

Evaluation of Ceftriaxone Utilization at Multicenter Study

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Background/Aims: As bacterial resistance to antimicrobial agents has grown due to the increasing use of antimicrobial agents, we sought to evaluate the suitability of ceftriaxone usage (representative of third generation cephalosporins) at 10 university hospitals in Korea.

Methods: We prospectively evaluated the appropriateness of antibiotic usage in 400 adult patients who received ceftriaxone between February 1, 2006 and June 30, 2006. Drug utilization evaluation (DUE) methods were based on standards set forth by the American Society of Hospital Pharmacists. The DUE criteria used in this study were modified to be more suitable in our hospital setting: justification of drug use, critical and process indications, complications, and outcome measures.

Results: The average patient age was 64.4 years. The utilization of ceftriaxone was appropriate in 262 cases (65.5%) for the justification of use, while inappropriate use was observed in 138 cases (34.5%). Common reasons for inappropriate use of ceftriaxone included continued empiric use for presumed infections, prophylactic perioperative injection, and empiric therapy for fever. Most of the critical indications showed a high rate of suitability (66.5-98.5%). Complications occurred in 37 cases (9.3%). With respect to outcome measures, clinical responses were observed in 60.7% of cases, while only 15.7% of cases showed evidence of infection eradication via negative cultures.

Conclusions: Appropriate use (65.5%) of ceftriaxone was higher than inappropriate use (34.5%) at university hospitals in Korea. Inappropriate utilization, however, including continued empiric use for presumed infections and prophylactic perioperative injection remained high. Intensification of educational programs and antibiotic control systems for ceftriaxone is needed to improve the suitability of antimicrobial use. (**Korean J Intern Med 2009;24:374-380**)

Keywords: Drug utilization review; Ceftriaxone

INTRODUCTION

Bacterial resistance to antimicrobial agents due to the increasing use of antimicrobial agents has become a worldwide concern. Over the past several decades, the increased prevalence of known resistant organisms and the emergence of newly resistant organisms such as

penicillin-resistant pneumococci, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase-producing *Escherichia coli*, *Klebsiella pneumoniae*, and imipenem-resistant gram-negative bacilli, have resulted in delays in effective therapy and the length of hospitalization, and have led to increased costs for patients [1]. Compared to infections

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Table 1. Criteria elements for the drug utilization evaluation of ceftriaxone

No.	Elements	Exceptions
<i>Justification of use</i>		
1	Culture and sensitivity (C&S) documented serious gram negative pulmonary infection (not <i>pseudomonas</i>) sensitive to ceftriaxone	Organism need not be resistant to ampicillin, and trimethoprim-sulfamethoxazole if patient has documented allergy to beta-lactam antibiotics or sulfonamides
2	C&S documented acute or chronic gram negative osteomyelitis Or	None
3	C&S documented meningitis due to enteric bacteria or <i>Hemophilus influenzae</i> Or	None
4	C&S documented gonorrhea, gonococcal infection Or	None
5	C&S documented pelvic inflammatory disease Or	None
6	C&S documented chancroid Or	None
7	C&S documented gram negative bacteremia (not <i>pseudomonas</i>) Or	None
8	C&S documented serious infection due to multidrug resistant gram negative microorganism Or	None
9	Empiric treatment of suspected gram negative bacteremia/septicemia in non-neutropenic patient or severe pneumonia Or	None
10	Empiric treatment of suspected gram-negative non-pseudomonal meningitis Or	None
11	Empiric treatment of sexually acquired epididymitis	None
<i>Critical (process) indicators</i>		
12	Appropriate C&S obtained within 48 hr before initial ceftriaxone dose	Ceftriaxone ordered in response to positive culture
13	Complete blood count (CBC) with differential obtained within 48 hr before initial ceftriaxone dose	None
14	Serum creatinine (Scr) concentration or urinary creatinine clearance (CrCl) obtained if severe hepatic and renal impairment occurs	If severe hepatic and renal impairment, total daily dose lower than or equal to 2 g
15	Liver function tests [total serum bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] obtained within 7 days before initial ceftriaxone dose	None
16	Previous hypersensitivity reaction to beta-lactam antibiotics NOT noted in patient's chart	None
17	Appropriate ceftriaxone dosage; (a) uncomplicated gonorrhea/gonococcal infection: 250 mg IM single dose (b) disseminated gonorrhea/gonococcal infection: 1 g IV q 24 hr for 7 days (c) pelvic inflammatory disease: 250 mg IM as a single dose followed by doxycycline (d) sexually acquired epididymitis: 250 mg IM as a single dose followed by doxycycline (e) chancroid : 250 mg IM as a single dose (f) moderate infection: 1-2 g IV/IM q 24 hr (g) severe infection: 1 g IV/IM q 12 hr or 2g IV/IM q 24 hr	None

No.	Elements	Exceptions
18	Vital signs monitored at least three times daily (<i>i.e.</i> , once each nursing shift) until patient becomes afebrile and at least one daily thereafter during ceftriaxone therapy	None
19	White blood cell (WBC) count obtained at least once weekly during ceftriaxone therapy	None
20	SCr or urinary CrCl obtained at least once weekly during ceftriaxone therapy	None
21	Appropriate treatment duration: 7-14 days	None
<i>Complications</i>		
22	Anaphylaxis: breathing difficulty, wheezing, laryngeal edema, flushing, tachycardia, and/or hypotension	Discontinue ceftriaxone Treat symptomatically with epinephrine or antihistamine with or without supportive care, <i>e.g.</i> , fluids, cardiopulmonary resuscitation, and assisted ventilation Use alternative anti-infective therapy
23	Cutaneous reactions: urticaria, angioedema, maculopapular eruptions, pruritus, erythema multiforme, and/or Stevens-Johnson syndrome	Identify other drug and nondrug causes If mild reaction, treat symptomatically with antihistamine or corticosteroid; pretreat with antihistamine or corticosteroid for subsequent doses If severe reaction, discontinue ceftriaxone; treat symptomatically with epinephrine or antihistamine with or without supportive care, including cardiopulmonary resuscitation and assisted ventilation; use alternative anti-infective therapy
24	Superinfection; overgrowth of another organism (<i>e.g.</i> , <i>Enterococcus</i> , <i>Candida</i> , <i>Pseudomonas</i> , or <i>Acinetobacter species</i>)	Discontinue ceftriaxone and treat primary infection with alternative antimicrobial if possible Begin appropriate anti-infective therapy for superinfection
25	Gastrointestinal effects: nausea, dyspepsia, diarrhea, constipation, vomiting, abdominal pain or discomfort, oral ulceration, dysphagia, intestinal perforation, ileus, dry mouth, and/or gastrointestinal bleeding	Identify other drug and nondrug causes Provide symptomatic care and supportive therapy If mild reaction, decrease dosage If severe reaction, discontinue ceftriaxone and switch to alternative anti-infective therapy
26	Bad taste	Identify other drug and nondrug causes If mild reaction, decrease dosage If severe reaction, discontinue ceftriaxone and switch to alternative anti-infective therapy
27	Antimicrobial-associated pseudomembranous colitis (AAPMS) characterized by at least two of the following: (a) fever, diarrhea, abdominal pain, or ileus (b) proctoscopy or colonoscopy revealing yellow-white exudative plaques or pseudomembranes (c) biopsy showing histologic changes consistent with AAPMS (d) fecal leukocytes (e) positive culture for <i>Clostridium difficile</i> with or without positive <i>C. difficile</i> tox	Identify and discontinue causative agent and use alternative anti-infective therapy if possible Replace fluid and electrolyte losses with IV or oral therapy if nothing-by-mouth order is discontinued Initiate therapy per severity of condition: IV metronidazole for patient with nothing-by-mouth orders ; or oral vancomycin, metronidazole, or bacitracin, each with or without anion-exchange resin, if nothing-by-mouth order is discontinued 22-24 hr
28	Neurologic effects: peripheral neuropathy manifested as paresthesia, numbness or ataxia, and/or incoordination or convulsion	Identify other drug and nondrug causes Discontinue ceftriaxone and treat symptomatically; use alternative anti-infective therapy
29	Central nervous system effects: drowsiness, fatigue, malaise, lethargy, psychosis, depression, mania, phobia, confusion, hallucinations, dizziness, lightheadedness, anxiety, tremor, and/or insomnia	Identify other drug and nondrug causes If mild reaction, treat symptomatically If severe or intolerable reaction, discontinue ceftriaxone and treat symptomatically; use alternative anti-infective therapy
30	Hepatotoxicity as measured by liver function tests (at least two times upper limit of normal) for one or more of the following: ALT, AST, ALP, lactate dehydrogenase, and bilirubin; or clinical symptoms of liver disease (<i>e.g.</i> , right upper quadrant pain or tenderness, jaundice, nausea, and vomiting)	(<i>e.g.</i> , right upper quadrant pain or tenderness, jaundice, nausea, and vomiting) Identify other drug and nondrug causes Discontinue ceftriaxone and switch to alternative anti-infective therapy Monitor liver enzymes at least twice weekly until values return to normal or to patient's baseline

No.	Elements	Exceptions
31	Bleeding disturbances: thrombocytopenia (platelet count < 70,000/mm ³) or Thrombocytosis (platelet count > 400,000/mm ³)	Identify other drug and discontinue ceftriaxone Use alternative anti-infective therapy Provide supportive care and symptomatic therapy; monitor PT, activated partial thromboplastin time, and platelet count at least twice weekly
32	Nonbleeding-related hematologic effects: leukopenia (leukocyte count < 500/mm ³), eosinophilia (absolute eosinophil count > 500/mm ³), or pancytopenia	Identify other drug and nondrug causes Discontinue ceftriaxone. Use alternative anti-infective therapy Provide supportive care and symptomatic therapy; monitor CBC with differential daily
33	Local effects of IV therapy: phlebitis, burning, pain and inflammation, erythema, pruritus, paresthesia, and/or swelling	Identify other drug and nondrug causes If mild reaction, treat symptomatically; consider alternative IV site in a larger vein and increase drug dilution to 1 mg/mL If severe reaction, discontinue infusion and remove IV catheter; use alternative anti-infective therapy
<i>Outcome measures</i>		
34	Eradication of infection as evidenced by negative (sterile) cultures 72 hours after discontinuation of ceftriaxone	New organism or another infection identified, clinical cure determined by absence of erythema and tenderness at affected site Patient discharged and unavailable for follow up patient expired Patient discharged before therapy completed
	Or	
35	Fever reduction (decrease of at least 1 °C from peak temperature) within 3 days of initial ceftriaxone dose	Fever not present initially Another cause of elevated temperature known or suspected new source of infection known or suspected Patient expired
	Or	
36	WBC count within normal limits (3.7-9.4 × 10 ⁹ /mm ³)	WBC count not elevated prior to therapy Patient neutropenic prior to therapy Another cause of elevated WBC count known or suspected Patient expired
	Or	
37	Clinical improvement noted in progress	New organism or another infection suspected or identified Patient discharged before therapy completed and unavailable for follow-up Patient expired

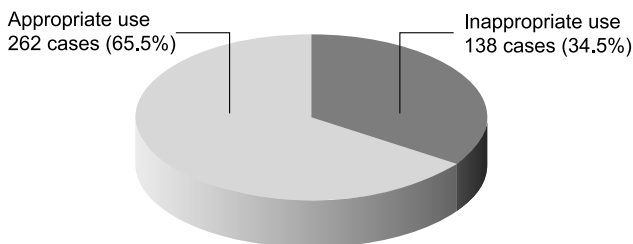
caused by susceptible pathogens, those caused by resistant pathogens are associated with higher rates of morbidity and mortality [2,3]. Furthermore, antimicrobial drug resistance has been projected to add between \$100 million and \$30 billion annually to health-care costs [4]. During the past several years, the problem of antibiotic resistance has noticeably worsened in Korea [5]. With gradual increases in expensive antimicrobial agents, the cost of antimicrobial agents relative to total medical insurance expenses has reached 33.1% [6]. When considering that misuse of antimicrobial agents is the most important cause of antibiotic resistance, the logical first step is to evaluate the suitability of antibiotic usage.

Only one usage analysis of cephalosporins and aminoglycosides for surgical prophylaxis has been conducted at

a university hospital in Korea, and most reports examining the appropriateness of antibiotic use have been individual studies [7-12]. Antibiotic use evaluations are a basic measure for evaluating the appropriate usage of antimicrobial agents; however, data gathered from individual hospitals have limited benefits for policy-making. For this reason, we examined antibiotic use status and evaluated the appropriateness of the antibiotic usage in 10 university hospitals in Korea. Specifically, in the present study, we evaluated the use of a specific antibiotic (ceftriaxone, a representative of third-generation cephalosporin) and attempted to compile basic data outlining the appropriate use of antibiotics.

Table 2. Distribution of ceftriaxone daily dosage

Daily dosage (g/day)						
1.0	1.5-2.0	2.0	2.0-2.5	3.0	4.0	Total
9 (2.2%)	2 (0.5%)	340 (85.3%)	1 (0.3%)	8 (2.0%)	40 (10.0%)	400 (100%)

**Figure 1.** Justification of the use of ceftriaxone.

METHODS

The criteria used for antibiotic selection included the following: antibiotics with a risk of abuse, those that were being used in high amounts in Korean hospitals, antibiotics that were likely causing resistance due to increased usage, and those that were not being controlled by an antibiotic prescribing restriction system. Ceftriaxone, a broad-spectrum parenteral cephalosporin, was selected as representative of unrestricted antibiotics. A drug utilization evaluation (DUE) was conducted to determine whether ceftriaxone was being used appropriately based on the "Criteria for Drug Use Evaluation" of the American Society of Hospital Pharmacists [13]. The criteria for DUE used in this study were modified based on their suitability in the Korean hospital setting: justification of drug use, critical and process indications, complications, and outcome measures. A DUE was performed prospectively by reviewing medical records for a total of 400 patients (10 hospitals with 40 patients each) who received ceftriaxone during hospitalization between February 1, 2006 and June 30, 2006, and these data were used in this study. Medical records were examined for the diagnosis, the reason for initiating and discontinuing therapy, gender, dose, frequency of administration, culture and sensitivity (C&S) results, renal function, and duration of antibiotic therapy. All medical records were examined for compliance to the clinical indicators listed above.

Indications for which ceftriaxone was deemed either acceptable or unacceptable are shown in Table 1. Any patients for whom therapy was deemed unacceptable

Table 3. Causes of inappropriate ceftriaxone use

Cause	Values (n=138)
Routine perioperative prophylaxis	69 (50)
Inappropriate empiric therapy (>5 days) for presumed infections	48 (34.8)
Systemic prophylaxis for infection or colonization	21 (15.2)

Values are number (%).

were reviewed with criteria established at the onset of the DUE. Enrolled hospitals were Dong-A University Hospital, Kangbuk Samsung Hospital, Samsung Medical Center, Chungbuk National University Hospital, Chonnam National University Hospital, Chungnam National University Hospital, Seoul Veterans Hospital, Kyungpook National University Hospital, Konkuk University Hospital, and Inje University Paik Hospital.

RESULTS

In total, 400 patients (247 men, 153 women) with a mean age of 64.4 years (range, 3 to 93; 95% CI, 32.4 to 96.4) were reviewed, with 10 cases at each of the 10 institutions. Most cases involved the department of internal medicine (58%); the remainders were in neurosurgery (12%), surgery (7.5%), orthopedic surgery (3.7%), thoracic surgery (3.7%), urology (2.7%), otolaryngology (2%), neurology (2%), and others (4.3%). Ceftriaxone dosing regimens are presented in Table 2. In 340 cases (85%), ceftriaxone was dosed as 2 g/day (range, 1 to 4). The mean duration of ceftriaxone use was 10.3 days (range, 1 to 61).

Justification of ceftriaxone use

The use of ceftriaxone was appropriate in 262 cases (65.5%), and inappropriate in 138 cases (34.5%; Fig. 1). The causes of inappropriate ceftriaxone use included routine perioperative prophylaxis (50%), inappropriate empirical therapy (>5 days) for presumed infections (34.8%), and systemic prophylaxis for infection or

Table 4. Ceftriaxone drug utilization evaluation: critical (process) indicators

Criteria	Accepted level	Unaccepted level
Appropriate cultures and sensitivities obtained within 48 hr before initial ceftriaxone dose	266 (66.5)	134 (33.5)
Complete blood count with differential obtained within 48 hr before initial ceftriaxone dose	371 (92.7)	29 (7.3)
Liver function test obtained within 7 days before initial ceftriaxone dose	382 (95.5)	18 (4.5)
Previous hypersensitivity reaction to beta-lactam antibiotics NOT noted in patient's chart	394 (98.5)	6 (1.5)
Appropriate ceftriaxone dosage	337 (84.2)	63 (15.8)
White blood cell count obtained at least 1/wk during therapy	379 (94.7)	21 (5.3)
Vital signs monitored at least three times daily	386 (96.5)	14 (3.5)
Serum creatinine (sCr) monitored at least 2/wk during therapy if baseline sCr within normal limit	376 (94)	24 (6)
Duration of therapy	229 (57.2)	171 (42.8)

Values are frequency (%).

Table 5. Ceftriaxone drug utilization evaluation: complications

Complication	Value (n=37)
Hepatotoxicity	16 (43.2)
GI trouble	12 (32.4)
Cutaneous reaction (e.g., skin rash)	6 (16.2)
Bleeding disturbance	2 (5.5)
Peripheral neuropathy	1 (2.7)

Values are number (%).

colonization (15.2%, Table 3).

Critical (process) indicators

Most of the critical and process indications showed high rates of appropriateness (84.2-98.5%), excluding inappropriate C&S tests prior to the initial ceftriaxone dose (33.5%) and inappropriate duration of therapy (42.8%, Table 4).

Complications

Hepatotoxicity occurred in 16 cases (43.2%), gastrointestinal trouble in 12 cases (32.4%), cutaneous reaction in 6 cases (16.2%), bleeding disturbances in 2 cases (5.5%), and peripheral neuropathy in 1 case (2.7%, Table 5). Each case was managed appropriately.

Outcome measures

Clinical improvement was noted in 243 patients (60.7%), while documentation of microbiological eradication evidenced by negative cultures 72 hours after discontinuation of ceftriaxone was inappropriate in 337 patients (84.3%).

DISCUSSION

The goal of antibiotic therapy is to achieve the best possible clinical outcomes while consuming the least amount of hospital resources. Health-care systems are under intense pressure to increase the quality of care and at the same time reduce costs. Pressure to reduce the cost of antimicrobial therapy is especially intense because these drugs may account for a large portion of a hospital's pharmacy budget. According to previous investigations on antibiotic use, antibiotics might account for 33.1% of the medical insurance budget in Korea, and 20-50% of these cases are suspected to have been abuse [6]. In many cases, antibiotics were prescribed for prophylaxis rather than for treatment [6,7]. Antibiotic abuse such as this in the community and hospitals fuels the crisis of antibiotic resistance, which ultimately results in virtually all pathogenic bacteria becoming resistant to older antibiotics. During the past several years, the problem of antibiotic resistance has noticeably worsened in Korea [5].

We performed a DUE for a specific antibiotic and attempted to gather basic data to examine the appropriate use of antibiotics. Furthermore, we sought to prevent antibiotic misuse and reduce unnecessary medical costs. The one limitation of previous studies for DUE is that most were retrospective and focused on a specific department. To overcome this problem, we prospectively evaluated the appropriate use of ceftriaxone usage (representative of thirdgeneration cephalosporins) at 10 university hospitals in Korea. Ceftriaxone is major drug that is used in the treatment of many important infections due to its high antibacterial potency, wide spectrum of activity, and low potential for toxicity. Its superior activity against Enterobacteriaceae, however, is being challenged by the

increasing frequency of beta-lactamase-mediated resistance. Kim et al. [8] reported that 47% of cases met the criteria for justified use in a retrospective study at a university hospital in 1999. In contrast, our study showed that the appropriate use of ceftriaxone was relatively higher (65.5%) as compared to other studies. This difference may be attributable to the fact that the justification of use criteria were stricter and our study allowed more acceptable cases for empirical therapy. Although the appropriateness (65.5%) of ceftriaxone usage was higher than inappropriateness (34.5%) in tertiary care hospitals in Korea, unsuitable utilization such as continued empiric use for presumed infections and prophylactic perioperative injection remained high. Furthermore, appropriate selection of an antibiotic according to C&S was relatively low. Of the critical indications, a lack of C&S prior to initial ceftriaxone dose and an inappropriate duration of therapy were most common. Others showed quite high rates of appropriateness (84.2-98.5%, Table 4). Ceftriaxone is considered to be low in side effects. Among the complications, hepatotoxicity (16 cases, 4%) and GI difficulties (12 cases, 3%) were most common (Table 5). Each case was managed appropriately.

Outcome analyses showed a relatively high clinical improvement rate of 60.7%, while microbiological documentation by follow-up culture was poor (84.3%). These results show that ceftriaxone, when used empirically, should be reevaluated within 72 hours of initiating therapy and when C&S data are reported. Therapy should be discontinued if the C&S report demonstrates that the organisms are sensitive to equally efficacious, less costly antibiotics. According to data generated by this DUE, a combination of physician education programs and feedback control systems directed toward rational ceftriaxone use is suggested for proper medical treatment.

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