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Clinical Evaluation Of Ciprofloxacin (NOVIDAT) In Enteric Fever

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SUMMARY

Novidat (Ciprofloxacin) 500 mg twice daily was given orally to 15 patients who had positive widal test in a concentration of more than 1:160 of both H & O antigens and clinical features suggestive of enteric fever. Other causes of fever were ruled out and blood cultures were performed in all patients for salmonella typhi. All patients were given Novidat for 14 days and followed for one month with cure rate of 100%. Although blood cultures were negative for salmonella typhi in all patients, widal test was positive in all. No adverse drug effects necessitated termination of therapy. In this study Novidat was well tolerated and highly effective in treatment of enteric fever.

INTRODUCTION

Enteric fever is an acute systemic bacterial infection caused by salmonella group of organisms i.e. Salmonella typhi, Salmonella paratyphi A, B, and C. Occasionally, other salmonella serotypes of the food poisoning variety may produce a similar illness. Salmonella organisms are gram negative, aerobic, generally motile non lactose fermenting bacilli. Serotypes are identified on the basis of their somatic (O) and flagellar (H) antigens. Enteric fever, although has been eradicated in the developed countries to a large extent, it is still a major health problem in tropical and developing countries like Pakistan. The incidence is reported at 540 cases per 100,000 people in developing countries[1]. In Pakistan enteric fever is endemic with epidemics occurring in the late summer months.

In the past, chloramphenicol, ampicillin, cotrimoxazole and amoxicillin have been used successfully to treat enteric fever. Recent reports, however, indicate that a substantial number of S. typhi strains are becoming resistant to one, two or even all four of these agents[2,3,4]. Treatment failure associated with such resistant strains has led to a search for alternative agents. Most of salmonella typhi strains have a low incidence of resistance to quinolones. Furthermore, ciprofloxacin (Novidat) a quinolones, has a low minimal inhibitory concentration for salmonella typhi[5].

This study was conducted to evaluate efficacy and safety of ciprofloxacin (Novidat) in the treatment of enteric fever.

PATIENTS AND METHODS

This study was conducted in the Gastroenterology department at the Shaikh Zayed Federal Postgraduate Medical Institute, Lahore from June 1994 to November 1995. Fifteen cases were included in the study. The criteria for selection included a clinical profile suggestive of enteric fever along with isolation of S. typi or P. typhi on blood culture or a rising titre of serum agglutinins O from an initial level of 1:160 or more in the standard agglutination test (Widal test). Although the specificity of Widal test does not match that of blood cultures but in the proper clinical setting, it is quite useful. Most of the patients admitted, had received empirical therapy with antibiotics from other physicians which reduces the chance of positive cultures. Thus, all patients with positive Widal test were included in our study while awaiting blood culture reports. Patients, thought to be terminally ill, receiving concomitant systemic antimicrobial therapy, history of hypersensitivity to the quinolones, serum creatinine > 2.0 mg/dl or history of convulsive disorders were excluded from the study.

Complete medical history and physical examination was performed. All patients underwent complete blood examination, widal test, liver function tests, blood culture, urine routine examination, stool routine examination, prothrombin time, urea and creatinine.

All patients were given ciprofloxacin (Novidat) 500 mg twice daily for 14 days and examined for relapse or adverse events through one month after symptoms. Treatment failure was defined as showing no improvement in pre-treatment signs and symptoms within 6 days of initiation of therapy.

Statistical analysis

Results were reported as percentage for qualitative variables and mean±S.D. for quantitative variables. Comparison of LFTs at the beginning and end of study were done using a paired t test. Results were considered significant at $P < 0.05$.

RESULTS

Of 15 patients, 9 were males and 6 females with a M:F ratio of 1.5:1. Mean age was 32.2 (range 18-43 years). Demographic and clinical features are given in Table 1. Blood cultures for salmonella typi were negative in all patients. Splenomegaly was present in 3 (20%), hepatomegaly in 7 (46%) of these patients. percentage of patients showed significant elevation of S. bilirubin, ALT, AST and alkaline phosphatase values. Data for liver function tests (LFTs) is presented in Table 2. All LFTs except alkaline phosphatase levels showed a significant decrease from pre treatment values ($P < 0.05$).

Mean temperature at presentation was 103°F (±SD. 2) with defervescnce noted on a mean of 4 days.

Table 1: Demographic and clinical features.

Total No of patients:	15
Males:	9
Females:	6
Mean Age:	32.3 (+) 18-43
Positive Blood Cultures:	None
Widal Test:	Positive in all
Splenomegaly:	3
Hepatomegaly:	7

Adverse effects noted were mild degree of dryness of mouth, weakness, anorexia, epigastric burning and vertigo. No patient required withdrawal of medication due to unacceptable side effects.

Table 2: Comparison of LFTs using t-test at beginning and end of study showing significant differences in all values except alkaline phosphatase levels ($P < 0.05$).

Parameters	Mean	± S.D.
Basal LFTs		
Total bilirubin (mg/dl)	2.65	3.10
Direct bilirubin (mg/dl)	1.23	1.81
ALT levels IU/L	58.53	21.03
AST levels IU/L	53.27	20.46
Alkaline phosphatase levels IU/L	406.47	627.88
LFTs at 2 weeks		
Total bilirubin (mg/dl)	0.94	0.55
Direct bilirubin (mg/dl)	0.37	0.30
ALT levels IU/L	39.20	18.08
AST levels IU/L	32.88	11.25
Alkaline phosphatase levels IU/L	251.40	171.40

DISCUSSION

Enteric fever is a common medical ailment of prolonged duration, marked by hectic fever, delirium, persistent bacteremia, enlargement of the spleen, abdominal pain, and a variety of systemic manifestations. The organisms responsible for typhoid fever are salmonella typhi, para typhi A, B, and C. Transmission is via food and water which has been contaminated by the feces and urine of patients and carriers of S. typhi, uncooked and unwashed fruits and vegetables grown in contaminated fields fertilized by human excreta. In its classical form, without treatment, typhoid fever lasts for about four weeks, evolving in a manner consistent with the pathological events. Prompt diagnosis and appropriate therapy interrupt the classic four weeks scenario, producing an aborted illness consisting of little more than a few days of fever and malaise.

The diagnosis of typhoid fever is established by isolating the organism. Blood culture is the primary diagnostic test. It is positive in 90% of patients during the first week and remains positive for several weeks thereafter, if the patient is untreated. Bone marrow culture also has a high yield, even in the treated patients. None of our patients had a positive blood culture, probably due to the antibiotics

started before they were enrolled in the study. The titre of agglutinins (Widal test) against somatic (O) antigen rises during the second and third week of illness. An O titre of 1:80 or more in non-immunized persons is suggestive of typhoid fever, and 1:320 is usually diagnostic in the appropriate clinical setting. There are many false positive and occasionally false negative Widal reactions, so that a diagnosis based on titre rise alone is tenuous1. All patients in our study had a positive Widal test, with associated features of typhoid fever.

Enteric hepatitis presenting as jaundice and elevation of ALT, AST occur in 25% of patients[6]. In our study 5% of patients had laboratory evidence of liver dysfunction. Significant reduction of mean serum bilirubin, AST and ALT levels were seen after 2 weeks of treatment with Novidat coinciding with clinical recovery. No patient in our study developed any significant intestinal or extra intestinal complication of typhoid fever.

The management of typhoid patients remained symptomatic and supportive until the discovery of Chloramphenicol in 1948[7]. It is still the drug of choice in patients with typhoid fever in sensitive strains of salmonella typhi[8]. Treatment with chloramphenicol has definitely shortened the course of acute illness[9]. Amoxicillin has also been used successfully in the treatment of typhoid fever but emergence of resistance appears frequently.

Until recently, resistance was seen only to chloramphenicol but now incidence of multiple drug resistance to salmonella typhi strains has been increasing. This has prompted use of third generation cephalosporins and quinolones.

Quinolones are synthesized chemically, are bactericidal against salmonella typhi and penetrate into phagocytes[5]. Ciprofloxacin, one of the quinolones, has been found to be effective in patients with multi drug resistant typhoid fever[10]. Furthermore, ciprofloxacin has excellent tissue penetration leading to high drug levels in the gall bladder and intestinal mucosa which might aid bacterial eradication and prevent typhoid carrier state.

This study showed that ciprofloxacin is safe and effective in the treatment of enteric fever, well tolerated by all patients, did not require withdrawal due to unacceptable side effects and did not show relapse on short term follow up. This may be an effective way of treatment in resistant cases.

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