

Ceftriaxone Adverse Events and its Extraction from Body Fluids: Review

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Abstract- *Ceftriaxone also called ceftriaxone/Rocephin third-generation cephalosporin mainly works against bacterial infection in the human body. Ceftriaxone is a beta-lactam stable antibiotic drug that mainly works on the principle of cell destruction cell using inhibition of peptidoglycan synthesis. Ceftriaxone works against both gram-positive and gram-negative classes of bacterial infections such as infections caused by prevotella, streptococcus, and E. coli. There are some known adverse effects but in rare cases, those are seen in a very aggressive manner. Forensically such drug extraction is crucial for purpose of toxicological and chemical analysis from body fluids found on the scene of the crime. Different types of extraction processes are used for drugs from body fluids such as SPE-GC, and SPE-MS/HPLC.*

Indexed Terms- *Cephalosporin, E. coli, Gram-positive bacteria, SPE-GC (Solid Phase Extraction-Gas Chromatography)*

I. INTRODUCTION

This article is a review of the different adverse effects reported by different hospitals in case reports, usually, ceftriaxone is considered safe. Ceftriaxone is 3rd generation cephalosporin class of drugs that shows similar properties to penicillin. The inhibition of cell wall synthesis which is required in bacterial cells for maintaining osmosis pressure is the key mechanism on which ceftriaxone acts. It bases the synthesis of the cell wall by binding at the active site of PBP (penicillin-binding Protein) which is also called a transpeptidase enzyme. It prevents the cross-linking between peptidoglycan which may give rise to osmotic pressure difference. Ceftriaxone is mainly used in combination with other drugs such as in the case of meningitis vancomycin used whereas, for

purpose of reduction in bacterial infection ceftriaxone salt i.e., ceftriaxone sodium is used. Ceftriaxone is usually prescribed in injection mode due to less absorption from the oral intake pathway. There are both intermuscular and intravenous modes for the administration of ceftriaxone. The allergic and adverse reactions data is associated with the world health organization's national adverse reaction terminology ^[1]. Generally, the generations of cephalosporins drugs are increased with increased activity against both gram-positive and gram-negative bacteria, and different diseases including infections in the urinary tract, infections in the ear, and other bacterial infections may be healed using cephalosporins. The cephalosporins are increasing their resistance against the beta-lactamases increasing generations. The fourth generations have more activity against gram-positive bacteria ^[2]. The fifth generation is very well against all beta-lactamase-producing organisms. Ceftriaxone has widespread use which confirms space safety and efficiency which is important for the administration of infections against multi-drug resistant gram-negative bacteria in situations where a long half-life is required ceftriaxone may be prescribed which is cost-efficient too.

Cephalosporins are usually known for their beta-lactam rings, the introductory cephalosporin was cephalosporin-C found from separation from fungi found in sewer water in 1948. The structure of cephalosporins was first characterized by Nuclear-Magnetic Resonance Spectroscopy ^[3].

II. MECHANISM OF ACTION AND PROPERTIES

Ceftriaxone is a 3rd generation of cephalosporin commonly prescribed against gram-negative, gram-positive, and anaerobic bacterial

infections. Cephalosporin along with penicillin resembling with the class of beta-lactam stable group of bacterial antibiotics if we move from the first generation to the 3rd generation the micro bacterial activity of Cephalosporin is strong or increasing against gram-positive organisms but against gram-negative organisms, it will also increase. The Peptidoglycan layer of bacteria serves as a protective code over a tremendous number of barriers and infiltrations. This is a peptidoglycan layer that will take place with the help of cross-linking manner in presence of PBP which is a penicillin-binding protein. cephalosporin binds at the active sites to stop their cross-linking and also stop their synthesis of the peptidoglycan layer which causes them to lysis due to osmotic pressure imbalance. the allergic reactions seen in patients after the administration of cephalosporins are as like as the penicillin class of drugs. Cephalosporins tend to have an affinity towards binding albumin at the place of bilirubin which may cause problems in jaundice patients. While the application of third-generation of cephalosporins is recommended for avoiding the consumption of alcohol^[2]. Ceftriaxone is used for the treatment of bacterial infections and this is a water-soluble drug. By method of inhibition of synthesis of the peptidoglycan layer, the drug works against gram-positive bacteria. The validation of ceftriaxone sodium takes place using different separation techniques such as HPLC, HPTLC, and capillary electrophoresis. the study was carried out in a place to understand selectivity, the limit of detection, the limit of quantification, and the accuracy^[14]. Ceftriaxone approaches antibiotic drug concentration in Central Nervous System by overcoming the barrier of the blood-brain. It has 2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino) acetylamino & [(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl) sulfanyl] methyl side-groups^[15]. Ceftriaxone shows chemical properties such as a molecular weight of 554.6 g/mol. And 155^oC melting point. Its basic molecular formula is (C₁₈H₁₈N₈O₇S₃)^[15].

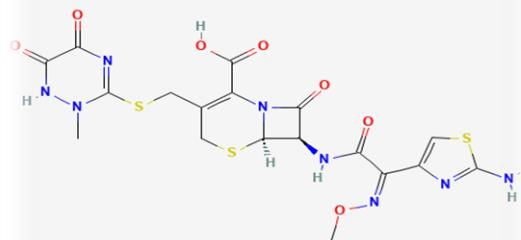


Fig.1 Ceftriaxone Chemical Structure Depiction

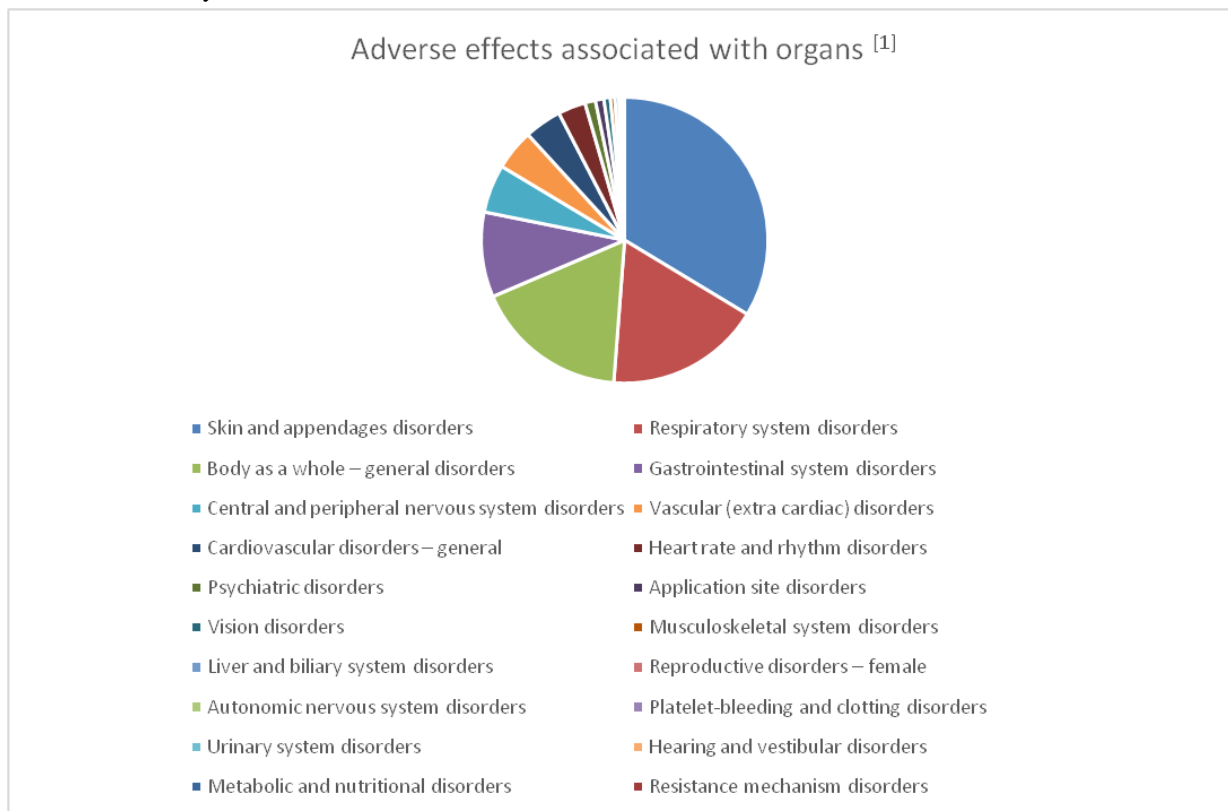
III. ADVERSE REACTIONAL CASES ASSOCIATED WITH CEFTRIAZONE

The study says that they found 152 serious adverse reaction response cases in time duration of 1995-2007, the study was carried out from data provided by the French pharmacovigilance center due to ceftriaxone the serious drop in creatinine clearance level was observed i.e. 35 mL/min. the ceftriaxone level in human plasma was observed having above the threshold limit in 19 patients which was a serious concern. Different detection methods were used such as plasma concentrations and EEG, which eventually indicates the caution for prescribing to older age or renal impairment populations^[4].

The different issues were reported as the age group changed, a 49-year-old lady suffering from hematuria because of a kidney stone was administered ceftriaxone after four successful injections by intramuscular mode at the time of the fifth injection she became unconscious and while performing cardio-pulmonary resuscitation she was resuscitated but undergoes coma with a minimum level of response for sensory and motor nerves. The elimination of ceftriaxone is usually very good as 33-67% of the urinary tract and the remaining will be eliminated from the biliary path. It was recorded that most of the adverse events were reported within 7-10 days of treatment beginning^[5]. Ceftriaxone has a distinctive pharmacokinetic property, unlike other cephalosporins. While most of the cephalosporins are highly dialyzable, ceftriaxone is not dialyzed during

hemodialysis. 65 years old woman who was suffering from kidney disease. Lost her consciousness after the introduction of ceftriaxone's second dose [6]. The beta-lactam antibiotic ceftriaxone act as a therapeutic drug in several diseases, after study of ceftriaxone's interaction with the alpha-synuclein (neuronal protein) at the molecular level using circular dichroism spectroscopy, shows that ceftriaxone binds with good affinity to alpha-synuclein and blocks the polymerization process in the laboratory-controlled environment. This likely concludes that ceftriaxone has neuroprotective action in the laboratory model study of Parkinson's disease [7]. The study for the long-term effect of antibiotics i.e., Ceftriaxone on the immune system and gut microbiota (a group of microbes that form colonies on our digestive tract) were carried out on mice with the introduction of ceftriaxone on daily basis as a mode of food for 150

days, it shows imbalance in level gut microbiota and also observed that it affects on immune regulation. The influence on gut microbiota and immune system of long-term exposure to ceftriaxone is definitely placed [8]. When beta-lactam/beta-lactamase is used to treat ceftriaxone-resistant E. coli bacteraemia the mortality rate was 20% whereas compared to using carbapenem is 37% which not changes if we use both in combination [9]. The study carried out 10 years review of ceftriaxone adverse events between 1998-2009, it was found that 375 cases case were categorized as serious threat events 21.07% of reactions events are associated with minors whose age is 10 years or below, the distribution of cases following organs are listed below the study carried out from data reported by Iranian pharmacovigilance centre [1].



IV. EXTRACTION OF CEFTRIAXONE FROM BODY FLUIDS

Ceftriaxone has usually introduced in the body either in the intravenous or intramuscular mode because of its low absorption rate by the oral path. Ceftriaxone is

hence found in human blood in marginal amounts and eliminated from the body by the urinary tract (33-67%) hence urine will be the second biological matrix from where we may find ceftriaxone traces. It is forensically important to understand different extraction techniques and methodologies for purpose

of determining of presence or absence of ceftriaxone in case of unnatural death, it may give a clue of medical history, drug allergy, and other bodily characteristics information. Different extraction techniques are present for the extraction of drugs from biological samples. HPLC is one of the prominent separation techniques the iron pair column is used with HPLC graded solvent system which has extra purity and avoids contamination, baseline was prepared by Cefazolin before using the sample the solvent system is water: methanol: triethyl amine in the ratio (750:240:4). The reversed-phase means the polar solvent system is used for better separation. The relative retention time was observed and it shows a peak at 270 nanometers in UV/Visible Spectrophotometer ^[10]. By the confirmation of widespread use of ceftriaxone, it ensures safety and reliability, and efficiency also it will definitely offer a greater alternative in case of multi-drug resistant gram-negative class of bacteria in cases where a long half-life is required ^[11]. For enhancements of absorption of ceftriaxone, the bile salt called chenodeoxycholate sodium is added 125mg with coupling 500mg dose of ceftriaxone then it was observed that 24% rectal absorption take place which was a maximum concentration in plasma i.e., 21 µg/ml which has good tolerance level in human beings ^[12]. The study of the determination of ceftriaxone level in blood plasma will be a new method called capillary electrophoresis. For extraction, the organic medium is used as chloroform and iso-butanol in the ratio of 3:1 the method gives express separation which consumes less time. This method is usually used for clinical laboratory analysis ^[13].

CONCLUSION

The article summarizes an introduction and different properties of ceftriaxone, its mode of action, and its induced adverse events also extraction methods which may prove helpful in the case of serological analysis. There will be vast scope for extraction techniques because the current sophisticated methods are high in cost and require accurate precision in terms of cleaning and chemical preparation whereas there is one alternative way to develop the extraction procedure commonly used in chemistry and forensic toxicology which may play a vital role in case of

cost-effectiveness and rapid extraction. Liquid-liquid extraction which is also called solvent extraction is one profound method that might feel suitable for the extraction of such polar compounds from blood plasma. In this study, we found that patients who did have not any allergic record toward the penicillin drug were also victimized by its adverse effects. A notable study was done on the adverse effects of ceftriaxone and it was concluded with the statement that clinicians may prescribe the drug with consciousness and Clinicians may be aware of the side effects of ceftriaxone.

ACKNOWLEDGMENT

We are thankful to the Department of Forensic science, Yashwantrao Chavan institute of science, Satara, India for valuable and informative guidance and cooperation and for allowing us to write a review article on this topic.

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