtration rate and the clearance of ceftazidime indicates the important role of the glomerular filtration rate on the clearance of ceftazidime. The ceftazidime clearance values are 30.7±5.9 and 41.6±9.0 ml/h/kg ($P < 0.05$) in days 3 and 10 of life, respectively. The distribution volume is 363±59 and 292±44 ($P < 0.005$) in the days 3 and 10 of life, respectively (8). During the first week of life a significant decrease of the extracellular water volume was observed (15). This may cause the decrease of the distribution volume of ceftazidime into the extracellular water compartment.

The effects of prenatal exposure to indomethacin and to indomethacin and betamethasone were studied in preterm infants. Preterm infants with gestational ages of less than 34 weeks received ceftazidime intravenously every 12 hours. Preterm infants with gestational ages between 34 and 37 weeks received ceftazidime 50 mg/kg intravenously every 12 hours (11). Prenatal exposure to indomethacin resulted in significantly lower glomerular filtration rate values (-0.15±0.03 ml/min, $P < 0.001$) at day 3 of life (11). Prenatal administration of betamethasone and indomethacin significantly increased the glomerular filtration rate in comparison with exposure to indomethacin alone to levels not different than those seen in patients who were not prenatally exposed to betamethasone or indomethacin (16).

Twice-daily administration of 25 mg/kg to infants with gestational ages of less than 34 weeks and 50 mg/kg to infants with gestational ages of more than 34 weeks results in high serum levels during the entire dosing interval. The values for half-life were increased markedly in less mature preterm infants. A positive linear relationship between gestational age and the glomerular filtration rate was observed by van den Anker et al. (11). The positive relationship ($r = 0.73$; $P < 0.001$) between

Archive of SID

www.SID.ir

the glomerular filtration rate and the clearance of ceftazidime indicates that glomerular filtration rate has an important effect on the clearance of ceftazidime. To ensure clinical efficacy, serum concentrations of ceftazidime should be above the MIC_{90} of ceftazidime for major neonatal pathogens such as Streptococcus agalactiae (MIC_{90} < 0.25 mg/l) and Escherichia coli (MIC_{90} < 0.25 mg/l) (11).

In preterm infants studied by van den Anker et al. (11), serum concentrations of ceftazidime were sufficiently high to obtain maximal clinical efficacy after 25 mg/kg twice-daily in infants with gestational ages of less than 24 weeks and 50 mg/kg to infants with gestational ages of more than 34 weeks during the entire dosing interval. The recommended dosage of ceftazidime for infants with gestational ages less than 28 weeks should be 7.5 mg/kg every 12 hours, and for infants with gestational ages between 28 and 32 weeks this should be 10 mg/kg every 12 hours.

Perinatal asphyxia is a result of complicated or traumatic deliveries and may exert profound effects on renal and liver functions. A redistribution of the fetal circulation leading to an increased blood flow to the brain, heart, and adrenals and a concomitantly decreased blood flow to the lungs, intestine, and kidney is responsible for this asphyxia-induced renal impairment (1). Ceftazidime is eliminated by the kidney and the clearance of ceftazidime is significantly lower (P < 0.001) in asphyxiated neonates than in controls and the half-life of ceftazidime is significantly longer in asphyxiated neonates compared with controls (17).

McCracken et al. (24) administered 50 mg/kg ceftazidime by infusion to neonates with a gestational age between ≤32 and ≥38 weeks. A considerable variation in serum levels of ceftazidime was observed. The Peak concentration ranged between 102±18 and 124±38 mg/l. The peak values occurred at 0.5 hours after the dose. The peak concentration was observed after multiple doses and correlated with smaller distribution volume. Single and multiple doses of ceftazidime were well tolerated, and there were no adverse effects observed in infants studied. The highest plasma concentration exceeded the MIC_{90} of most gram-negative enteric bacilli and Pseudomonas aeruginosa by at least 25- to 50-fold, and trough (12-hours or pre-dose) concentrations were equal to or several-fold greater than the MIC_{90} for these bacteria (13, 14). Against group B streptococci, the principal pathogen of neonates, peak and trough plasma levels exceeded the $MICs_{90}$ by circa 200 and 20-fold, respectively. The peak and trough bactericidal titers against Escherichia coli and group B streptococcus strains were at least 1:16 and 1:32, respectively, and frequently exceeded 1:512.

5- CONCLUSION

In conclusion, ceftazidime is a valuable third-generation cephalosporin. It is active against common aerobic nosocomial gram-negative pathogens. It inhibits the biosynthesis of bacterial cell peptidoglycan, causing inhibition of bacterial growth or cell lyses and death. Twice-daily administration of 25 mg/kg to infants with gestational ages of less than 34 weeks and 50 mg/kg to infants with gestational ages of more than 34 weeks ceftazidime results in serum levels > MIC_{90} of major gram-negative bacteria during the entire dosing interval. The recommended dosage of ceftazidime for infants with gestational age less than 28 weeks is 7.5 mg/kg every 12 hours, and for infants with gestational ages between 28 and 32 weeks this should be 10 mg/kg every 12 hours. Ceftazidime is widely distributed in most body tissues and biological fluids including the cerebrospinal fluid and binds to plasma proteins at a percentage of 10% to 17%.

Archive of SID

www.SID.ir

Ceftazidime is administered intravenously or intramuscularly and is not absorbed when it is administered orally. When ceftazidime is administered intramuscularly, the peak values occur 3 hours after the dose. Ceftazidime is eliminated by renal route and ceftazidime clearance correlates with the glomerular filtration rate. Postnatal or prenatal administration of indomethacin reduces the clearance of ceftazidime. In asphyxiated infants, serum trough concentrations and the half-life of ceftazidime are significantly higher than in not-asphyxiated infants and the clearance of ceftazidime is lower in asphyxiated than in non-asphyxiate infants. After intravenous or intramuscular administration of ceftazidime, its serum concentrations range in a wide interval. Single and multiple doses of ceftazidime are well tolerated, and there are no adverse effects.

6- CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7- ACKNOWLEGMENTS

The authors thank Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

8- REFERENCES

1. Neonatal Formulary. Seventh Edition. John Wiley and Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis, West Sussex, PO22 9NQ, UK. 2015. Pp. 138-9.

2. Rains CP, Bryson HM, Peters DH. Ceftazidime. An update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. Drugs 1995; 49(4):577-617.

3. Young TE and Mangum B. NEOFAX. Twenty-third edition. Antimicrobials 2010. Pp. 30-31.

4. Assael BM, Boccazzi A, Caccamo ML, Giunta A, Marini A, Padoan R, et al. Clinical pharmacology of ceftazidime in paediatrics. J Antimicrob Chemother 1983; 12 (Suppl.A):341-6.

5. Low DC, Bissenden JG, Wise R. Ceftazidime in neonatal infections. Arch Dis Child 1985; 60(4):360-4.

6. Viscoli C, Gargani G, Facco F, Mantero E, Tuo P, Giacchino R, et al. Evaluation of ceftazidime in the treatment of 80 infectious episodes in compromised children. Int J Clin Pharmacol Ther Toxicol 1985; 23(11):629-34.

7. Mulhall A, de Louvois J. The pharmacokinetics and safety of ceftazidime in the neonate. J Antimicrob Chemother 1985; 5(1):97-103.

8. van den Anker JN, Schoemaker RC, van der Heijden BJ, Broerse HM, Neijens HJ, de Groot R. Once-daily versus twice-daily administration of ceftazidime in the preterm infant. Antimicrob Agents Chemother 1995; 39(9):2048-50.

9. Gentry LO. Antimicrobial activity, pharmacokinetics, therapeutic indications and adverse reactions of ceftazidime. Pharmacotherapy 1985; 5(5):254-67.

10. Neu HC. In-vitro activity of ceftazidime, a beta-lactamase stable cephalosporin. J Antimicrob Chemother 1981; 8(Suppl. B):131-4.

11. van den Anker JN, Hop WC, Schoemaker RC, van der Heijden BJ, Neijens HJ, de Groot R. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. Br J Clin Pharmacol 1995; 40(5):439-43.

12. Craig WA and Ebert SC. Continuous infusion of beta-lactam antibiotics. Antimicrob Agents Chemother 1992; 36(12):2577.

13. Neftel KA, Hauser SP, Müller MR. Inhibition of granulopoiesis in vivo and in vitro by beta-lactam antibiotics. J Infect Dis 1985; 152(1):90-8.

Archive of SID

www.SID.ir

14. van den Anker JN, Schoemaker RC, Hop WC, van der Heijden BJ, Weber A, Sauer PJ, et al. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. Clin Pharmacol Ther 1995; 58(6):650-9.

15. Heimler R, Doumas BT, Jendrzejczak BM, Nemeth PB, Hoffman RG, Nelin LD. Relationship between nutrition, weight change, and fluid compartments in preterm infants during the first week of life. J Pediatr 1993; 122(1):110-4.

16. van den Anker JN, Hop WC, de Groot R, van der Heijden BJ, Broerse HM, Lindemans J, et al. Effects of prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in the preterm infant. Pediatr Res 1994; 36(5):578-81.

17. Van Den Anker JN, Van Der Heijden BJ, Hop WC, Schoemaker RC, Broerse HM, Neijens HJ, et al. The effect of asphyxia on the pharmacokinetics of ceftazidime in the term newborn. Pediatr Res 1995; 38(5):808-11.

18. al-Zahawi MF, Sprott MS, Hendrick DJ. Hallucinations in association with ceftazidime. BMJ 1988; 297(6652):858.

19. Douglas MA, Quandt CM, Stanley DA. Ceftazidime-induced encephalopathy in a patient with renal impairment. Arch Neurol 1988; 45(9):936-7.

20. Geyer J, Höffler D, Demers HG, Niemeyer R. Cephalosporin-induced encephalopathy in uremic patients. Nephron 1988; 48(3):237.

21. Richards DM, Brogden RN. Ceftazidime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1985; 29(2):105-61.

22. Slaker RA, Danielson B. Neurotoxicity associated with ceftazidime therapy in geriatric patients with renal dysfunction. Pharmacotherapy 1991; 11(4):351-2.

23. Jackson GD, Berkovic SF. Ceftazidime encephalopathy: absence status and toxic hallucinations. J Neurol Neurosurg Psychiatry 1992; 55(4):333-4.

24. McCracken GH Jr, Threlkeld N, Thomas ML. Pharmacokinetics of ceftazidime in newborn infants. Antimicrob Agents Chemother 1984; 26(4):583-4.

25. Clarke AM, Zemcov SJ. Ro 13-9904 and GR 20263, two new cephalosporins with broad-spectrum activity: an in vitro comparison with other beta-lactam antibiotics. J Antimicrob Chemother 1981; 7(5):515-20.

26. Verbist L, Verhaegen J. GR-20263: a new aminothiazolyl cephalosporin with high activity against Pseudomonas and Enterobacteriacae. Antimicrob Agents Chemother 1980; 17(5):807-12.

Archive of SID

www.SID.ir