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Ceftriaxone: a suspected cause for increased hepatic transaminases and blood urea nitrogen

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ABSTRACT

Ceftriaxone is a third-generation cephalosporin antibiotic that has been associated with the development of biliary sludge and biliary colic when given parenterally and in high doses. Ceftriaxone is also associated with rare instances of immune allergic, usually cholestatic hepatitis similar to the injury associated with other cephalosporins. The parenteral cephalosporins are widely used in medicine for serious infections and can be safely given to patients with advanced liver disease, dose modifications being required mainly for renal insufficiency. Previous studies have reported a few cases of high aspartate aminotransferase and alanine aminotransferase levels, along with three cases of hepatitis caused by ceftriaxone.

INTRODUCTION

Ceftriaxone is a semisynthetic third-generation cephalosporin that is widely used for infections caused by gram-positive and gram-negative aerobic bacteria because of its long half-life, single daily dosing, beta-lactamase resistance.[1,2] The drug shows its potent antimicrobial activity against *Streptococcusfaecalis, streptococcus pyogenes, streptococcus pneumonia, Brucellamelitensis, Haemophilus influenza, and Neisseria gonorrhoeae. [3,4,5,6,7]* Approximately 33%-67% of administered through renal excretion, 40% are secreted in bile which is eliminated through the gastrointestinal tract.[8,9,10] Some studies show that ceftriaxone can be concentrated in the bile 20150 times more than in serum.[11,12,13,14]

CASE HISTORY

A 15years old male patient came to Hospital and got admitted with complaints of generalized edema, a History of altered sensorium for 1 week with a case of seizures with a known case of Epilepsy since childhood, and with a known case of Hypothyroidism since 3 years. The chief complaints were Swelling of the whole body especially both lower limbs and face and associated with generalized weakness, excessive drowsiness, Intermittent attacks of involuntary movements, Tonic-clonic contractions of both upper limbs and lower limbs, Uprolling of eyeballs, Froth from the mouth. 2-3 episodes were observed. The patient used to take T.SODIUM VALPROATE 500mg 1-0-1 but stopped using them. Presently using T.PHENYTOIN, T.CLOBAZAM, T. LEVOTHYROXINE, T. CITICHOLINE-(may be recommended for cognitive impairment), T. PHENOBARBITONE-(if this is used for anxiety should not be used for more than 2weeks), T. RANITIDINE, T. LEVITRIACETAM, SYP.MULTIVITAMIN.

On the first day of admission, the patient was conscious, disoriented, incoherent (may be due to clobazam or phenobarbitone), Pallor is present(maybe due to iron deficiency

Table 1 : PAST ADMINSTERING MEDICATIONS

SNO	DRUG	DOSE	FREQUENCY
1	T.PHENYTOIN	100mg	1-0-2
2	T.CLOBAZAM	10mg	0-0-1
3	LEVOTHYROXINE	50mg	1-0-0
4	CITICHOLINE	500mg	1-0-1
5	T. RANITIDINE	150mg	1-0-1
6	T.LEVITRIACETAM	500mg	1-0-1
7	T. PHENOBARBITONE	50mg	1-0-1
	Syp. MULTIVITAMIN		1-1-1

or hypothyroidism), bilateral pedal edema was present, lower limbs were presented with edema which was pitting type, facial edema was present (it was thought that fibroblast stimulation by the thyroid-stimulating hormone [TSH] receptor increases the deposition of glycosaminoglycan, which results in osmotic edema and fluid retention. It was thought that many cells responsible for forming connective tissue react to increase TSH levels). Pulse rate was normal, hypotension was present (adrenal fatigue-collection of nonspecific symptoms like fatigue, body aches, low blood pressure, lightheadedness, loss of body hair, skin discoloration). By abdominal examination, abdominal distention (swollen due to pressure) was observed.

The patient was treated on the first day, after proper examination with O2 inhalation-2lit/min-FACE MASK (INHALED) -SOS, INJ. FUROSEMIDE 40mg IV 1-0-1, INJ.METHYLCOBALAMIN-1 AMP IN 100ml NS IV 0-0-1, T.PHENYTOIN 100mg PO 1-0-2,T. LEVETIRACETAM 500mgnPO1-0-1, T.CLOBAZAM 10mg PO 0-1-0, T. LEVOTHYROXINE 50mg PO 1-0-1, T.PANTOPRAZOLE 40mg PO 1-0-0, T.FOLIC ACID 5mgPO 0-1-0 and advised to perform CBP (complete blood picture), LFT, RFT, USG abdomen, MRI brain

The provisional diagnosis was done as ANASARCA DECREASED ON EVALUATION WITH EPILEPSY WITH HYPOTHYROIDISM, ruled out for RENAL IMPAIRMENT, Ruled Out for HYPOPROTEINEMIA. On the second day, the patient was treated with the same medication, and decreased hemoglobin along with increased ESR count was observed. Normal LFT, RFT were observed. No abnormalities were found in the ultrasound abdomen. Glucose levels were normal. In MRI brain, CALCIFIED GRANULOMA IN LEFT OCCIPITAL LOBE(may cause seizures, may affect memory, object and face recognition, visuospatial processing, distance, and depth perception, color determination) was observed. On the 3rd day, the Patient was conscious, coherent, Swelling was decreased. hypotension, normal pulse rate with distended abdomen was observed. The same treatment was continued but clobazam was stopped.

On the 4th day, the Patient was conscious and drowsy, Fever was present, 2 spikes since yesterday, hypotension continues. the same treatment was Continued and the following drugs were added INJ.CEFTRIAXONE 2g IV 1-0-1, T.PARACETAMOL 500mg PO 6THhrly, T.LEVOTHYROXINE 100mcgPO1-0-0, T.BC PO 0-1-0, T.CALCIUM PO 0-1-0, T.IFA PO 0-1-0.

FINAL DIAGNOSIS was done as EPILEPSY WITH HYPOTHYROIDISM. On the 5th day, the Patient was conscious, disoriented. Normal vitals were observed. the same treatment was Continued and the following drugs were added T.AMOXICILLIN +CLAVULANATE 500mg+125mg PO BD 1-0-1. After the 5th day when RFT AND LFT are performed, their values were increased. This treatment was continued for the next 5 days. After this, the patient was discharged without performing any diagnostic tests and the patient was prescribed Tab. CEFIXIME 200 mg PO 1-0-1 for 5Days, T. PARACETAMOL 500 mg PO SOS, T. LEVOTHYROXINE 100 mcg PO1-0-0, T. PANTOPRAZOLE 40 mg PO1-0-0, T. PHENYTOIN 100 mg PO1-0-2, T.LEVITRIACETAM 500 mg PO1-0-1, T.BC PO 0-1-0, T. CALCIUM PO 0-1-0, T.IFA PO 0-1-0.

Interventions are done in this case study. Levothyroxine dose was increased from 50 mcg to 100mcg without performing any laboratory investigation, In-lab data The Blood Urea levels are increased it may be due to either severe dehydration or damage to kidney functioning. The SGOT and ALP levels were increased which may suggest Liver impairment but they did not rule out liver disease. Cholesterol levels are haven't checked. Ceftriaxone was started with a high dose and ESR was not rechecked. Irrational use of amoxicillin with clavulanate. Clobazam was stopped on the third day, sudden stoppage of clobazam may cause withdrawal symptoms (headache, trouble sleeping, restlessness, shaking, hallucinations/ confusion, seizure). Lowering the dose was recommended. Phenobarbital was not given in the treatment, it may cause withdrawal symptoms (trouble sleeping, seizures [status epilepticus] hallucinations, twitching, anxiety). Lipid profile is not checked, hypothyroidism may cause hypercholesterolemia and an increase in fatty acids. Serum Electrolytes were not checked, Saturation levels were not checked but the patient was supplied with oxygen 2L/min which produce fio2(fraction of inspired oxygen) of approximately 28%.

Lifestyle modifications like Exercising in the early evening if possible. Take warm showers or have a back rub before bedtime to decrease muscle tension. Limiting naps and avoiding naps in the early evening, Changing times or doses at night may help sleep. Limiting salt. Asparagus, green beans, parsley, pineapple, and onions act as they act as natural diuretics can be helpful. Use oils that are high in oleic acid and omega 9 fatty acids like olive, grape, and avocado oil, while cooking and in salads. Prevent iodine deficiency by choosing to eat the right amounts of iodine-rich foods such as seaweeds, iodized salt and seafood may become beneficial.

Table 2 : SUMMARY OF TREATMENT CHART

S.No	Drug	Dose	R.O.A	Frequency
1	Oxygen inhalation	2lit/min	Face mask	S.OS
2	Inj. Furosemide	40mg	IV	1-0-1
	Inj.methylcobalamine	1 amp in 100ml NS	IV	0-0-1
3	T. Phenytoin	100mg	PO	1-0-2
4	T. Levetiracetam	500mg	PO	1-0-1
5	T.Clobazam	10mg	PO	0-1-0
6	t.pantoprazole	40mg	PO	1-0-0
7	t.folic acid		PO	0-1-0
8	t. levothyroxine	50mcg	PO	1-0-1
9	Inj.ceftriaxone	2g	IV	1-0-1
10	t.paracetamol	500mg	PO	1-1-1-1
11	t.levothyroxine	100mcg	PO	1-0-0
12	t.b complex		PO	0-1-0
13	T.calcium		PO	0-1-0
14	t. Iron folic acid		PO	0-1-0
15	t. amoxicillin + clavulanate	500mg + 125mg	PO	1-0-1

Table 3 : LABORATORY INVESTIGATIONS

DAY	**TEST**	**TEST VALUE**	**NORMAL RANGE**
Day 1	RANDOM BLOOD SUGAR	120mg/dl	79-140mg/dl
day	test	Test value	Normal range
Day 1	SERUM CREATININE	1mg/dl	0.6-1.2mg/dl
Day 2	TC	10400cells/cumm	4000-11000 (cells/cumm)
Day 2	SGOT	20 IU/L	5-40 IU/L
Day 2	SGPT	22 IU/L	7-56 IU/L
Day 2	ALP	125IU/L	40-125IU/L
Day 2	N	62%	40-60%
Day 2	L	32%	20-40
Day 2	E	5%	2-3%
Day 2	M	1%	1-2%
Day 2	ESR	20mm/hr	0-15mm/hr
Day 2	BLOOD UREA	20mg/dl	8-25mg/dl
Day 2	SERUM CREATININE	0.6mg/dl	0.6-1.2mg/dl
Day 2	SGOT	20 IU/L	5-40 IU/L
Day 2	HB	**11.2**	**14-16(g/dl)**
Day 2	SERUM BILIRUBIN	0.3mg/dl	0.3-1.3mg/dl
Day 5	BLOOD UREA	34mg/dl	8-25mg/dl
Day 5	SERUM CREATININE	0.6mg/dl	0.6-1.2mg/dl
Day 5	SGOT	42 IU/L	12-38 IU/L
Day 5	SGPT	38IU/L	7-56 IU/L
Day 5	ALP	146 IU/L	40-125 IU/L
Day 5	SERUM BILIRUBIN	0.4mg/dl	0.3-1.9mg/dl
Day 5	SERUM ALBUMIN	4.1g/dl	3.1-4.3g/dl
Day 5	SERUM GLOBULIN	2.9g/dl	2.6-4.1g/dl
Day 5	SERUM PROTEINS	7g/dl	6.4-8.3g/dl
Day 5	Serology HIV HBsAG	Non reactive	
Day 5	SGPT	38IU/L	7-56 IU/L

DISCUSSION

Parenteral administration of ceftriaxone has been associated with the development of biliary sludge in 3% to 46% of patients. The incidence may be higher in children than adults because of higher doses and long term treatment and may be associated with fasting or dehydration which was referred to as "pseudo-lithiasis", as the sludge and stones consist largely of ceftriaxone and they resolve spontaneously when the drug is stopped, indicating that surgery can be avoided. Most cases occur with minimal or no symptoms. [15,16]

Blood transfusion, recent tooth extraction, surgery, direct contact with a patient with hepatitis, history of traveling or use of any drugs other than ceftriaxone, other medications, including herbal remedies and vitamins, led us to consider ceftriaxone as the responsible agent with the absence of a specific cause for the elevated liver function tests, including AST, ALT, ALP, GGT, and total and direct bilirubin. For the evidence that ceftriaxone is responsible for ceftriaxone-induced hepatitis, a direct correlation with ceftriaxone use could be verified by measurement of drug levels in the serum or by liver biopsy, or the re-use of the drug, in which case elevated transaminase levels would support our diagnosis of ceftriaxone-induced hepatitis. Measurements of the antibody for liver-kidney microsome (anti-LKM) and cytochrome P450 may be useful for demonstrating drug-induced hepatotoxicity[17]. In some cases, serum measurement of anti-LKM was positive but for technical reasons, serum ceftriaxone levels could not be performed. A prominent increase in the levels of GGT suggest a toxic cause[18] Even though only a few cases of elevated liver enzymes caused by ceftriaxone have been reported only three cases of hepatitis have been reported in the literature[19,20,21]In some previous studies also demonstrated impaired renal function in 72.7% of the patients with ceftriaxone calculi [22]It is speculated that metabolic disturbances such as hypercalciuria, hyperuricosuria, cystinuria, hyperoxaluria, and hypocitraturia may predispose to the development of nephrolithiasis.[23]In another study, nephrotoxic agents have been reported to be a risk factor for large ceftriaxone-induced nephrolithiasis.[24] In addition to the ceftriaxone dose, a longer treatment time can increase a patient's risk for renal complications and nephrolithiasis. [25]

CONCLUSION

This study suggests that multiple treatments with high-dose antibiotics may cause altered liver function tests and renal function tests even for a short duration.

INFORMED CONSENT FORM

The information regarding the study has been read by me/ read to me and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature or left thumb impression to indicate my consent and willingness to participate in this study.

Signature/ left thumb impression of the patient/ patient attender

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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