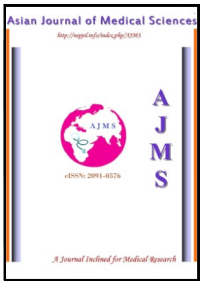
Asian Journal of Medical Sciences 2 (2011) 14-17

ASIAN JOURNAL OF MEDICAL SCIENCES



Salmonella Paratyphi A in India-Changing trends in presentation and antibiotic susceptibility

Sanjay V kulkarni[1], Arun Narayan[1], Vrithmani Aprameya Indumathi[2], Tejas Suresh Rao[1] and Punith Kempegowda[1*]

[1]Department of Medicine, [2]Department of Microbiology, Gokula Metropolis Labs, M S Ramaiah Memorial Hospital, Bangalore-560054, India

Abstract

Objective: Not only has the prevalence of enteric fever due to Salmonella paratyphi A increased over the last decade, there has also been a change in common presenting symptoms and antibiotic sensitivity pattern of these organisms. Knowledge of the existing epidemiology of the disease is essential for a rational approach to treat the same. Hence the present study was done to establish the existing epidemiology of enteric fever due to Salmonella paratyphi A-their common presenting symptoms and antibiotic sensitivity pattern- at our setting.

Material & Methods: This prospective study was conducted in MS Ramaiah Hospitals, Bangalore between January 2008 and December 2008. Patients admitted to the hospital with clinical suspicion of enteric fever and whose blood culture grew paratyphi A were included in the study. Common presenting symptoms and signs were recorded in these patients and the sensitivity patterns of the causative organisms were studied. The difference in their response to Ciprofloxacin and Ceftriaxone was studied. The analysis was done using the statistical software package-SPSS Version 16. The difference in the defervescence period was calculated by 2-way Independent two-sample t-test.

Results: A total 32 patients were included in the study. Fever and hepatomegaly were the most common symptom and sign among the study subjects. All isolates were susceptible to commonly used antibiotics except for Nalidixic acid. The mean defervescence period was shorter in patients treated with Ceftriaxone as compared to those treated with Ciprofloxacin ($p<0.002$).

Conclusion: We report a change in the presentation and antibiotic sensitivity of paratyphi A infection as compared to existing literature. Ceftriaxone is a better drug as choice as it has shorter defervescence time.

Key Words: Salmonella paratyphi A; Ceftriaxone; Ciprofloxacin; Defervescence

1. Introduction

Enteric fever is a major health problem in India accounting for nearly 300,000 cases every year.[1] Although Salmonella enterica serotype Paratyphi A (Paratyphi A) species were classically considered as a minor causative organism of enteric infection, there has been an increase in the proportion of the cases due to this organism lately.[2] Sood et al evaluated the blood culture records in a major tertiary center in North India over a period of 5 years and found the proportion of enteric fever due to Paratyphi A rose from 6.5% in 1994 to 44.9% in 1998.[3]

Ciprofloxacin is considered as the drug of choice for treatment of enteric fever due to Paratyphi A.[4] However, Chandel et al found a sudden surge in Paratyphi A organisms resistant to chloramphenicol and cotrimoxazole and a higher MIC to ciprofloxacin.[5] Harish et al reported a sudden increase in the enteric fever cases caused by S. Paratyphi A with increasingly high level fluoroquinolone resistance in a recent study in South India.[6] Similar reports of increased incidence of drug-resistant Paratyphi A have been reported worldwide.[7-11] In the past few years, increased number of patients with enteric fever tested positive for Paratyphi A at our center. With the reports of changing trends of Paratyphi A and their response to the commonly used antibiotics, this study was conducted to study the common presentation and antibiotic sensitivity pattern of Paratyphi A induced enteric fever at our center.

***Correspondence:**
Dr. Punith K, Department of Medicine, M S Ramaiah Medical College, Bangalore-560054, India. E-mail: drpunith@gmail.com

2. Material and Methods

The study was conducted in M S Ramaiah Hospitals, Bangalore between January 2008 and December 2008. Ethical clearance was obtained from the institution's ethical committee. Subjects aged above 18 years presenting to the Medicine out-patient department with fever of 5 days or more and with clinical suspicion of enteric fever were included in the study. These patients were explained in detail about the study and a written informed consent was obtained from each of the subjects prior to their inclusion in their study. A questionnaire regarding the symptoms and signs of the current illness was completed by the primary physician on the first visit. Evaluation of signs and symptoms was done following the completion of questionnaire.

5-8 ml of venipuncture blood was drawn under aseptic precautions for culture to diagnose the causative organism for the infection. The blood was then transferred into the redox-1 blood culture broth and inserted into the VersaTrek [Trek Diagnostics, USA], a fully automated continuous monitoring non-radiometric blood culture detection system. The detection of colonies was done by standard biochemical and slide agglutination methods.[12]

The antimicrobial susceptibility of the isolates were tested by Kirby- Bauer disc diffusion method on Mueller- Hinton agar for Ampicillin, Aztreonam, Azithromycin, Ciprofloxacin, Ceftriaxone, Cefixime, Chloramphenicol, Co-Trimoxazole, Ofloxacin and Nalidixic Acid [Plateq Labs, India] according to CLSI Guidelines.[13]

All study subjects were treated empirically in such a way that alternate patients received ciprofloxacin [500 mg BD for 7 days] and Ceftriaxone [2g OD for 7 days] intravenously to compare the efficacy of these drugs. Both these drugs are established first line therapeutic agents for empirical treatment of Paratyphi A infection.4 Time to defervescence was defined as the number of days from initiation of treatment until the point at which the temperature became normal and remained so. The subjects whose blood cultures grew Paratyphi A were considered for final analysis.

2.1. Statistical Analysis

The analysis was done using the statistical software package-Version 16 [SPSS Inc., Chicago, USA]. Age, gender, symptoms and signs of patients, antibiotic sensitivity of the organism and defervescence period in the two treatment regimens were included as variables in the model. The difference in the defervescence period was calculated by 2-way Independent two-sample t-test. Two tailed 'p' values below 0.05 were considered significant. The results were tabulated and graphically represented using Microsoft Office for Windows 2007.

3. Results

Overall, 289 patients were screened based on the inclusion criteria during the study period and 32 patients with positive blood culture for Paratyphi A were included in the study. The mean age was 28.38±15.40 years. The mean age of patients receiving Ciprofloxacin and Ceftriaxone was 29.33±20.75 years and 28.80±11.69 years respectively. The overall male: female ratio was 2.56:1

The various symptoms and their frequencies are given in table 1. Fever was a universal symptom among the study subjects. 62.5% of them had intermittent pattern of fever followed by continuous type and remittent type in 25% and 12.5% respectively.

Table-1: common symptoms with which the patients presented

Symptom	Frequency (percent)
Fever	100
Headache	18.7
Vomiting	12.5
Diarrhoea	18.7
Constipation	9.3

Clinical examination was not significant in most of the study subjects. Hepatomegaly was the most common sign in the present study seen in 18.7% of them. The other signs attributed to the Paratyphi A infection in the present study were splenomegaly and jaundice in 12.5% of the study subjects each.

All isolates were sensitive to Aztreonam, Azithromycin, Ciprofloxacin, Ceftriaxone, Cefixime, Chloramphenicol, Co-Trimoxazole and Ofloxacin but were resistant to Nalidixic acid. Drug resistance to Ampicillin was noted in one patient.

20 patients [62.50%] and 12 patients [37.50%] were treated with Ceftriaxone and Ciprofloxacin respectively. The mean defervescence period was shorter in patients treated with Ceftriaxone [mean = 3.85±1.04 days] as compared to those treated with Ciprofloxacin [mean = 5.08±0.90 days] and the difference was statistically significant [$p<0.002$].

4. Discussion

Existing literature states the common presentation of Salmonella enterica serotype Paratyphi A induced enteric fever is mainly gastro-intestinal.[4] Shlim and colleagues reported that while Diarrhea was the presenting symptom in 56% of the patients, headache was almost universal among them.[14] While 33% of them had splenomegaly, liver was not involved in any of their study subjects. In contrast, intermittent fever was the most common pattern of presentation among our study subjects. 18.7% of them presented with Diarrhea and headache. Liver involvement presenting as Hepatomegaly and sometimes with icterus was seen in 18.7% of the patients in the present study. All these findings indicate that the presentation of Paratyphi A infection is probably evolving over time.

The sensitivity pattern in the present study appeared favorable to a variety of antibiotics. All isolates were resistant to Nalidixic Acid in the present study and only one isolate showed resistance to Ampicillin. There was 100% sensitivity to Chloramphenicol, a drug to which high resistance was reported two to three decades ago. Gupta et al reported 92.5% resistance to Nalidixic acid in their study.[7] Similar results have been reported from studies from elsewhere in India.[8,15,16] Gupta et al suggested that replacement of Chloramphenicol by ciprofloxacin as the drug of choice for the treatment of enteric fever would have led to withdrawal of selective pressure resulting in re-emergence of Chloramphenicol sensitivity.[7] But the clinical correlate of this in-vitro sensitivity is yet to be re-established.

It is suggested that Nalidixic acid resistance is a marker of low level resistance to ciprofloxacin and also an indicator of treatment failure to ciprofloxacin.[17] This is due to similar mechanism of resistance for the two drugs.[18] Gupta et al suggested avoiding treatment of enteric fever with ciprofloxacin in Nalidixic acid resistant cases although higher doses may be helpful in a few cases.[7] In the present study, there was 100% resistance to Nalidixic acid, but patients in the ciprofloxacin group showed complete recovery. This indicates that even though the mechanisms of resistance of the two drugs are similar, there are many other factors which significantly contribute to development of resistance.

An extensive review of literature yielded us with no results regarding defervescence in Paratyphi A infection. Dimitrov and colleagues reported a defervescence period of 8 days for ciprofloxacin and 6 days for Ceftriaxone in enteric fever. The longer defervescence period was attributed to decreasing sensitivity to these antibiotics.[19] In the present study, the average defervescence period noted was 3.85 days for Ceftriaxone and 5.08 days for ciprofloxacin. A shorter defervescence period with the use of Ceftriaxone indicates that Ceftriaxone is a better choice for empirical therapy of Paratyphi A infection. But caution is advised as the resistance to antibiotic is on the rise.[20] Also hypersensitivity to Penicillin should also be considered. In such conditions, Azithromycin has been suggested as an alternative.[21] A prompt and compliant course of empiric therapy could help in reducing the morbidity associated with the condition and also prevent resistance to these antibiotics.

Summary: Intermittent fever was the most common presenting symptom in the present study. While Nalidaxic acid resistance was noted in all the isolates, none were resistant to either of the antibiotics under study. The defervescence period was shorter with use of ceftriaxone in comparison with ciprofloxacin.

Limitations: Although data regarding recent antibiotic usage was obtained, history of vaccination in recent past was not considered during data collection. Recent vaccination makes an important confounder in the present study and hence a major drawback. Also, the small sample size of the present study is not sufficient to detect changing pattern in the presentation and antibiotic sensitivity of the Paratyphi A isolates with confidence. A large multi-centric scale study considering all the limitation in the present study is necessary to validate the present findings.

5. Conclusion

The present study reports a changing pattern in the presentation and antibiotic sensitivity of the Paratyphi A isolates, indicating a greater suspicion for the same during the differential diagnosis of similarly presenting conditions and a higher vigilance regarding the antibiotic sensitivity pattern. More has to done in this field at larger scale to unmask the full mystery of these changing patterns.

6. References

1. Lathi N, Sudarsana J. Changing Sensitivity Pattern of Salmonella typhi in Calicut. Calicut Med J 2004;2:e2.

2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004;82:346-53. PMid:15298225 PMCid:2622843

3. Sood S, Kapil A, Dash N, Das BK, Goel V, Seth P. Paratyphoid fever in India: An emerging problem. Emerg Infect Dis 1999;5:483-4. doi:10.3201/eid0503.990329 PMid:10341194 PMCid:2640769

4. Pegues DA, Miller SI. Salmonellosis. In Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine, 17th edition. New York: McGraw Hill. 2008;959.

5. Chandel DS, Chaudhry R, Dhawan B, Pandey A, Dey AB. Drug-resistant Salmonella enterica serotype paratyphi A in India. Emerg Infect Dis 2000;6:420-1. doi:10.3201/eid0604.000420 PMid:10905982 PMCid:2640898

6. Harish BN, Menezes GA, Sarangapani K, Parija SC. Fluoroquinolone resistance among Salmonella enterica serovar Paratyphi A in Pondicherry. Indian J Med Res 2006;124:585-7. PMid:17213529

7. Gupta V, Kaur J, Chander J. An increase in enteric fever cases due to Salmonella Paratyphi A in & around Chandigarh. Indian J Med Res 2009;129:95-8. PMid:19287065

8. Bhattacharya SS, Dash U. A sudden rise in occurrence of Salmonella paratyphi A infection in Rourkela Orissa. Indian J Med Microbiol 2007;25:78-9. doi:10.4103/0255-0857.31077 PMid:17377367

9. Prajapati B, Rai GK, Rai SK, Upreti HC, Thapa M, Singh G, et al. Prevalence of Salmonella typhi and paratyphi infection in children: a hospital based study. Nepal Med Coll J 2008;10:238-41. PMid:19558061

10. Bormann AM, Boulware DR. The trials of the returning traveler: ciprofloxacin failure in enteric fever. Minn Med 2008;91:43-4. PMid:19108546 PMCid:2768140

11. Krishnan P, Stalin M, Balasubranian S. Changing trends in antimicrobial resistance of Salmonella enterica serovar typhi and Salmonella enteric serovar paratyphi A in Chennai. Indian J pathol microbiol 2009;52:505-8. doi:10.4103/0377-4929.56140 PMid:19805957

12. Old DC. Salmonella. In Collee JG, Frazer AG, Marmion BP, Simmons A, editors. Mackie and McCartney Practical Medical Microbiology, 14th Edition. London: Churcill Livingstone. 1996;385-404.

13. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 16th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA. 2006; M100-S16.

14. Shlim DR, Schwartz E, Eaton M. Clinical Importance of Salmonella Paratyphi A Infection to Enteric Fever in Nepal. J Travel Med 1995;2:165-8. doi:10.1111/j.1708-8305.1995.tb00645.x PMid:9815378

15. Tankiwale SS, Agarwal G, Jalgaonkar SV. An unusually high occurrence of Salmonella enterica serotype Paratyphi A in patients with enteric fever. Indian J Med Res 2003;117:10-2.

16. Mendiratta DK, Deotale V, Thamke D, Narang R, Narang P. Enteric fever due to S.paratyphi A - An emerging problem. Indian J Med Microbiol 2004;22:196 PMid:17642734

17. Ray P, Sharma J, Marak RSK, Garg RK. Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolones resistance in Salmonella enterica var Typhi. Indian J Med Res 2006;124:105-8. PMid:16926465

18. Ruiz J, Castro D, Goni P, Santamaria JA, Borrego JJ, Vila J. Analysis of mechanism of quinolone resistance in nalidixic acid resistant clinical isolates of Salmonella serotype Typhimurium. J Med Microbiol 1997;46:623-8. doi:10.1099/00222615-46-7-623 PMid:9236748

19. Dimitrov T, Udo EE, Albaksami O, Al-Shehab S, Kilani A, Shehab M, et al. Clinical and microbiological investigations of typhoid fever in an infectious disease hospital in Kuwait. J Med Microbiol 2007;56:538-44. doi:10.1099/jmm.0.46814-0 PMid:17374897

20. Verma S, Thakur S, Kanga A, Singh G, Gupta P. Emerging Salmonella Paratyphi A enteric fever and changing trends in antimicrobial resistance pattern of salmonella in Shimla. Indian J Med Microbiol 2010;28:51-3. doi:10.4103/0255-0857.58730 PMid:20061765

21. Threlfall EJ, de Pinna E, Day M, Lawrence J, Jones J. Alternatives to ciprofloxacin use for enteric Fever, United Kingdom. Emerg Infect Dis 2008;14:860-861. doi:10.3201/eid1405.071184 PMid:18439388 PMCid:2600221