Ceftriaxone versus Chloramphenicol for Treatment of Acute Typhoid Fever

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Abstract: Typhoid fever is a global health problem, with an estimated 20 million cases and 700.000 deaths annually. In Egypt, since the beginning of the 1980s, there had been an increase in the prevalence of multidrug resistance to the first line antimicrobials used in the treatment of the disease such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) and thus other drugs , the fluoroquinolones and third generation cephalosporins, had to be evaluated for their efficacy in the treatment and their side effects. The aim of this study was to compare the efficacy of chloramphenicol, which was the classical drug for treatment of acute typhoid fever in Abbassia fever hospital (AFH), with ceftriaxone which became a first line drug for treatment of it after the appearance of multidrug resistant (MDR) isolates of Salmonella typhi (S. typhi)in the last fifteen years. As a part of the study we investigated whether or not the organisms were still sensitive to the quinolones and third generation cephalosporins. We also investigated if multidrug resistant (MDR) typhoid fever was still a problem in Egypt. A phase IV open label, prospective, randomized clinical trial study was implemented in the period between March 2007 and June 2009. Fifty two patients with positive blood culture for S. typhi were included in this study. They were 32 (62%) males and 20 (38%) females ranging in age from 3 to 47 years (mean±SD: 22±8.5years). Drug sensitivity tests showed that 4 (8%) of Salmonella typhi isolates were resistant to chloramphenicol and 18 (35%) and 21 (40%) isolates were resistant to ampicillin and TMP-SMX respectively. Two (4%) isolates were resistant to chloramphenicol, ampicillin and TMP-SMX. No isolates were resistant to ciprofloxacin or ceftriaxone. Twenty seven (52%) patients were treated with chloramphenicol and twenty five (48%) patients were treated with ceftriaxone. All patients were cured. The mean time (mean±SD) for patients to become afebrile was 3.3±1.2 days for ceftriaxone and 5.8±1.2 days for chloramphenicol. In patients treated with ceftriaxone the time taken to become afebrile was shorter with chronic infection as compared to those treated with chloramphenicol(P value= 0.0001 95% CI= 1.831-3.169). From this study, it can be concluded that: ceftriaxone was associated with a significantly shorter period of defervescence making it the drug of choice for treatment of typhoid fever.There is a marked reduction of the prevalence of MDR Salmonella typhi isolates and marked increase in the susceptibility of these isolates to chloramphenicol, returning it to be one of the drugs that could be used in the treatment of acute typhoid fever.No drug resistance to ceftriaxone and ciprofloxacin was reported after many years of using them for treatment of acute typhoid fever.Due to high degree of resistance to ampicillin and TMP-SMX, they should not be used as first line drugs for treatment of acute typhoid fever.

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1. Introduction

Typhoid fever occurs in over 20 million cases annually, with at least 700.000 deaths. The main burden of disease is in developing countries, particularly the Indian subcontinent and South East Asia (1). Historically, the infection was treated with chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole (TMP-SMX). However, the widespread emergence of antibiotic resistant Salmonella typhi (S.typhi) has presented an important public health problem during the past decades (2). In Egypt, chloramphenicol resistant Salmonella typhi was first reported in 1981 (3). Mourad et al. (4) found that 43% of Salmonella typhi isolates at Alexandria fever hospital were multidrug resistant (MDR) isolates. In another study done in Egypt, Wasfy et al. (5) found that 71% of patients with typhoid fever had MDR Salmonella typhi isolates. Recently, Salmonella typhi strains resistant to quinolones and third

generation cephalosporins have been documented by many authors (6-7).

Typhoid fever caused by MDR organisms is a significant public health and therapeutic problem as a large number of cases of MDR typhoid fever occur in childhood and are accompanied with significantly high morbidity and mortality rates (8).

The aim of this study was to evaluate the efficacy of chloramphenicol,which remained for many for many years as the drug of choice for treatment of acute typhoid fever in Abbassia Fever Hospital (AFH) and compare it to ceftriaxone which became the main drug for treatment of typhoid fever after the appearance of MDR isolates in the last fifteen years. As a part of the study we investigated whether or not the organisms were still sensitive to the quinolones and third generation cephalosporins. We also investigated if multidrug resistant (MDR) typhoid fever was still a problem in Egypt.

2. Patients and Methods

A phase IV open label, prospective, randomized clinical study was implemented in the period between March 2007 and June 2009. After having their informed consent to participate in our study, fifty two patients with acute typhoid fever in Abbassia Fever Hospital (AFH) "The main fever hospital in Cairo Governorate, Egypt" were included in this study.

Our Inclusion criteria were to have a diagnosis for typhoid fever with a positive blood culture for Salmonella typhi and a consent to participate in this study. Criteria for exclusion were patients with deteriorated general condition, hyperpyrexia (40.5 C or above), hypotension, meleana, bleeding per rectum and or disturbed level of consciousness

All recruited patients were subjected to: Careful history and thorough clinical examination, complete blood picture. On the day of admission to the hospital before initiation of antibiotic therapy, an aliquot of each patient blood was collected and inoculated onto bi-phasic blood culture bottles and incubated at 37oC. Bottles were checked daily for 7 days and when growth was noted, an aliquot of blood was streaked onto MacConkey and blood agar plates to allow for final identification of the organism by using standard serological and biochemical methods (9).Widal agglutination test was done to all patients (10).

Susceptibility of Salmonella typhi to ampicillin (10 ug), chloramphenicol (30 ug), TMP-SMX (25 ug), ciprofloxacin (5 ug) and ceftriaxone (30 ug) was performed using the disc diffusion Kirby-Bayer method (11).

Twenty seven (52%) patients were randomly allocated to be treated with chloramphenicol (50 mg/kg/day orally or intravenously) given 6 hourly till defervescence (primary outcome measure) and for a further 5 days (secondary outcome measure). The time of defervescence was defined as the time interval from starting an appropriate antimicrobial chemotherapy until the documentation of normal body temperature (8).

Twenty five (48%) patients were randomly allocated to be treated with ceftriaxone parenterally (80 mg/kg/day for children and 2 gm/day for adults) given once daily for 7 days.

Any patient infected with a strain resistant to the drug with which he was being treated, was shifted to another drug to which the isolates were sensitive and was not included in final analysis of results.

Patients presenting with complications (gastrointestinal hemorrhage or perforation, toxic myocarditis, hepatitis) were excluded from the study.

Subjects were randomized with equal distribution to the 2 treatment regimens using block of 6 and randomization envelops were prepared by the biostatician

This study was open label, therefore no blinding procedures were required.

Patient was considered cured if there was no fever,abdominal tenderness,,toxic look or tympanitic abdomen at the end of treatment course.

Statistical analysis:

Regarding our sample size, a time frame was applied to recruit all cases of typhoid fever diagnosed clinically with confirmed laboratory diagnosis from the period between the 1st of March 2007 till the end of June 2009 after signing an informed consent to participate.

Descriptive summaries were presented using summary statistics for continuous (quantitative) variables and frequency for discrete (qualitative) variables.

Data were collected coded and analyzed using SPSS software version 15 under windows XP. Unpaired student t-test was used to compare time of defervescence between those who were treated with chloramphenicol versus ceftriaxone. The threshold of significance was fixed at the 5% level.

No interment analysis was done and the final analysis was conducted at the end of the study after all patients had completed the study protocol.

Ethical Consideration: All patients participating in this study were asked to sign an informed consent form describing all study procedures, risk and benefits. For children and minors "less than 21 years" parent guardian informed consent was taken

3. Results:

Fifty two patients of acute typhoid fever with positive blood culture for Salmonella typhi were enrolled in this study. They were 32(62%) males and 20(38%) females ranging in age from 3 to 47 years (mean±SD 22±8.5 years). The clinical picture of these patients upon admission is shown in table (1).

Table (1) Clinical picture of (52) acute typhoid fever patients

Symptoms	Number (%)		
	Chloramphenicol treated patients No. = 27	Ceftriaxone treated patients No. = 25	Total No. = 52
Fever	27 (100)	25 (100)	52 (100)
Abdominal discomfort	22 (81)	18 (72)	40 (77)
Headache	21 (72)	19 (76)	40 (77)
Epistaxsis	13 (48)	14 (56)	27 (52)
Cough	16 (59)	16 (64)	32 (62)
Vomiting	12 (44)	11 (44)	23 (44)
Diarrhea	9 (33)	8 (32)	17 (33)
Signs			
Fever	27 (100)	25 (100)	52 (100)
Toxic look	21 (78)	22 (88)	43 (83)
Abdominal tenderness	23 (85)	21 (81)	44 (85)
Splenomegaly	22 (81)	18 (72)	40 (77)
Abdominal distension	20 (74)	19 (76)	39 (75)
Hepatomegaly	10 (37)	10 (40)	20 (38)
Jaundice	0	1 (4)	1 (2)

The hematological profile and Widal agglutination test results are shown in table (2). Normal hematological profile was seen in most of the patients. Thirty eight (73%) and forty patients (77%) had anti-O antibody and anti-H titers of $\geq$ 1/160 respectively

Table (2) Haematological profile and Widal agglutination titer of (52) acute typhoid fever patients

Complete blood picture	Range	Mean	
Haemoglobin	5.5-14.8 gm%	11 ± 1.8	
Total white blood cell count	2.3 - 11.4X 10^3 / cmm	5 ± 2.3	
Platelet count	46-458 x 10^3/ cmm	185 ± 87.4	
Widal agglutination titer	Chloramphenicol treated patients (27) No. (%)	Ceftriaxone treated patients (25) No. (%)	Total patients (52) No. (%)
Anti-O = 1/80 - Anti-H = 1/80	1 (4) - 2 (7)	1 (4) - 2 (8)	2 (4%) - 4 (8%)
Anti-O = 1/160 - Anti-H = 1/160	7 (26) - 5 (19)	5 (20) - 5 (20)	12 (23%) - 10 (19%)
Anti-O = 1/320 - Anti-H = 1/320	6 (22) - 9 (33)	5 (20) - 6 (24)	11 (21%) - 15 (29%)
Anti-O = 1/640 - Anti-H = 1/640	8 (30) - 8 (30)	7 (28) - 7 (28)	15 (29%) - 15 (29%)
Anti-O $\geq$ 1/160 - Anti-H $\geq$ 1/160	21 (78) - 22 (81)	17 (68) - 18 (72)	38 (73%) - 40 (77%)

Drug sensitivity tests revealed that 4 (8%) of isolates were resistant to chloramphenicol and 18 (35%) and 21 (40%) isolates were resistant to ampicillin and TMP-SMX respectively. Two (4%) isolates were MDR resistant to chloramphenicol, ampicillin and TMP-SMX. No isolates were resistant to ciprofloxacin or ceftriaxone (table 3).Seven isolates had no resistance to any of the tested five drugs.

Table (3): Antimicrobial susceptibility patterns of 52 Salmonella typhi isolates

Susceptibility pattern	Number of isolates	%
Any resistance		
Chloramphenicol	4	8
TMP-SMX	21	40
Ampicillin	18	35
Ciprofloxacin	0	0
Ceftriaxone	0	0
Multidrug resistance (MDR) to chloramphenicol,TMP- SMX and ampicillin	2	4
Isolates with no resistance to any of the five tested drugs	7	13

There were no reported complications throughout the study.

All patients were cured. The mean time (mean±SD) of defervescence for ceftriaxone and chloramphenicol was 3.3±1.2 and 5.8±1.2 days respectively. P value= 0.0001 95% CI= 1.8-3.2. Ceftriaxone was significantly associated with a short time of defervescence compared with chloramphenicol

4. Discussion

Enteric fever continues to be a major public health problem, especially in the developing countries of the tropics. The sensitivity pattern of S. typhi is changing and there is re-emergence of sensitivity to chloramphenicol but rising resistance to ciprofloxacin (12). In this study, 4%, of the isolated strains of Salmonella typhi were resistant to chloramphenicol, ampicillin and TMP-SMX. In a study done by Mourad et al.(4) MDR Salmonella typhi isolates were detected in 15 (43%) of 35 patients with culture positive S. typhi. Wasfy et al.(5) studied 537 S.typhi isolates collected between 1990-1994 in Egypt; 71% of isolates were MDR. This period represented the peak of MDR reisolates in Egypt. In another study done in Abbassia Fever Hospital, Wasfy et al. (2) reported that MDR Salmonella typhi increased from 19% in 1987 to 100% in 1993, but it subsequently decreased again to only 5% by the year 2000. In Fayoum Governorate "One of Upper Egypt governorates",MDR Salmonella typhi isolates were detected in 26 (29%) of 90 patients with culture positive S.typhi (13). Decline of MDR Salmonella typhi isolates were reported in many studies world wide and was reported to be 5.6% by Chitnis et al. (14), 5% by Pokharel et al. (15), 18.6% by Ray et al. (16) and 22% by Cooke et al. (17). In Imbaba fever hospital, Giza province, Egypt El-Din et al. (18) reported that 25% of Salmonella typhi isolates were resistant to chloramphenicol.

In our study, 8% of the isolates were chloramphenicol resistant. Due to the development of MDR isolates, there was a decrease in the use of chloramphenicol for treatment of typhoid fever in Egypt and this, in addition to the use of more-effective antibiotics could have caused a decrease in the prevalence of persons with chronic infection in the community and hence the circulation of resistant strains. The improvement in susceptibility of Salmonella typhi to chloramphenicol (although its lower performance compared to ceftriaxone), will cause it to be re-considered as one of the drugs of choice for treatment of typhoid fever in Egypt. Similar studies should be considered in some parts of the world where medical resources are limited. Chloramphenicol has a cheaper price and well established efficiency. (2,14,19). In this study, 35% and 40% of isolates were resistant to ampicillin and TMP-SMX respectively and this is in agreement with that reported by Srikantiah et al. (13). Until improvement in the susceptibility of Salmonella typhi to these two drugs, they should not be used as a first line drugs for treatment of typhoid fever. None of our Salmonella typhi isolates were resistant to ciprofloxacin or ceftriaxone. This was in agreement with Wasfy et al. (2) and Ray et al.(16). Resistance to ciprofloxacin (3%) and ceftriaxone (2%) were documented by Srikantiah et al. (13) in the Fayoum governorate,Egypt. Resistance to ciprofloxacin was reported by Butt et al. (20); Capoor et al. (6) and Dimitrov et al. (7).

The main symptoms in our 52 patient with acute typhoid fever were fever (100%), headache (77%), vomiting (44%) abdominal discomfort (77%) cough (62%) and epistaxsis (52%). The main signs were fever (100%), toxic look (83%), abdominal tenderness (85%), abdominal distention (75%), splenomegaly (77%), and hepatomegaly (38%). These symptoms and signs agreed with Abdel Wahab et al. (21)

As regards the blood picture, our patients showed anemia (mean hemoglobin ±SD 11±1.8 gms %), within normal white blood cell count (mean 5±2.3) and within normal blood platelets (mean 185±87.4). Anemia may be due Salmonella endotoxaemia. Within normal white blood cell count is similar to that reported by Abdool Gaffar et al.(22). In accordance with our results, The peripheral blood changes did not influence the outcome of the disease, since all patients recovered completely after treatment (23).

In our patients anti-O $\geq$ 1/160 and anti-H $\geq$ 1/160 titers were detected in 73% and 77% of the patients respectively. This was considered as a

significant titer suggestive of acute typhoid fever in Egypt and this is in agreement with Hassanein et al. (24) and Frimpiong et al. (25).The results of Widal test should be interpreted in concerns with a patients clinical presentation in making a diagnosis of typhoid fever. Both the somatic and flagellar agglutinins are important for this purpose (26).

Both chloramphenicol and ceftriaxone were effective for treatment of our 52 patients with acute typhoid. Ceftriaxone was significantly associated with a shorter time of defervescence compared to chloramphenicol. This agrees with other studies (8, 21).

From this study, we concluded that ceftriaxone was significantly associated with short time of defervescence making it the drug of choice for treatment of acute typhoid fever .There is marked reduction in the prevalence of MDR Salmonella typhi isolates and marked increase in susceptibility of these isolates to chloramphenicol, returning it to be one of the drugs of choice for treatment of acute typhoid fever. No drug resistance to ceftriaxone and ciprofloxacin were reported after many years of using them in the treatment of acute typhoid fever. Due to the high degree of resistance to ampicillin and TMP-SMX, they should not be used as first line drugs for treatment of acute typhoid fever.

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