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RESEARCH ARTICLE

THE EFFECT OF CEFIXIME IN TREATING RESPIRATORY TRACT AND URINARY TRACT INFECTIONS IN CHILDREN

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Abstract

Third generation cephalosporins are commonly used for the treatment of diverse infections in children. Cefixime is an oral third-generation cephalosporin with a broad-spectrumantibacterial activity and a relatively long elimination half-life. It is available in oral, intravenous, and intramuscular forms. It is effective against certain bacteria, such as Streptococci, Neisseria gonorrhoeae, Moraxella catarrhalis, Haemophiles influenzae, and Gram-negative bacilli. However, it is poorly active against Staphylococcus aureus, Coagulase-negative Staphylococci, and Enterococci. Clinical trials have shown that cefixime is comparable to amoxicillin and cefaclor in treating acute otitis media in children caused by various organisms, including Streptococcus pneumoniae. It is more potent than other cephalosporins against Enterobacteriaceae but less activeagainst ciprofloxacin. The recommended dosage for children is 8 mg/kg/day orally, once daily or in two divided doses and the most prominent side effect is diarrhea, which occurs in up to16% of children. Cefixime is a safe and effective for treating upper respiratory tract infections and acute otitis media. However, there is insufficient evidence regarding its efficacy in treating sinusitis and lower respiratory tract infections in children as its antimicrobial spectrum does cover the bacteria commonly associated with these infections. Due to its partial excretion through the kidneys, cefixime is frequently used to treat urinary tract infections in children.

Introduction:-

Cefixime Potent Activity and Pharmacokinetics

Cefixime is an orally active cephalosporin of the amino-thiazole group with a broad-spectrum antibacterial activity and an extended elimination half-life allowing a simple treatment regime. It is categorized as class IV in the Biopharmaceutics Classification System (BCS) with low solubility and permeability. The drug has been approved for marketing by the United States Food and Drug Administration in 1989 (1,2). The determination of its activity is based on minimum inhibitory concentrations (MIC) in rational numbers of microorganisms. Cefixime is broadly used in the treatment of acute otitis media, pharyngitis, tonsillitis, and acute urinary tract infections (UTI) in adults and children (3). It is also available in oral and intravenous forms(4). Its role in treating complicated UTI or respiratory tract infection (RTI) is still under investigation.

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Cefixime is potent against most Gram-negative aerobic bacteria but is poorly active against Staphylococci, Enterococcus and Bactericides species. Most strains of Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Citrobacter diversus and Providencia rettgeri) are inhibited by cefixime (5–8). In comparisons with other antibacterial drugs, the potency of cefixime in-vitroagainst Enterobacteriaceae was greater than that of cefaclor and cephalexin(9,10). Cefixime is less active than ciprofloxacin against Enterobacteriaceae, but its activity is close similar to cefpodoxime(7,11). The good response activity of cefixime against limited numbers of strains of Acinetobacterand Corynebacterium has been reported (12). Cefixime has a weak activity against Staphylococcus aureus, Neisseria gonorrhoeae and is poorly active against Pseudomonas aeruginosa, Streptococcus epidermidis and Enterococcus faecalis, and 90% of gram-positive cocci including Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus agalactiae, and all strains of Haemophiles influenzaeand strains resistant to ampicillin, chloramphenicol, cotrimoxazole, cefaclor and cephalexin(3,6,13–15). Campylobacter jejuni showed varied responses between studies and Flavobacterium and Chlamydia trachomatis are quite resistant to cefixime antibiotic(12,14,16,17).

Cefixime exhibits a strong affinity for penicillin-binding proteins (PBP), resulting in its rapid lytic action compared to other orally active cephalosporins such as cefaclor and cephalexin(12,18,19). Similar to other newly developed oral cephalosporins, cefixime's pharmacokinetics are characterized by incomplete absorption following oral administration. The bioavailability of cefixime after oral ingestion typically ranges from 40% to 50%(20,21). The average volume of distribution (Vd) for cefixime is approximately 0.1L/kg (22). Extensive research has been conducted on the pharmacokinetic properties of cefixime in both healthy volunteers and patients, including adults and children, who were administered single doses of capsules, tablets, or suspension. It is widely acknowledged that the pharmacokinetics of cefixime in children are more intricate due to the vigorous physiological changes associated with maturation and growth (23). Following oral administration to healthy adults, peak plasma concentration is achieved within 3-4h(20,22). Its concentration is not influenced by the food(20). In adults, the mean greatest plasma concentrations were 4.16, 4.18 and 4 mg/L after a 400mg dose administered as a single tablet, oral suspension or tablets, respectively. In children, single oral doses of cefixime (1.5 and 3mg/kg) in a suspension formulation resulted in mean peak plasma concentrations of 0.6 to 1.2 and 1.15 to 1.6 mg/L, respectively(24,25). The mean maximum plasma concentration after 4h of drug administration was 2.5mg/L (26). The administration of cefixime for 15 days in healthy adults did not result in high plasmaconcentration of the drug(27). The pharmacokinetics of cefixime at a dose of 8mg/kg in children were found to be comparable to those observed in healthy adults receiving a 400mg dose (28). Due to its approximately 70% protein binding in healthy individuals, cefixime exhibits rapid volume distribution following intravenous administration. The elimination of cefixime occurs primarily through the liver, accounting for 50%-60% of clearance, while the kidneys contribute to approximately 20%-40% of clearance (29). No biologically active metabolites of cefixime have been detected in plasma or urine, and approximately 20% of a 200mg dose is excreted unchanged in the urine within a 24-hour period(27,30,31).

In comparisonto other cephalosporins such as cefotaxime and beta-Lactam antibacterial drugs, cefixime is more effective than other cephalosporins such as cefaclor and cephalexin against Enterobacteriaceaebut poorly active against ciprofloxacin (18). Matsumoto et al found that the stability of beta-lactamase of cefixime was similar to that of ceftizoxime (18). The lack of activity of cefixime against Staphylococcus aureusmay be due to its poor binding to PBP(19).

Cefixime Elimination and Its Biological Activity

Cefixime exhibits a notable elimination half-life of 3h in healthy individuals with normal kidney function, allowing for once or twice daily dosing (22,32). However, in patients with impaired renal function and a creatinine clearance (CL) below 20ml/min, dosage adjustment becomes necessary as the elimination half-life may be prolonged (33). Patients with mild renal dysfunction typically do not require dosage adjustment. Additionally, the half-life of cefixime is significantly longer compared to other orally active cephalosporins, such as cefaclor (0.5h), cephalexin (1h), and cefadroxil (1.5h) (34).

In adults, clinical and bacteriological efficacy can be achieved with cefixime doses of 200-400mg daily (single dose or two divided doses). For the treatment of upper respiratory tract infections in children, the most commonly used dosage is cefixime 8mg/kg/day (single dose or two divided doses). In patients with severe renal dysfunction (CL < 20ml/min), half the standard dose of cefixime once daily is recommended. Dosage for children with renal dysfunction isrecommended to be lower (3-6mg/kg/day). However, higher dosages (12mg/kg/day) are recommended for severe infections and non-responders. The absolute bioavailability of cefixime is 40% for 400mg capsules, 47%

for 200mg capsules, and 50% for an oral solution (35). Due to its approximately 70% protein binding in healthy individuals, cefixime has a rapid volume distribution after intravenous administration. No biologically active metabolites of cefixime have been identified in plasma or urine, and approximately 20% of a 200mg dose is excreted unchanged in the urine over 24 hours. Mean maximum urinary concentrations of 70-165mg/L have been reported 4-6h after single doses of cefixime ranging from 100-400mg.

Cefixime Adverse Effect

Adverse effects observed in clinical settings among patients receiving cefixime treatment have generally been of a transient nature and of mild to moderate severity. The most commonly reported adverse effects, namely diarrhea and changes in stool consistency, are typically mild and transient, and commonly occur early in the treatment. An analysis of adverse effects in a large number of adult and children revealed an overall incidence of diarrhea at 14% in both groups (36). McLinn et al. reported that out of 60 children treated with cefixime, ten experienced diarrheas, which was comparable to the rate (15%) observed in the amoxicillin-treated group (37). Other gastrointestinal complaints associated with cefixime, including nausea, abdominal pain (6%), dyspepsia (3.5%), and vomiting (1.2%), occurred with similar frequency in patients treated with amoxicillin. Headache and dizziness were reported by 11% and 3% of patients treated with cefixime, respectively. Whilst, the same proportion of patients experienced symptoms indicative of drug hypersensitivity (36).

Indications of Cefixime Treatment in Children

Cefixime is commonly prescribed for a limited number of patients who have acute pharyngitis or tonsillitis, lower respiratory tract infections, and uncomplicated or complicated UTIs. Currently, there is a scarcity of controlled therapeutic trials that directly compare the clinical and bacteriological effectiveness of cefixime with other antibacterial drugs in children with respiratory tract infections. However, it has been compared to amoxicillin and cefaclor in children with acute otitis media, as well as to amoxicillin in adults with tonsillitis or pharyngitis. Similarly, the number of comparative studies in UTIs is also limited, with only a few studies comparing cefixime to cotrimoxazole and amoxicillin in uncomplicated UTIs, and to norfloxacin and ciprofloxacin in patients with complicated infections. In the case of lower respiratory tract infections, a small number of trials have been published comparing cefixime to cefaclor or amoxicillin for the treatment of acute or chronic bronchitis.

Cefixime and Upper Respiratory Tract Infection (URTI)

Resolution of signs and symptoms of pharyngitis have been achieved in all children treated with cefixime 5-12mg/kg daily. Outstanding results were also attained in children with tonsillitis, pharyngitis or scarlet fever (38). In a series of small studies in a total of 20 Japanese children, clinical results were reported as excellent in 70% of patients(39–41). Clinically excellent resultswere acquired in 80% of children with tonsillitis treated with cefixime (5-12mg/kg daily in divided doses)(39,40). Treatment of children with cefixime was also effective in eradicating Streptococcus pyogenes and Hemophilus influenzas in patients with pharyngitis or tonsilitis (41).

The most frequently identified bacteria in middle ear aspirates of infants and children with acute otitis media are Streptococcus pneumoniae, Hemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes, and occasionally Staphylococcus aureus. Amoxicillin and cefixime demonstrate superior activity against Hemophilus influenzae and Moraxella catarrhalis compared to ampicillin, erythromycin, or cefaclor. Due to limited effectiveness of amoxicillin against beta-Lactamase-producing bacteria, cefixime is considered a preferred alternative for treating uncomplicated acute otitis media in children, offering excellent activity and a prolonged elimination half-life against beta-Lactamase-producing Hemophilus influenzae and Moraxella catarrhalis. Cefixime is conveniently available in liquid form and can be administered once daily. While amoxicillin is more effective than cefixime against Pneumococcal otitis media, there is a tendency for cefixime to exhibit greater efficacy against Hemophilus influenzae(42).

Most of clinical trials concluded that cefixime isa safe effective drug for the treatment of acute otitis media in infants and children older than one year of age (43,44). Children with acute otitis media with effusion have shown good results to cefixime withthe usual standard dosage and this to be typically effective as cefaclor and amoxycillin equivalent to the same dose range(31). In children with acute otitis media, the pathogens are eradicated from the middle ear within 3-5 days of therapy in more than 80% of children treated with cefixime butless than 80% of those treated with amoxicillin (45). The effectiveness of cefixime against Streptococcus pneumoniae and Streptococcus pyogenes is slightly lower than that of ampicillin. In a study involving 211 children with acute otitis media, cefixime demonstrated significantly higher bacteriological efficacy compared to cefaclor (44). Rodriguez et al., found that the

clinical cure rate for patients with baseline organisms was 94% for cefixime and 68% for cefaclor, suggesting that once-daily cefixime treatment is equivalent to three-daily cefaclor treatment for acute otitis media(46). Leigh's study involving 300 children showed that more than 80% of patients treated with cefixime oral suspension (100-300mg once daily) and 90% treated with amoxicillin (187-750mg daily in 3 divided doses) experienced complete resolution of symptoms(47).

According to numerous clinical trials, cefixime has been identified as a viable alternative to amoxicillin for the treatment of acute otitis media in infants and children. This recommendation specifically applies to cases where the child is infected with beta-Lactamase-producing Hemophilus influenzae or Moraxella catarrhalis, has a documented history of delayed hypersensitivity to penicillin, and shows no clinical improvement with amoxicillin (45). In situations where the child exhibits allergic hypersensitivity to penicillin, erythromycin or trimethoprim sulfamethoxazole are advised as alternatives. If the patient's allergic reaction to penicillin is not immediate, one of the cephalosporins, such as cefaclor, may be recommended. However, it is important to note that cefaclor may not be as effective against beta-Lactamase-producing Moraxella catarrhalis and its in-vitro activity against Hemophilus influenzae is questionable.

It is worth mentioning that cefixime does have some limitations. While it is not commonly associated with acute otitis media, cefixime exhibits poor in-vitro activity against Staphylococcus aureus. Additionally, cefixime is relatively more expensive compared to amoxicillin, although in certain cases, it may be slightly more cost-effective than other newer antimicrobial agents.

Cefixime and Lower Respiratory Tract Infection (LRTI)

The current evidence regarding the use of cefixime in lower respiratory tract infections (LRTI) is limited, particularly in pediatric populations compared to adults. However, a collection of non-comparative Japanese studies conducted on small patient populations have shown promising results. These studies demonstrated a favorable clinical response in approximately 80% of patients with acute pneumonia and acute bronchitis when treated with cefixime at daily doses of 200-400mg, divided into two doses (32,48–52). Among 62 patients with acute pneumonia, nearly 25% of them exhibited an excellent clinical response to cefixime (50).

In a multicenter trial involving 172 patients with bacterial, mycoplasmal, or primary atypical pneumonia, cefixime at a dosage of 200mg twice daily was compared to amoxicillin at a dosage of 2000mg daily. The trial found similar rates of clinical cure between the two treatments. However, no comparative studies specifically focusing on children have been conducted. Eradication of pathogenic bacteria was evaluable in 42 patients, most of whom were infected with either Hemophilus influenza or Streptococcus pneumoniae. Pathogens were eradicated in 100% of patients treated with cefixime and in 80% of those who received amoxycillin (53). A study conducted by Sengupta et al. compared cefixime with cefpodoxime in the treatment of LRTI in children (54). Cefpodoxime was found to be a well-tolerated and superior alternative to cefixime, demonstrating an extended spectrum of activity and high efficacy with a low incidence of side effects.

Overall, cefixime remains a favorable choice for the treatment of lower respiratory tract infections, although further research is needed to establish its efficacy and safety in pediatric populations.

Cefixime and Urinary Tract Infection (UTI)

Urinary tract infection (UTI) is a commonly occurring bacterial infection in infants and children. It has a prevalence of 5% in febrile infants and affects 10%-20% of febrile patients, potentially leading to permanent renal damage. The long-term effects of this damage, such as hypertension or proteinuria in previously healthy kidneys, are not yet fully understood. Since 20% of the drug is eliminated through the kidneys as an active form, cefixime may serve as a viable treatment option for UTIs. Recent studies indicate that oral cefixime or amoxicillin/clavulanic acid can effectively treat febrile UTIs in children for a duration of 10 to 14 days (55). The overall therapeutic efficacy of cefixime in uncomplicated UTIs is excellent in over 50% of patients, but poor in 3% of patients who receive the standard dose of 100mg daily for 3-7 days(56–59).The administration of cefixime, primarily targeting E. Coli pathogens, leads to complete eradication of the infecting pathogens by the end of the treatment period (60). A multicenter study comparing cefixime and amoxicillin demonstrated a clinical cure rate of 90% in patients with uncomplicated UTIs treated with cefixime, while amoxicillin achieved a cure rate of nearly 85%. Additionally, isolated pathogens were eradicated in up to 90% of the patients (61).

In a study conducted by Mamozoridi et al, involving six children aged 6-13 years who were treated for UTIs, an oral dose of cefixime in the form of a suspension formulation at a dosage of 8mg/kg was administered. All children exhibited good tolerance to cefixime, and no adverse effects were observed (62).Cefixime has been compared with cotrimoxazole and amoxycillin in patients with uncomplicated UTI and with ciprofloxacin, amoxycillin and norfloxacin in complicated UTI. Studies reported almost identical bacteriological cure rates with cefixime and cotrimoxazole (63). Another multicenter trial has compared cefixime and amoxycillin in 192 patients described as having acute UTI, acute cystitis, cysto-urethritis or pyelonephritis (64). Both cefixime and amoxicillin demonstrated clinical cure in treated patients. Based on the response criteria established by the Japanese UTI committee, the clinical efficacy rate for 26 cases of uncomplicated cystitis exceeded 95%. For 5 patients with complicated UTI and 5 with uncomplicated pyelonephritis, the clinical effectiveness rate was 80%. Even in the remaining 23 cases that did not meet the response criteria, the efficacy rate remained high. These findings strongly suggest that cefixime is a highly effective medication for the treatment of urinary tract infections (65).

Japanese researchers have utilized cefixime to treat complicated UTIs in adults. The typical dosage regimen consisted of 200mg of cefixime administered daily in divided doses, occasionally increased to 400mg daily. The overall outcomes were excellent in 40% of the patients (57,66,67). The majority of urinary pathogens identified belonged to the Enterobacteriaceae family, with Escherichia coli being the most prevalent, and were successfully eradicated by the end of the treatment period.Limited research has been conducted on children with UTIs, but the efficacy of cefixime was reported to be excellent in nearly 50% of cases when administered at a dosage of 3-12mg/kg daily, divided into 2 or 3 doses(27,68,69).For children over two years of age with complicated acute pyelonephritis, initial treatment with a parenteral antibiotic such as ceftriaxone is recommended, followed by a switch to oral antibiotic therapy. The preferred oral antibiotic for this purpose is cefixime, administered for a duration of 7-10 days.

Moreover, oral cefixime has demonstrated effectiveness in treating uncomplicated gonorrhea in teenagers and young adults(70). The comparison between oral cefixime and intramuscular injection has also been investigated in the literature. Gok F et al. conducted a study to assess the efficacy of oral cefixime compared to intramuscular ceftizoxime followed by oral cefixime for the treatment of UTIs in 54 children. The children were randomly assigned to receive either oral cefixime at a dosage of 8mg/kg/day for 10 days or intramuscular ceftizoxime at a dosage of 50 mg/kg twice a day for 2 days, followed by oral cefixime for 8 days(71). The majority of cases involved Escherichia coli. Urine cultures were repeated multiple times and were found to be sterile for 24 hours in all children. The cure rates were similar in both groups, and no significant adverse effects were observed.

In conclusion, the administration of a single oral dose of cefixime suspension (8mg/kg) in children with UTIs was well tolerated without adverse effects. The pharmacokinetic values were comparable to those achieved with intramuscular injection of ceftizoxime and were consistent with previous reports in healthy adults using equivalent mg/kg doses.

Summarized Guidelines for the Use of Cefixime in Children

- Cefixime does not possess any advantage over amoxicillin, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole for the treatment of otitis media caused by Streptococcus pneumoniae, which is the most common bacterial pathogen. Amoxicillin has been found to be effective against beta-Lactamase producing Hemophilus influenzae and Moraxella catarrhalis, which are common pathogens in otitis media.
- Penicillin V remains the preferred treatment for Streptococcal pharyngitis, but effective alternative antibiotics include erythromycin and cephalosporins. Cefixime is also effective in treating streptococcal sore throat.
- There is insufficient evidence from controlled studies to support the effectiveness of cefixime in treating sinusitis, acute bronchitis, or pneumonia in children.
- Cefixime is effective for the treatment of urinary tract infections (UTIs).
- Cefixime is effective in treating uncomplicated gonorrhea.
- Cefixime is effective in treating gastroenteritis in young children, particularly against Salmonella and Shigella bacterial pathogens that are resistant to amoxicillin and trimethoprim-sulfamethoxazole. However, it is not yet known if resistance would develop in these pathogens.

Declaration

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