

Adverse events induced by ceftriaxone: a 10-year review of reported cases to Iranian Pharmacovigilance Centre

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SUMMARY

What is known and Objectives: Ceftriaxone, a third-generation cephalosporin antibiotic, is used for a vast variety of infectious diseases. Different types of adverse reactions are reported to be induced by ceftriaxone; however, there is limited published information on spontaneous adverse reactions collected by a national pharmacovigilance centre. This study was conducted to evaluate ceftriaxone-induced adverse drug events, registered in the Iranian pharmacovigilance database during a 10-year period, and to identify preventive measures for reducing ceftriaxone-induced adverse events.

Method: All adverse events registered in the Iranian pharmacovigilance database from 1998 through 2009 were screened for ceftriaxone-related adverse events. The extracted data were categorized based on patients' demographics and previous history of allergic reactions to antibiotics. Assessment of system-organ classes, seriousness and causality of reactions was performed according to World Health Organization scale. The preventability was analysed based on Schumock questionnaire.

Results and Discussion: Ceftriaxone was responsible for the highest number of deaths in our database (49 cases). Of 20 877 reports, 1205 (5.8%) were related to ceftriaxone; 357 reports (30%) are categorized as serious including cardiac arrest, anaphylactic and anaphylactoid reactions. The high number of serious cases makes it necessary to develop preventive measures for reducing those adverse events. Unlabelled use of the drug (2.9%) is identified as one of the risk factors for adverse events. Evaluation of the 1030 intravenous injections of the drug shows that rapid intravenous injection of ceftriaxone is another risk factor. One hundred and sixteen patients (9.6%) had a previous history of allergic reaction to ceftriaxone, penicillin or both. We recommend an alternative antibiotic, if possible, in the case of a positive history of allergic reaction to cephalosporins, penicillins and/or other beta-lactam antibiotics.

What is new and Conclusion:

Severe and life-threatening adverse reactions induced by ceftriaxone are of great concern. Rapid intravenous injection, unlabelled use and previous patient history of allergic reactions to cephalosporins or penicillins are risk factors that should be guarded against.

WHAT IS KNOWN AND OBJECTIVES

Ceftriaxone, a semi-synthetic, third-generation cephalosporin antibiotic, has a wide spectrum of activity and is used for a vast variety of infections. Ceftriaxone is the drug most frequently associated with safety signals in the Iranian National Pharmacovigilance (IPC) database.¹ Adverse drug events (ADEs) induced by ceftriaxone may occur in about 10% of patients receiving the product, but have led to drug discontinuation in <2% of these patients.² Immunoglobulin E-mediated hypersensitivity reactions to cephalosporins may occur because of antibody complexes with the beta-lactam ring or various cephalosporin side chains.³ Anaphylactic reactions from cephalosporins are extremely rare, with the risk estimated at 0.0001–0.1%.⁴ However, the rate of such reactions is much higher than has been reported for penicillins (0.004–0.15%).⁴ Misconceptions regarding the nature of cephalosporin allergic reactions complicate antibiotic selection and may lead to inappropriate drug exposure and anaphylaxis.³ There are also cases of fatal anaphylactic reactions following ceftriaxone intradermal testing.⁵ Some studies suggest that parenteral ceftriaxone should be administered in outpatient settings only where there is the facility for cardiopulmonary resuscitation.⁶ In this study, we evaluate all reports of ceftriaxone-induced adverse events made to the Iranian Pharmacovigilance Centre (IPC) from 1998 through 2009. This is the first cumulative report of ceftriaxone-induced adverse events presented by a national pharmacovigilance centre. As safety information is usually incomplete when based on clinical trials only, careful consideration of spontaneous case reports is necessary.

METHODS

All adverse events associated with ceftriaxone in the IPC database from 1998 through 2009 were reviewed. The adverse events are registered in our database using the World Health Organization (WHO) adverse reaction terminology. All reports of suspected ADEs included information on the sex and age of the

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patients, patient history, and previous history of allergy to antibiotics, and system–organ class of the reaction. The data were categorized based on seriousness and preventability of reported adverse events. Preventability assessment of adverse events was carried out based on the questionnaire of Schumock and Thornton.⁷ Causality and seriousness assessment was performed according to the WHO scale.⁸ To compare ceftriaxone and penicillin, all registered ADEs related to penicillin were also extracted from the database. The information related to market distribution of ceftriaxone and penicillin vials in the country was reported from analysis of pharmaceutical statistics reported by Drug Regulatory Authority.⁹

RESULTS AND DISCUSSION

The frequency of reported ceftriaxone-induced adverse events has been increasing over the last decade (Fig. 1). Of 20 877 ADE reports, 1205 (5.8%), reporting 2173 reactions, were associated with ceftriaxone. This makes ceftriaxone the drug most frequently implicated in adverse events reported to the IPC. At least 15.2% of reported cases are considered preventable; 357 cases (30% of the 1205 cases) are categorized as serious. The most frequently reported serious events with ceftriaxone were cardiac arrest, and anaphylactic and anaphylactoid reactions. Of 232 reports of deaths related to different medicinal products registered in the IPC database, 49 (21.12%) were associated with ceftriaxone, making it the drug most frequently linked to a fatal outcome. The leading cause of death was cardiac arrest. Ceftriaxone is also associated with the highest number of fatal case reports in an analysis of the Italian spontaneous reporting database.¹⁰ We estimate that the real number of probable ceftriaxone-related deaths and other serious adverse events is probably higher than reported to the IPC, because under-reporting is a common problem in spontaneous reporting systems.¹¹

Females were more frequently involved than males in the reported cases (57.01%). This is in consistent with information available in the literature.¹² The highest number of ADEs (204 cases, 57.01%) occurred in the age group 21–30 years (Fig. 2). About 21.07% of the reactions are related to children aged 10 years or younger. Children are considered more susceptible to adverse reactions to medicines because of less well-developed drug-metabolizing capacity. In a study conducted in hospitalized Iranian children, ceftriaxone and rifampin were the most frequently implicated antibiotics in observed adverse drug reac-

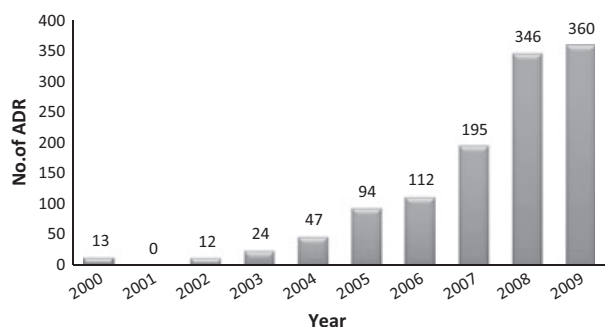


Fig. 1 Total number of received reports of adverse drug events suspected to be induced by ceftriaxone vs. year.

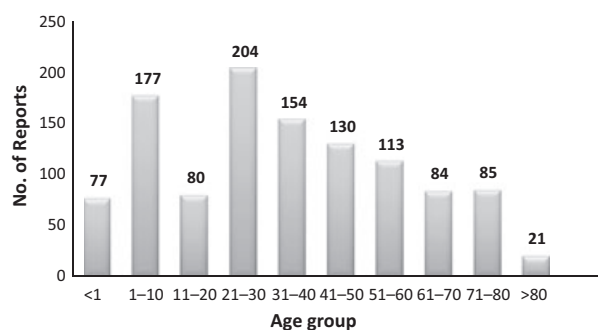


Fig. 2 Number of reports of adverse events suspected to be induced by ceftriaxone according to age-group of patients.

tions.¹³ The concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and young infant may result in a life-threatening adverse reaction.¹⁴ However, there was no conclusive report of such concurrent use among our cases.

Of the 65 patients (5.4%) with a history of asthma disease, there were six deaths and 33 serious reactions. Unlabelled use of the drug was a risk factor for ceftriaxone-induced reactions. This review suggests that 35 cases (2.9%) were avoidable by limiting prescription to appropriate cases. Inappropriate use of parenteral antibiotics is a matter of concern especially in developing countries. Of 1181 patients for whom the route of drug administration was known, 1030, 142 and nine received intravenous, intramuscular and subcutaneous ceftriaxone, respectively. Rapid intravenous injection is a risk factor for adverse events. To this antibiotic, it is recommended that when an intravenous

Table 1. Adverse events associated with ceftriaxone according to organ system

System/organ class	Number of reports
Skin and appendages disorders	593
Respiratory system disorders	310
Body as a whole – general disorders	306
Gastrointestinal system disorders	169
Central and peripheral nervous system disorders	96
Vascular (extra cardiac) disorders	81
Cardiovascular disorders – general	74
Heart rate and rhythm disorders	55
Psychiatric disorders	21
Application site disorders	17
Vision disorders	13
Musculoskeletal system disorders	9
Liver and biliary system disorders	8
Reproductive disorders – female	3
Autonomic nervous system disorders	2
Platelet-bleeding and clotting disorders	2
Urinary system disorders	2
Hearing and vestibular disorders	1
Metabolic and nutritional disorders	1
Resistance mechanism disorders	1

Table 2. Total reported adverse events induced by ceftriaxone based on WHO terminology

Adverse event	No.	Adverse event	No.	Adverse event	No.
Pruritus	266	Tremor	11	Hypothermia	1
Urticaria	242	Palpitation	9	Hypoxia	1
Dyspnea	220	Bradycardia	7	Injection site mass	1
Rash	176	Allergic reaction	6	Mouth dry	1
Vomiting	144	Angioedema	6	Ocular haemorrhage	1
Flushing	138	Anxiety	6	Oedema mouth	1
Anaphylactic reaction	108	Bronchospasm	6	Oedema peripheral	1
Cyanosis	63	Dizziness	6	Oliguria	1
Hypotension	52	Hypertension	6	Pain	1
Oedema	45	Cholelithiasis	5	Pancytopenia	1
Fever	43	Confusion	5	Pharyngitis	1
Agitation	39	Myalgia	5	Respiratory disorder	1
Rash erythematous	39	Phlebitis	5	Serum sickness	1
Sweating increased	35	Rhinitis	5	SGOT increased	1
Rigors	34	Stupor	5	Somnolence	1
Asthenia	31	Coma	4	Thrombocytopenia	1
Cardiac arrest	29	Epidermal necrolysis	4	Tinnitus	1
Tachycardia	29	Syncope	4	Uterine inflammation	1
Nausea	28	Vision abnormal	4	Vaginal discomfort	1
Vertigo	27	Application site reaction	3	Vaginitis	1
Apnoea	22	Skin disorders	3	Gait abnormal	1
Headache	21	Stevens Johnson syndrome	3	Haematemesis	1
Bullous eruption	19	Abscess	2	Haemorrhage intracranial	1
Respiratory Depression	19	Arthralgia	2	Hepatic enzyme increased	1
Abdominal pain	18	Conjunctivitis	2	Biliary tract disorder	1
Cough	18	Cramp	2	Dyspepsia	1
Anaphylactoid reaction	16	Gingivitis	2	Dysphonia	1
Convulsion	15	Glossitis	2	Fibrillation ventricular	1
Rash maculopapular	15	Hiccup	2	Back pain	1
Diarrhoea	14	Laryngitis	2	Circulatory failure	1
Chest pain	12	Moniliasis	2	Delirium	1
Paraesthesia	12	Purpura	2	DRESS	1
Injection site reaction	11	Throat tightness	2	Dysaesthesia	1

injection is judged necessary, the dose should be given slowly over a period of at least 30 min.

Subcutaneous injections given to test for hypersensitivity led to life-threatening anaphylaxis in two asthmatic patients. Seven other patients also developed allergic reactions following a subcutaneous test dose of ceftriaxone. Skin testing with ceftriaxone

Table 3. History of allergic reactions to antibiotics among patients with ceftriaxone-associated adverse events

Name of the medicine(s)	Number of patients (% of the total patients with ADE)
Ceftriaxone	55 (4.6)
Natural penicillins	49 (4.06)
Natural penicillins and ceftriaxone	5 (0.41)
Cephalexin	2 (0.16)
Amoxicillin and clavulanate	2 (0.16)
Ampicillin	1 (0.08)
Cefazolin	1 (0.08)
Cefixime	1 (0.008)
Total	116 (9.6)

ADE, Adverse drug events.

is used to minimize the frequency of allergic reactions to the drug, but this is not part of the protocol for ceftriaxone administration in our country. It is necessary for equipment and trained personnel to be available for managing such serious allergic reactions wherever test doses or subsequent doses of ceftriaxone are administered.

The adverse reactions most frequently involved the skin and appendages (593 reactions) and the respiratory system (310 reactions; Table 1). The reported events based on WHO terminology are summarized in Table 2. Studies suggest that anaphylactic reactions to cephalosporins are rare with estimated frequency of 0.0001–0.1%.¹⁵ Sudol *et al.* reported that ceftriaxone was associated with 69 cases of probable allergic reactions during 1985 through 1990, of which three were anaphylactoid, 17 were anaphylactic/anaphylaxis, 28 were urticarial and 21 were undefined allergic reactions.¹⁶ In another study, administration of ceftriaxone was associated with 11 reports of anaphylaxis among 7.5 million users during 1986 through 1990.¹⁶

Among patients with reported adverse events, 116 cases (9.6%) had a previous history of allergic reaction to ceftriaxone (55 cases, 4.56%), penicillins (52 cases, 4.3%) or both (five cases, 0.41%). Four patients (0.33%) were previously sensitive to one of the other cephalosporins (Table 3). A considerable proportion of the ADEs could have been avoided if administration of the drug was avoided in patients with such a positive history of allergic drug reactions. Cross-sensitivity between penicillin and

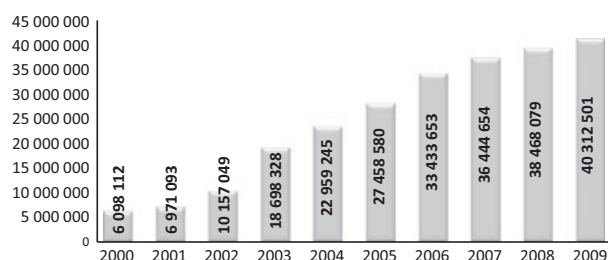


Fig. 3 Number of ceftriaxone vials distributed.

ceftriaxone is a subject of controversy in the literature. Some studies indicate that administration of cephalothin, cefadroxil and cefazolin in penicillin-allergic patients was associated with a significant increase in the rate of allergic reactions, whereas administration of cefprozil, cefpodoxime, ceftazidime and ceftriaxone was not.³ Some studies emphasize caution when administering ceftriaxone to patients with a history of penicillin allergy. The results of our study suggest that an alternative antibiotic might be wiser in patients with a history of allergy to the penicillins or cephalosporins.

The number of ceftriaxone vials distributed yearly in Iran is shown in Fig. 3. Although the distribution statistics do not reflect drug consumption precisely, they are useful estimates. Ceftriaxone, despite its lower extent of use (241 001 294 vs. 1 189 505 735 vials), accounted for more adverse events (about 2.7 times more) than the penicillins (1205 vs. 436 reports and 49 vs. 15 deaths). Causality assessment of the ADEs cases shows that 54.8% were judged definite and 36.26% probable. To reduce the frequency of ceftriaxone-associated adverse events, the IPC

issued a warning letter to healthcare professionals stressing the following points:

- 1 Avoid rapid intravenous injection of ceftriaxone. The intravenous injection of ceftriaxone should last at least 30 min.
- 2 Avoid administration of ceftriaxone for indications not approved for this medicine. Do not use ceftriaxone for common cold or infections that could be treated by oral forms of effective antibiotics.
- 3 Avoid administration of ceftriaxone in patients with a previous history of allergic reactions to ceftriaxone or other cephalosporins.
- 4 Administration of ceftriaxone for patients with a history of penicillin allergy should be limited to necessary situations. Cautions must be performed while administering ceftriaxone to these patients.
- 5 Necessary equipment and trained personnel for managing serious allergic reactions must be available wherever a test dose or subsequent doses of ceftriaxone are administered.
- 6 Avoid concurrent administration of ceftriaxone and calcium-containing solutions within 48 h of each other.
- 7 Avoid reconstitution of ceftriaxone with calcium-containing solutions such as Ringer solutions.

WHAT IS NEW AND CONCLUSION

Ceftriaxone can induce serious, potentially fatal adverse reactions. Rapid intravenous injection of the medicine, unnecessary administration of the drug and administration of the drug to patients with a previous history of allergic reactions to cephalosporins or penicillins should be avoided to reduce the frequency of such reactions.

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