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Comparative Study of Efficacy of Cefuroxime and Ceftriaxone in Enteric Fever

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Abstract: *Enteric fever (Typhoid fever) is an acute systemic disease resulting from infection with Salmonella typhi. The peak incidence of disease is between the age of 15 and 35 years. Currently the III generation Cephalosporins like Ceftriaxone and Cefotaxime are being used in multi drug resistant typhoid fever. These drugs are bactericidal and are very effective. A second generation Cephalosporins, Cefuroxime is also active against Salmonella typhi. The aim of the present study is to compare the efficacy of Cefuroxime and Ceftriaxone in treatment of typhoid fever. Patients who attended the department of Medicine with fever were selected as per the exclusion and inclusion criteria. They were divided into two groups. 25 patients were treated with ceftriaxone under*
Group – I *and another 25 patients were treated with cefuroxime under*
Group – II*. The results of both groups were recorded . There were no significant differences observed among patients in the two groups with regard to age, sex, duration of fever before admission and clinical findings. The mean number of days for patients to become afebrile was significantly lowered in those receiving ceftriaxone (P < 0.001) than in those receiving cefuroxime. Ceftriaxone in the treatment of typhoid fever was proved safe and effective in the present study*
Keywords: *Cephalosporins, Ceftriaxone, Cefuroxime, Typhoid fever .*

I. Introduction

Enteric fever (Typhoid fever) is a major public health problem, causing enormous morbidity and mortality in developing countries. Typhoid fever is an acute systemic disease resulting from infection with Salmonella typhi. The causative organism was first isolated by *Ebreth* in 1880. The disease has world wide distribution and endemic in Tropical Countries.

The peak incidence of disease is between the age of 15 and 35 years. Typhoid fever is an acute systemic disease resulting from infection with Salmonella typhi. The disease is unique to humans. It is characterized by Malaise, fever, abdominal discomfort, transient rash, splenomegaly and leucopaenia[5].

The most important and prominent major complications are intestinal ulceration, haemorrhage and perforation[18].

II. Pathogenesis

Portal of Entry

The organisms gain entry in the human being through oral route. They gain access in the body by crossing the lymphoid tissues of the pharynx.

Distribution and Multiplication

On reaching the gut, the bacilli attach themselves to the epithelial cells of the intestinal villi and penetrate to the lamina propria and submucosa. They are phagocytosed by polymorphs and macrophages. The ability to resist intracellular killing and to multiply within these cells is a measure of their virulence. They enter the mesenteric lymph nodes, where they multiply and via the thoracic duct, enter the blood stream. The bacilli are seeded in the liver, gall bladder, spleen, bone marrow, lymph nodes, lungs and kidneys, where further multiplication takes place. Towards the end of the incubation period, there occurs a massive bacteraemia.

Bile is a good culture medium for the bacillus, it multiplies abundantly in the gall bladder and is discharged continuously in to the intestine where it involves Payer's patches and lymphoid follicles of the ileum. These became inflammed, undergo necrosis and slough off, leaving behind the characteristic typhoid ulcers. Ulceration of the bowel leads intestinal perforation and haemorrhage. During the course of 3 - 4 weeks, the intestinal lesions undergo healing.

Clinical Features of Typhoid Fever

The incubation period is usually 14 days, but may range from 5 - 20 days, and appears to be related to the dose of the infection.

The First Week

The disease is gradual in onset with malaise, loss of appetite and headache. There is sore throat and cough. From third day on wards the symptoms become more severe. The temperature raises to step ladder fashion. Evening raise being greater by 0.5 to 1^0 F[6].

There is vomiting , abdominal discomfort and constipation. The tongue is dry and coated centrally. There is enlargement of liver. The spleen enlarges towards the end of the week[8].

Rose spots appear on the 7^{th} or 8^{th} day. They occur more commonly on the trunk They are slightly raised and fade on pressure.

The Second Week

The temperature is raised and continuous. The patient becomes toxic there is mental apathy and he may become delirious. The relative bradycardia disappears towards the end of the week. The mouth and lips become dry and cracked and sticky mucus covers the mouth and tongue.

The patient develop diarrhoea and spleen become larger.

The Third Week

In cases which recovered the temperature fall by about the fifteenth day. Toxaemia diminishes and appetite returns to normal.

In complicated cases, symptoms become more severe and the patient becomes profoundly toxic. They may lapse into a stage of 'Coma Vigil' in which he is semi conscious, dehydrated, unaware of the surrounding and tremulous.

The fourth Week

Severe cases run a downhill course and die.

Uncomplicated cases after about 10 days of cessation of therapy, the attack is milder and less severe, complications are uncommon.

III. Complications

Gastrointestinal Tract

superficial ulcers develop towards the end of first week on the anterior pillars of the fauces, soft palate and the pharyngeal wall. The importance of these ulcers in that the case may be mistaken for Diptheria, specially in children.

Diarrhoea at the end of second week, may herald serious complications like haemorrhage or perforation.

Intestinal haemorrhage occurs during third or fourth week. It is rare in children below the age of 12 years.

Perforation of the bowel is the next dreadful complication of typhoid. It occurs in 2-4% of cases, usually in the third week.

Cardiovasuclar System

In severe cases acute myocardial failure or peripheral circulatory failure are common complications . Venous thrombosis occurs in the third or fourth week after convalescence. It frequently affects the left femoral vein which feels like a cord and is tender.

Urinary System

Acute haemorrhagic nephritis may occur cystitis, pyelitis or pyelonephritis are not uncommon complications during the third week. They are cause either by S.typhi or E.coli. Typhoid bacilluria is common.

Skin Eruptions are found in many cases over the abdomen and in the axillae. Abscesses and boils may develop late in the disease or convalescence.

Clinical Diagnosis

The following clinical criteria should be applied.

a) Pyrexia of remittent type
b) Low pulse-temperature ratio
c) Characteristic toxemia
d) Splenic enlargement
e) Eruption of rose-spots.

IV. Treatment

General

The patient should be isolated. The patient should rest in bed for at least one weak after the normalization of temperature.

Oral Hygiene: The mouth should be kept clean. If chewing gum is acceptable, fifteen minutes chewing after good keep the mouth clean.

Bowels and bladder: No measures should be taken to relieve constipation unless of more than 3 days of duration. If at all anything liquid paraffin should be given by mouth. Enema should be avoided and if necessary only normal saline enema without much pressure should given. Flatus tube may be used for abdominal distension. Diarrhoea may be treated with appropriate measures. For retention of urine when patient is toxic and comatose, catherisation should be done.

Hyperpyrexia: Tepid sponging should be done. Antipyretics can be used.

Diet

A diet low in roughage and having adequate calories, proteins and glucose should be prescribed. He should be given a diet containing 2500 to 3000 calories/day.

Severe Toxic Cases

In such cases a diet of 1,500 calories should be given because the patient is anemic, apathetic, with abdominal distension. The diet may have to be given by parentral or intra gastric route.

Skimmed milk given 2nd hourly is the best in between he should be encouraged to take orange or lemon juice with glucose.

Moderate and Mild Cases

The diet should consist of high protein and calories with low residue. In mild cases with good appetite milk puddings, vegetables, soups, mashed potatoes, soft rice, bread, can be given.

Specific Treatment

1. Chloramphenicol, Ampicillin, Co-Trimoxazole, Ciprofloxacin are used in the treatment of typhoid previously. Now,resistance develops to these drugs. They may also side effects like bone marrow depression, aplastic anaemia, gastrointestinal symptoms, ,hypertensitivity and also tendonitis etc[10].
2. Cephalosporins Third generation cephalosporins are now considered as the first line of treatment against multi drug resistant typhoid fever.

Ceftriaxone: It is a III generation cephalosporin, bactericidal, it prevents relapse and carrier state. Mechanism of action is same as penicillin. It can be safely used in children.

Cefuroxime: It is II generation cephalosporin. Bactericidal, mechanism of action is same as penicillin. It is well tolerated, attains higher CSF levels.

Ceftriaxone

It is administered parenterally plasma half life is 8 hrs. Longer duration of action it has good CSF penetration. Ceftriaxone is well tolerated.

Side effects are local reactions including pain, induration and tenderness at injection site. Typhoid fever responded very well. It is safe in children and adults.

Dosage and administration

Preparation: 250 mg, 500 mg, 1 g vials are available.

Dose : 4 gms i.v. once a day for 2 days followed by 2gms per day till 2 days after fever subsides.

Cefuroxime

It is administered parentally. Plasma half life is 1.7 hrs. It has good CSF penetration and attain higher CSF levels. 85-90% in excreted in urine in unchanged form. Cefuroxime is well tolerated.

Side effects are headache, pain at injection site. Hypersensitivity reactions including skin rashes, urticaria, pruritis, intestinal nephritis.

Dosage and Administration

Preparation: 250 mg, 750mg, 1.5 gm vials are available.

Dose: 750 mg IM/Iv 8th hrly.

V. Materials And Methods

The study was under taken in Typhoid fever patients attending Department of Medicine .

Materials

Group – I Patients of Typhoid fever taking Injection Ceftriaxone.
Group – II Patients of Typhoid fever taking Injection Cefuroxime.
Ceftriaxone – 1gm (Woukhardi – Pharma), Injection, Powercef.
Cefuroxime – 750mg (Glenmark – Pharma), Injection, Altacef.

Selection Of Patients

- Patients aged between 15-40 years male and female were selected with history of continuous fever for more than 5 days duration with nausea, vomiting, abdominal discomfort. On examination raised body temperature, toxic look, coated tongue, hepatomegaly, splenomegaly were selected.
- After selection ,consent was obtained from all patients.
- Diagnosis was made on the basis of signs and symptoms and specific tests like widal, blood culture, stool and urine culture.
- X-ray chest was taken to rule out tuberculosis and other long diseases.
- Blood picture was taken to exclude malaria and fever due to other diseases.
- Typhoid cases complicated with perforation, peritonitis, meningitis, and encephalitis were excluded from the study.
- They were divided into two groups.

Group – I (n =25) Treatment was started with ceftriaxone parenterally 4gms iv once a day for 2 days followed by 2gms/day till 2 days after fever subsides and results were recorded on the basis of signs, symptoms and investigations and they are kept under.
Group- II (n =25) Treatment was started with cefuroxime 750mg im/iv and 8^{th} hrly results were recorded in the basis of signs and symptoms and specific investigations.

Methods

The clinically suspected typhoid fever cases were subjected to detailed clinical examination. The blood was sent for culture examination and widal test. The other investigations like complete blood picture, E.S.R., urine analysis, stool examination and screening for Chest for both Group I and II patients were done.

In all cases clinical findings, medications, dosage and adverse drug reactions were monitored daily till the temperature falls. Clinical defervescence was defined as body temperature remaining below 38^0 C (100^0 4 F) for 24 hours without the use of antipyretics. 4^{th} hourly temperature chart was maintained for each case.

After completion of therapy the patients were reviewed weekly for 4 weeks for any relapse of temperature or any other complaints.

VI. Results

The duration of illness in Group I was mean 9.76 days and in Group II the duration was mean 10.20. The onset was insidious.

Clinical Presentation

In Group - I All patients were presented with fever more than 102^0 F at the time of admission 16/25 (64%) of patients had headache, 22/25 (88%) were presented with abdominal discomfort and tenderness. 13/25(52) had vomiting, 6/25(24%) with diarrhoea, 20/25 (80%) were with splenomegaly and 10/25(40%) presented with hepatomegaly.

In Group – II All 25 patients (100%) were presented with more than 102^0F temperature at the time of admission headache in 15/25(60%), abdominal discomfort and tenderness in 14/25 (56%), vomiting in 15/25(60%), diarrhoea in 5/25(20%), splenomegaly in 19/25 (76%), and hepatomegaly in 9/25 (36%) were present.

Days required for disappearance of signs and symptoms

There were no significant differences observed among patients in the two treatment groups with regard to age, sex, duration of fever before admission and clinical findings. The mean number of days for patients to become afebrile was significantly lowered in those receiving ceftriaxone ($P < 0.001$) than cefuroxime.

Table – I: Days required for disappearance of signs and symptoms

Sl. No.	Signs & Symptoms	Ceftriaxone-I	Cefuroxime-II	Statistics
1.	Afebrile	4.68±0.74	5.32±0.47	P<0.001
2.	Abdominal Distension	3.22±0.42	4.26±0.46	P<0.001
3.	Splenomegaly	4.20±0.41	4.26±0.48	P<0.001

The mean number of days for regression of splenomegaly was significantly lowered in those receiving ceftriaxone ($P < 0.001$) and Cefuroxime ($P < 0.001$) There is significant difference ($P < 0.001$) in the means of number of days for disappearance of abdominal discomfort and tenderness in those patients receiving ceftriaxone, and cefuroxime

Blood Culture

Blood samples were sent for culture (S. Typhoid) from all 25 patients in ceftriaxone group, out of which only 8 blood samples had shown growth of S.Typhi. The blood culture was repeated after completion of therapy and found all 8 cases were sterile .

In cefuroxime group 5/25 blood samples has shown growth of salmonella typhi. The blood culture was repeated after completion of therapy and found all 5 cases were sterile.

Table – II: Blood Culture

Group	No. of samples sent	No. of samples +ve for Salmonella Typhi	After treatment Salmonella Typhi
Ceftriaxone-I	25	8	-ve
Cefuroxime-II	25	5	-ve

Widal Test

Widal test was done in both groups (group I and group II) before starting the therapy. The widal test was positive for both 'O' and 'H' in titre of more than 1:160 dilutions. After therapy the widal test was repeated and find significantly reduced titre of less than 1:160 dilution (0 and H) in both.

Table III: Widal Test

Group	No. of samples sent	No. of samples +ve for Salmonella Typhi	After treatment O&H positive
Cefriaxone-I	25	25	-
Cefuroxime-II	25	25	3

Results of therapy

Clinical cure: In ceftriaxone group the clinical cure was seen in 25/25 (100%).

In cefuroxime group : The clinical cure was seen in 22/25 (88%) patients. 3 Patients were shifted to ceftriaxone as they have not responded to cefuroxime therapy. Adverse drug reactions:

The adverse effects were mild in ceftriaxone group, 2 patients had mild throphelbitis which was subsided with in two days. In cefuroxime group 6 patients had adverse effects like headache and pain at injection site.

Table – III

Response	Groups and Number of Patients		
Group	Ceftriaxone-I	Cefuroxime-II	
Clinical cure	25	22	P<0.001
Not responded to therapy	0	3	P<0.001
Adverse drug reactions	2	6	P<0.001

VII. Discussion

Ceftriaxone in the treatment of typhoid fever was proved safe and effective in the present study.

Males are frequently affected than females in the ratio of 3:2 in all the 3 groups. The fever was mostly of continuous type and gradual onset. In ceftriaxone group the patients were responded and clinical cure was 25/25 (100%) cases.

The days required for the reduction of temperature to normal was even and significant in ceftriaxone and cefuroxime There was significant difference in the number of days required in disappearance of abdominal discomforts. There was significant difference in the number of days required in the regression of splenomegaly between ceftriaxone and cefuroxime.

There was no serious adverse affects in ceftriaxone group and noted only two patients complained of thrombophlebitis.

In the present study the clinical cure was 100% with ceftriaxone. The positive cultures for salmonella typhi were turned sterile after the completion of therapy. The stool and urine culture were negative. There were no relapses reported during the therapy and also after the follow up study period of four weeks. There was significant reduction in the widal agglutination titre after therapy.

In cefuroxime group the clinical cure was 22/25 (98%) and 3 patients showed resistance. The days required for the disappearance of signs and symptoms was not superior to ceftriaxone group. Adverse effects like rashes and headache were seen in 6 patients of cefuroxime groups.

VIII. Conclusion

Comparative study of 25 cases in each group, ceftriaxone and cefuroxime are done. Ceftriaxone belongs to β-lactam group of drugs which are bactericidal, broad spectrum with less chance of development of resistance, with high therapeutic index and minimum adverse effects, taken for its effectiveness in the treatment of typhoid fever.

Third generation cephalosporin, ceftriaxone is effective in the treatment of typhoid fever in children as well as adults with less adverse effects.

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