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Review Article

Clinical Pharmacology of Ceftriazone

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Abstract

Ceftriazone is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriazone is active against *Escherichia coli*, Klebsiella, Providence, Serratia, and Haemophilus species. Single dose of ceftriazone is used to manage ureteral, cervical, rectal, pharyngeal infections, gonorrhoea and Lyme disease. Ceftriazone is used to treat bacterial meningitis in combination with vancomycin and ampicillin owing to the excellent activity against *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides*, and gram-negative enteric bacteria. About half of ceftriazone is recovered in the urine and the remainder is eliminated by bile secretion. The efficacy and safety of ceftriazone have been reported. Following intravenous administration, ceftriazone is rapidly absorbed with a mean absorption half-life of about 14 min and ceftriazone mean elimination half-life is 6.4 hours in patients with normal renal function and 21.4 h in patients with renal failure. Ceftriazone is eliminated in part by renal route thus ceftriazone elimination half-life is longer in patients with renal failure. The prophylaxis, treatment, and trials with ceftriazone have been extensively studied. Ceftriazone penetrates into the cerebrospinal fluid in significant amounts and treats bacterial meningitis. Ceftriazone may become resistant to bacteria and ceftriazone is poorly transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review ceftriazone the efficacy and safety, pharmacokinetics, prophylaxis, treatment, trials, penetration into the cerebrospinal fluid, treatment of bacterial meningitis, resistance to bacteria, and transfer across the human placenta, and migration into the breast-milk.

Keywords: Breast milk; Ceftriazone; Cerebrospinal fluid, Efficacy safety; Meningitis; Pharmacokinetics; Placenta; Prophylaxis; Resistance; Treatment; Trials

Introduction

General pharmacology of ceftriazone

Ceftriazone is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria. Ceftriazone has an elimination half-life of about 8 hours allowing for once-daily dosing for most indications. Administration of ceftriazone twice-daily has been effective for patients with meningitis. About half of ceftriazone can be recovered from the urine and the remainder is eliminated by biliary secretion. Single dose of intramuscular ceftriazone has long been used in the management of ureteral, cervical, rectal, pharyngeal infections and gonorrhoea; increasing the resistance has necessitated the use of higher doses (250 mg instead of 150 mg) and routine administration of azithromycin [1].

Antimicrobial spectrum of ceftriazone

Ceftriazone is the drug of choice for serious infections caused by *Escherichia coli, Klebsiella, Providence, Serratia*, and *Haemophilus species*. Ceftriazone is the therapy of choice for all forms of gonorrhoea and for severe forms of Lyme disease. Ceftriazone is used for the empiric treatment of meningitis in non-immunocompromised adults and children (in combination with vancomycin and ampicillin pending identification of the causative agent), owing to their excellent activity against to *Haemophilus influenzae*, sensitive *Streptococcus pneumoniae*, *Neisseria meningitides*, and gram-negative enteric bacteria. Ceftriazone lacks activity against *Listeria monocytogenes* and penicillin-resistant pneumococci, which may cause meningitis. The antimicrobial spectrum of ceftriazone is excellent for the treatment of community-acquired pneumonia [1] (Figure 1).

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "ceftriazone efficacy safety", "ceftriazone pharmacokinetics", "ceftriazone prophylaxis" "ceftriazone treatment", "ceftriazone trials", ceftriazone CSF", "ceftriazone meningitis", "ceftriazone resistance", "ceftriazone placental transfer", and "ceftriazone breast-milk". In addition, the book "The pharmacological basis of therapeutics" has been consulted [1].

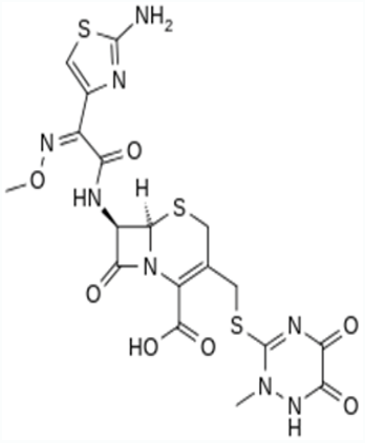

Figure 1: Ceftriazone molecular structure (Molecular weight: 554.58 gm/mole).

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Results

Efficacy and safety of ceftriazone

Ceftriazone is efficacy and safety in treatment of community-acquired pneumonia [2]. Ceftriazone is efficacy and safety in treatment of community-acquired pneumonia [3]. Ertapenem and ceftriazone therapy have similar efficacy and safety in hospitalized patients with community-acquired pneumonia [4]. Ceftriazone is efficacy and safe in treatment of amyotrophic lateral sclerosis [5]. Ceftriazone is efficacy and safety in treatment of uncomplicated gonorrhoea [6]. Ceftriazone is efficacy and safe in treatment of serious infections due to gram-negative organisms [7]. Ceftriazone is safe and effective in the treatment of serious infections in children [8]. The efficacy, safety and convenience of ceftriazone monotherapy make this antimicrobial agent a candidate for the treatment of choice of selected serious paediatric infections [9].

Pharmacokinetics of ceftriazone in patients with severe sepsis 5.

Pharmacokinetics of ceftriazone studied by Joynt et al. [10] in 12 patients with nosocomial pneumonia, intraabdominal sepsis, or urinary sepsis and ceftriazone was intravenously infused at a dose of 2 gm once-daily. Two of these patients had a renal failure. The patients were aged 45 ± 16 years (range, 33 to 68) had a body-weight of 62 kg ± 13 kg (range, 52 to 96), creatinine serum concentration of 70.7 µmol/L ± 24.2 µmol/L (range, 41 to 111), creatinine clearance of 97.7 ml/min ± 49.6 ml/min (range, 21 to 167), albumin concentration of 22.2 grams/L ± 6.1 grams/L (range, 19 to 31) and a bilirubin concentration of 39.6 µmol/L ± 50 µmol/L (range, 9 to 155).

Ceftriazone rapidly distributes in the body as the mean distribution half-life is 14 min in all patients and ceftriazone is slowly eliminated as the mean elimination half-life is 9.2 hours show in Table 1. There is remarkable inter-patient variability of ceftriazone trough plasma concentrations and pharmacokinetic parameters. This variability is accounted by the wide variability in patient demographic characteristics and diseases. The comparison of ceftriazone pharmacokinetic parameters obtained in patients with normal renal function to those obtained in patients with renal failure is difficult because the small number of patients however the impression prevails that the ceftriazone pharmacokinetic parameters are different in patients with renal failure from those obtained in patients with normal renal failure. Ceftriazone is excreted largely unchanged and is dealt with in approximately equal proportions in the bile. Thus, renal function is an important factor for the clearance of ceftriazone from the body. Joynt et al. [10] stated that that moderate or severe renal failure causes approximately three-fold increase in the distribution half-life, a 50% increase in the distribution volume at steady-state and halved total body clearance.

Prophylaxis with ceftriazone

Ceftriazone is superior to other antibiotics in preventing both local and remote postoperative infections [11]. Prophylaxis with ceftriazone plus metronidazole is more effective in preventing postoperative infections than broader-spectrum antibiotics [12]. Intravenous ceftriazone is more effective than oral norfloxacin in the prophylaxis of bacterial infections [13]. One dose of ceftriazone was as effective as ampicillin/cloxacillin in preventing post-caesarean section complications [14]. The prophylaxis with ceftriazone for the prevention of surgical infections is superior to that of other cephalosporins [15]. Prophylaxis with ceftriazone prevented infections due to colorectal surgery [16]. Prophylaxis with ceftriazone prevented infections following orthopaedic surgery [17]. Prophylaxis with ceftriazone prevented the infection in patients undergoing liver transplantation [18]. In patients undergoing elective orthopaedic and traumatic surgery ceftriazone prevented the infection in 95% of patients [19]. Prophylaxis with ceftriazone prevented the postoperative infections and pyrexia [20]. Prophylaxis with ceftriazone prevented the infection in patients undergoing chest surgery [21].

Treatment of bacterial infection with ceftriazone

Ceftriazone is similarly effective as benzylpenicillin for treatment of neurosyphilis [22]. Ceftriazone administered at a dose of 2 gm treated endocarditis, spondylodiscitis, and prosthetic joint infections caused by *Cutibacterium acnes* [23]. A short-course treatment of 3 to 6 days with ceftriazone, administered at a dose of 2 gm daily, treated severe forms of leptospirosis [24]. Ceftriazone effectively and safety treated acute tonsil-pharyngitis [25]. A single-dose of 2 gm ceftriazone treated epidemic meningococcal meningitis [26]. Ceftriazone administered at a dose of 2 gm effectively treated typhoid fever [27]. Ceftriazone sodium was administered once-daily at a dose of 2 gm and effectively treated streptococcal endocarditis [28].

Table 1: Concentration of ceftriazone in plasma and pharmacokinetic parameters of ceftriazone which are obtained in 12 patients with severe sepsis and two of these patients had renal failure. Values are the minimum, maximum, mean, and ± SD, by Joynt et al. [10].

										Trough conc. (µg/ml)[a]	
Value	Vc (L)	Vss (L)	K_{el} (min)	K_{12} (min)	K_{21} (min)	$t_{1/2}\alpha$ (min)	$T_{1/2}\beta$ (h)	TBC (ml/min)	Peak conc. (µg/ml)	24 h	Day 3
Patients with normal renal function (N=10)											
Minimum	1.3	13.6	0.00022	0.013	0.012	6.0	4.8	23.0	148	< 5	< 5
Maximum	7.2	22.6	0.0108	0.085	0.026	26.0	7.2	62.0	242	14.0	13.0
Mean	5.9	19.9	0.0072	0.042	0.017	13.3	6.4	41.3	205	8.8	9.6
± SD	1.3	3.3	0.0022	0.023	0.008	6.8	1.1	11.7	31.3	3.0	7.2
Patients with renal failure (N=2)											
---	7.0	25.7	0.0031	0.022	0.008	21.0	14.5	22.0	205	21.0	25.0
---	6.5	41.2	0.0027	0.038	0.007	15.0	28.4	18.0	184	27.0	49.0
Mean	6.8	33.5	0.0029	0.030	0.008	18.0	21.4	19.9	194	24.2	36.9
± SD	0.3	11.0	0.0003	0.011	0.001	4.7	9.8	3.1	15.0	4.0	17.1
All patients (N=12)											
Mean	6.0	22.4	0.0064	0.041	0.015	14.0	9.2	37.0	203	12.0	16.0
± SD	1.2	7.1	0.0026	0.022	0.008	7.0	6.9	14.0	29.0	7.0	14.0

[a]Measured trough concentrations at 24 hours and on day 3.

Vc: Volume of the Central Compartment; Vss: Distribution Volume at Steady-State; K_{el}: Elimination-Rate Constant; K_{12}, K_{21}: Rate Constant between the Two Compartments; $t_{1/2}\alpha$: Distribution Half-Life; $t_{1/2}\beta$: Elimination Half-Life; TBC: Total Body Clearance; Peak conc: Peak Concentration

Ceftriazone, administered at a dose of 2 gm, successfully treated primary and secondary syphilis [29]. Ceftriazone was found efficacy as trimethoprim-sulfamethoxazole in the treatment of urinary-tract infection [30]. In patients with acute disseminated Lyme disease, oral doxycycline or parenterally administered ceftriazone are equally effective in treating this disease [31]. Ceftriazone, administered at a dose of 2 gm, successfully treated skin and soft tissue infections [32]. Ceftriazone given at a dose of 2 gm once-daily treated many serious skin and soft tissue infections [33]. Ceftriazone, administered at a dose of 2 gm, treated respiratory-tract infections, urinary-tract infections, skin, soft tissue infections, bone, and joint infections [34] and ceftriazone, administered at a dose of 2 gm, successfully treated serious bacterial infections [35].

Trials with ceftriazone

Trials showed that ceftriazone has anti-inflammatory effects and treats bacterial infections [36]. Ceftriazone successfully treated infections due to methicillin-susceptible *Staphylococcus aureus* [37]. Ceftriazone, administered at a dose of 1 gm daily, treated community-acquired pneumonia [38]. Ceftriazone is effective as penicillin in treating early syphilis with regard to serological response and treatment failure-rate [39]. Ceftriazone is highly effective and safe for the treatment of acute pyelonephritis and complicated urinary-tract infections [40]. Intravenous ceftriazone is highly effective and well-tolerated for the treatment of acute pyelonephritis [41]. Ampicillin/sulbactam and ceftriazone similarly treats infections during neurosurgery [42]. A single-daily dose of ceftriazone has similar efficacy as multiple-daily dose of cefotaxime in treating bacterial infections [43].

Penetration of ceftriazone into the Cerebrospinal Fluid (CSF)

The penetration of ceftriazone was investigated by Nau et al. [44] into the CSF in 7 patients with uninflamed meninges aged 59.7 years ± 3.3 years (range, 49 to 76) and with a body-weight of 78.6 kg ± 3.0 kg (range, 65 to 90). All patients had respiratory-tract infection, 2 patients had intracerebral blending, and 2 patients had cerebral ischemic infarction. Ceftriazone was intravenously infused at a dose of 2 gm twice-daily, and these authors studied the pharmacokinetics of ceftriazone in the CSF.

Ceftriazone peak concentration exceeds the minimum inhibitory concentration for highly susceptible (*Neisseria meningitides*, *Haemophilus influenzae*, penicillin G-sensitive *Streptococcus pneumoniae*, *Borrelia burgdorferi*, and some members of family Enterobacteriaceae) approximately 10-fold, thus ceftriazone should be bactericidal *in-vivo* shown in Table 2. Ceftriazone slowly penetrates into the CSF as the mean Tmax is 11.4 hours. The mean $AUC_{0-\infty}$ in CSF to $AUC_{0-\infty}$ in serum ratio is 0.0075 suggesting that the ceftriazone mainly resides in serum. Ceftriazone is slowly eliminated from CSF as the mean elimination half-life of ceftriazone in CSF is 17.0 hours. In addition, there is a remarkable interindividual variability in the ceftriazone pharmacokinetic parameters and this vide variability is accounted by the patient's diseases.

Ceftriazone was administered at a dose of 6.5 gm (range, 4 to 9) corresponding to a median of 97.5 mg/kg (range, 77 to 131). The median CSF ceftriazone concentration was 13.3 µg/ml (range, 0.9 to 91.2). Thus, ceftriazone penetrates into the CSF in significant amounts and this concentration is higher the minimum inhibitory concentration (≤ 1 µg/ml) of *Streptococcus pneumoniae* which caused the meningitis [45]. Ceftriazone was intravenously infused at a dose of 50 mg/kg or 75 mg/kg to 17 paediatric patients aged 0.6 to 52 months with meningitis caused by *Haemophilus influenzae*. Ceftriazone mean peak plasma concentrations were 267 and 184 µg/ml for the 75 mg/kg and 50 mg/kg dosage groups, respectively. The harmonic mean elimination half-life was 4.2 hours, and the mean percent drug penetrance into CSF was 4.8% ± 3.5%. CSF concentration of ceftriazone exceeded the minimal inhibitory concentrations of bacteria causing infection by 480 to 5,600 times thus ceftriazone is a useful agent to treat meningitis in paediatric patients [46].

Treatment of bacterial meningitis with ceftriazone

A single daily intravenous dose of 100 mg/kg was administered on day one followed by 80 mg/kg daily. A total of 22 patients with meningitis were treated. Fourteen patients had the meningitis caused by *Haemophilus influenzae* type b, 5 patients had the meningitis caused by *Streptococcus pneumoniae* and 3 patients had the meningitis caused by *Neisseria meningitides*. The cerebrospinal fluid of all patients became sterile within 24 to 48 hours after dosing. The cerebrospinal fluid of ceftriazone concentrations 24 hours after dosing was 10 to 100-fold higher than the MIC of the pathogenic bacteria early in therapy, and five to 50-fold higher at the end of therapy. Ceftriazone is a safe and effective antibiotic for the treatment of bacterial meningitis even when administered once-daily [47]. A single intravenous daily dose of 50 mg/kg ceftriazone was administered to patients for treating the meningitis caused by *Neisseria meningitides* (N=34) by *Streptococcus pneumoniae* (N=25), by *Escherichia coli* (N=25), by *Klebsiella pneumoniae* (N=3), by *Haemophilus influenzae* (N=2), by *Viridians streptococci* (N=2), or by unknown organism (N=16). The mean trough concentration of ceftriazone in cerebrospinal fluid was 3.5 µg/ml, and the median trough bactericidal titre was 1:128. A single daily dose of 50 mg/kg ceftriazone treated the meningitis caused by different bacteria [48]. Ceftriazone was intravenously administered at a dose of 100 mg/kg once-daily to 106 children aged 3 years (range, 42 days to 16 years) with bacterial meningitis caused by *Haemophilus influenzae* and the cerebrospinal fluid was sterilized after 18 to 36 hours after dosing. Ceftriazone is a useful agent to treat bacterial meningitis in children [49].

Resistance of bacteria to ceftriazone

The non-typhoid Salmonella was isolated from 50 children

Table 2: Single-dose pharmacokinetics of ceftriazone in the cerebrospinal fluid. Values are the minimum, maximum, mean, and ± SD, by Nau et al. [44].

Results determined after the first dose						Results obtained after the last dose	
Value	Peak Conc. (µ/ml)	Tmax (h)	$AUC_{0-12\,h}$ (µg*h/ml)	$AUC_{0-\infty}$ (µg*h/ml)	$^{\$}AUC_{0-\infty}$ CSF/serum	[a]Conc. (µg/ml)	*Half-life (h)
Minimum	0.18	1	2.3	5.8	0.006	0.3	15.7
Maximum	1.04	16	18.1	41.3	0.018	1.03	18.4
Mean	0.52	11.4	9	18.9	0.0075	0.62	17
± SD	0.15	2.7	2.82	6.12	0.0024	0.21	0.78

$^{\$}AUC_{0-\infty}$ in cerebrospinal fluid to serum ratio. [a]Concentrations 12 hours after the end of the last infusion. *Elimination half-life.
AUC: Area Under Concentration-Time Curve

and the isolates resulted in an increased prevalence of ceftriazone resistance in these children. The high rate of multidrug-resistance of ceftriazone is increasing and constitutes a serious problem in children [50]. Ceftriazone was widely prescribed and multiple ceftriazone prescriptions and ceftriazone misuse induced resistance in non-typhoid *Salmonella*. The resistance of ceftriazone in non-typhoid *Salmonella* infection is an increasing problem and limits treatment options for serious infections [51]. Salmonella producing β-lactamases has spread rapidly worldwide and poses a serious problem to human health. Resistance to ciprofloxacin was found in 33.6% of isolates and the resistance genes were *blaCTX-M*, *blaTEM*, and *blaOXA* which were detected in 207 (94.1%), 99 (45.0%), and 53 (24.1%) isolates, respectively [52]. Ceftriazone-resistant *Salmonella enterica* serotype typhimurium β-lactamase-producing was isolated from stool specimens and the minimum inhibitory concentration of ceftriazone was 256 μg/ml. The ceftriazone-resistance was transferred by a 3.2-kb plasmid and the plasmid produced high-level of resistance to ceftriazone [53]. Three-hundred-twenty-seven non-typhoid *Salmonella enterica* were isolated from stool specimens and ceftriazone resistance was attributed to the *CTX-M-14* and *CMY-2* β-lactamase genes [54]. A study of all spontaneous bacterial peritonitis episodes with positive blood and or ascitic culture was performed in 246 patients. The resistance of ceftriazone was due to extended-spectrum β-lactamase-producing gram-negative bacilli, other resistant gram-negative bacilli, and enterococci. Risk factors for resistance were previous use of cephalosporins, diabetes mellitus, and upper gastrointestinal bleeding [55]. The proportion of Enterobacter cloacae isolates resistant to ceftriazone increased from 64.3% to 77.6% during the period 1999 to 2002 and the extent of resistance correlated with the use of ceftriazone [56].

Transfer of ceftriazone across the human placenta

Ceftriazone was administered intravenously at a dose of 1 gm to 133 gm pregnant women at the third trimester of pregnancy. The concentration of ceftriazone ranged between 3.02 μg/ml to 18.92 μg/ml in umbilical cord vein and between 3.07 μg/ml to 78.20 μg/ml in the maternal vein thus ceftriazone is poorly transferred across the human placenta [57]. Ceftriazone was administered intravenously at a dose of 2 gm to 17 pregnant women at term of gestation and Kafetzis et al. [58] studied the pharmacokinetics of ceftriazone in the maternal serum and umbilical cord serum.

AUC obtained in the umbilical cord is about one third of that in the maternal serum suggesting that ceftriazone is poorly transferred across the human placenta shown in Table 3. The ceftriazone AUC in the amniotic fluid is similar to that of the umbilical cord serum and the concentration of ceftriazone in the placenta is about one half of that in the umbilical cord serum. Ceftriazone elimination half-life is similar in maternal serum, umbilical cord serum, amniotic fluid, and in placenta.

Table 3: CeftriazoneAUC and elimination half-life in maternal serum, umbilical cord serum, amniotic fluid, and placenta. Values are the mean, by Kafetzis et al. [58].

Parameter	$AUC_{0\text{-}24h}$ (μg*h/ml)	Elimination half-life (h)
Maternal serum	652	6
Umbilical cord serum	234	7
Amniotic fluid	256	6.8
Placenta	162	5.4

AUC: Area Under the Concentration-time curve

Migration of ceftriazone into the breast-milk

Kafetzis et al. [58] administered ceftriazone at dose of 1 gm to 20 gm lactating women. Ten women received ceftriazone intravenously and 10 women received ceftriazone intramuscularly.

Ceftriazone poorly migrated into the breast-milk, is rapidly absorbed in breast-milk and is slowly eliminated from the breast-milk shown in Table 4.

Discussion

Ceftriazone is resistant to many narrow-spectrum β-lactamases and is active against most gram-positive and gram-negative aerobic bacteria. Ceftriazone is used to treat meningitis in non-immunocompromised patients (in combination with vancomycin and ampicillin) owing to the excellent activity against to *Haemophilus influenzae*, sensitive *Streptococcus pneumoniae*, *Neisseria meningitides*, and gram-negative enteric bacteria. Ceftriazone is used to treat community-acquired pneumonia, ureteral, cervical, rectal, pharyngeal infections, all forms of gonorrhoea, and severe Lyme disease. About half of ceftriazone is recovered from the urine and the remainder is eliminated by biliary secretion [1]. The efficacy and safety of ceftriazone has been reported [2-9]. Ceftriazone effectively and safety treats community-acquired pneumonia [2,3]. Ertapenem and ceftriazone have similar efficacy and safety in treatment of patients with community-acquired pneumonia [4]. Ceftriazone effectively and safety treats amyotrophic lateral sclerosis [5], uncomplicated gonorrhoea [6], serious infections due to gram-negative bacteria [7], and serious infections in paediatric patients [8,9]. The pharmacokinetics of ceftriazone have been studied in 10 patients with normal renal function and in 2 patients with renal failure and ceftriazone was intravenously infused at a dose of 2 grams once-daily [10]. The mean elimination half-life and the total body clearance of ceftriazone are 6.4 hours and 41.3 ml/min, respectively, in 10 patients with normal renal function and 28.4 hours and 18.0 ml/min, respectively, in 2 patients with renal failure. Ceftriazone is cleared in part from the body by renal route thus the elimination half-life is longer in patients with renal failure than in patients with normal renal function. Consequently, the total body clearance is lower in patients with renal failure than in patients with normal renal function. The prophylaxis with ceftriazone has been extensively studied [11-21]. Prophylactic ceftriazone prevents postoperative infections [11]. Prophylaxis with ceftriazone plus metronidazole is more effective than broader-spectrum antibiotics in preventing postoperative infections [12]. Intravenous ceftriazone is more active than oral norfloxacin in the prophylaxis of bacterial infections [13], and ceftriazone is effective as ampicillin/cloxacillin in preventing post-caesarean complications [14]. Prophylaxis with ceftriazone is superior to that of other cephalosporins in preventing surgical infections [15]. Prophylaxis with ceftriazone prevents infections due to colorectal surgery [16], infections following orthopaedic surgery [17], infections in patients undergoing liver transplantation [18], infections in patients undergoing orthopaedic and traumatic surgery [19], postoperative infections and pyrexia [20], and infections in patients undergoing chest surgery [21]. The treatment of bacterial infections with ceftriazone has been extensively studied [22-35]. Ceftriazone effectively treats neurosyphilis as benzylpenicillin [25]. Two grams daily of ceftriazone treats endocarditis, spondylodiscitis and prosthetic joint infections caused by Cutibacterium acnes [23], and a short-course treatment with ceftriazone, administered at a dose of 2 gm, treats severe forms of leptospirosis [24]. Ceftriazone treats tonsil-

Table 4: Ceftriazone AUC and elimination half-life which have been obtained in maternal serum and breast-milk. Values are the mean ± SD, by Kafetzis et al. [58].

	Maternal serum		Breast-milk		
	$AUC_{0-\infty}$ (μg*h/ml)	Elimination Half-life (h)	$AUC_{0-\infty}$ (μg*h/ml)	Absorption half-life (h)	Elimination half-life (h)
Administration route (N)					
Intravenous (N=10)	392 ± 23.0	5.3 ± 0.2	11.8 ± 4.5	1.7 ± 0.9	12.8 ± 3.7
Intravenous (N=10)	379 ± 56.3	5.3 ± 0.4	21.0 ± 2.5	1.7 ± 0.2	17.3 ± 2.1

pharyngitis [25], epidemic meningococcal meningitis [26], typhoid fever [27], streptococcal endocarditis [28], and primary and secondary syphilis [29]. Ceftriazone treats urinary-tract infections as trimethoprim-sulfamethoxazole [30], and oral doxycycline treats Lyme disease as parenteral ceftriazone [31]. Two grams daily of ceftriazone treats skin and soft tissue infections [32,33], respiratory-tract, urinary-tract, skin, soft tissue and joint infections [34] and serious bacterial infections [35]. Trials with ceftriazone have been reported [36-43]. Ceftriazone has anti-inflammatory effects and treats bacterial infections [36], ceftriazone treats infections due to methicillin-susceptible Staphylococcus aureus [37], and treats community-acquired pneumonia [38]. Ceftriazone is effective as penicillin in treatment of early syphilis [39], and ceftriazone effectively treats acute pyelonephritis and complicated urinary-tract infections [40,41]. Ampicillin/sulbactam treats infections during neurosurgery as ceftriazone [42], and a single-daily dose of ceftriazone has similar efficacy as multiple-daily dose of ceftriazone in treating bacterial infections [43]. The penetration of ceftriazone into the cerebrospinal has been reported [44-46]. Following an intravenous dose of 2 gm ceftriazone, ceftriazone penetrates into the cerebrospinal fluid with a mean Tmax of 11.4 h, the mean elimination half-life of ceftriazone in the cerebrospinal fluid is 17.0 h, the mean area under the concentration-time curve ($AUC_{0-\infty}$) is 18.9 μg*h/ml, and the mean $AUC_{0-\infty}$ in cerebrospinal fluid to the $AUC_{0-\infty}$ in serum ratio is 0.0075. These results indicate that ceftriazone slowly penetrates in the cerebrospinal fluid and is slowly eliminated from the cerebrospinal fluid, ceftriazone penetrates into the cerebrospinal fluid is significant amounts, and ceftriazone resides in serum in higher amounts than in the cerebrospinal fluid [44]. Ceftriazone was administered at a mean dose of 6.5 gm and the mean concentration in the cerebrospinal fluid was 13.3 μg/ml and this concentration is higher than the minimum inhibitory concentration (≤ 1 μg/ml) of *Streptococcus pneumoniae* which was the organism causing the meningitis [45]. Ceftriazone was administered at a dose of 50 mg/kg or 75 mg/kg to 17 paediatric patients and the ceftriazone concentration in the cerebrospinal fluid is 480 to 5,600 times higher the minimum inhibitory concentration of Haemophilus influenzae which was the organism causing the meningitis [46]. The treatment of bacterial meningitis with ceftriazone has been reported [47-49]. Ceftriazone administered at a dose of 100 mg/kg treated the meningitis caused by Haemophilus influenzae type b, *Streptococcus pneumoniae* or *Neisseria meningitides* [47]. Ceftriazone, administered at a dose of 50 mg/kg, treats the meningitis caused by *Neisseria meningitides*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae* or *Viridians streptococci* [48]. Ceftriazone, administered at a dose of 100 mg/kg to children, treated the meningitis caused by *Haemophilus influenzae* and the cerebrospinal fluid was sterilized 18 to 36 hours after dosing [49]. Ceftriazone may become resistant to bacteria [50-56]. The non-typhoid Salmonella may become resistant to ceftriazone [50], and multiple ceftriazone prescriptions and ceftriazone misuse cause resistance to non-typhoid Salmonella [51]. The resistance of Salmonella producing β-lactamases to ceftriazone was caused by resistance genes of *blaCTX-M*, *blaTEM*, and *blaOXA* [52]. The resistance of *Salmonella enterica* serotype typhimurium β-lactamase-producing became resistant to ceftriazone by transfer of a plasmid [53], and non-typhoid *Salmonella enterica* became resistant to ceftriazone and the resistance was due to *CTX-M-14* and *CMY-2* β-lactamase genes [54]. The resistance of ceftriazone was due to extended-spectrum β-lactamase-producing gram-negative bacilli, other resistant gram-negative bacilli, and enterococci and the risk factors for resistance were previous use of cephalosporins, diabetes mellitus, and upper gastrointestinal blending [55]. The resistance of *Enterobacter cloacae* to ceftriazone correlates with the use of ceftriazone [56]. Ceftriazone is poorly transferred across the human placenta [57,58], ceftriazone elimination half-life is 6 h in the maternal serum and 7.0 h in the umbilical cord serum [58]. Ceftriazone poorly migrates into the breast-milk, ceftriazone is rapidly absorbed in breast-milk as the absorption half-life is 1.7 h, and ceftriazone elimination half-life is 5.3 h in the maternal serum and about 13 h in the breast-milk indicating that ceftriazone is slowly eliminated in the breast-milk [58].

Conclusion

Ceftriazone is resistant to many narrow-spectrum β-lactamases and has good activity against most gram-positive and gram-negative aerobic bacteria, and about half of ceftriazone is cleared from the body with the urine and the remainder is eliminated by biliary secretion. Ceftriazone is used to treat ureteral, cervical, rectal, pharyngeal infections, gonorrhoea, and Lyme disease. The efficacy and safety of ceftriazone have been reported. Ceftriazone mean elimination half-life is 6.4 h in patients with normal renal function and 21.4 h in patients with renal failure. The prophylaxis, treatment, and trials with ceftriazone have been extensively studied. Ceftriazone penetrates into the cerebrospinal fluid in significant amounts and treats bacterial meningitis. Ceftriazone may become resistant to bacteria and ceftriazone is poorly transferred across the human placenta and poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of ceftriazone.

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