Rapid communications

TREATMENT FAILURE IN CASE OF TYPHOID FEVER IMPORTED FROM INDIA TO CZECH REPUBLIC, DECEMBER 2008 - JANUARY 2009

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In this report we describe a case of typhoid fever in a Czech patient with history of travel to India and discuss antibiotic treatment failure which led to the relapse of fever.

Case report

Travel history

A previously healthy 31-year-old man from the Czech Republic visited India from 2 October to 28 November 2008. Before leaving the Czech Republic he had received neither vaccination (travellers to India are advised to get vaccinated at least against viral hepatitis A and typhoid fever) nor antimalaric chemoprophylaxis. He climbed the Himalayas, and in the last week of his stay he visited Varanasi at the Ganga River. There, he drunk a soft drink from a cup washed in water of unsure origin at the market place. His travelling companion had the same food without this soft drink, and had no problems afterwards.

A week before returning home the man experienced fever (temperature 40°C), fatigue and vomiting without diarrhoea. While still in India he took ciprofloxacin bought at the chemist's. He returned home on 28 November 2008. On 1 December the patient was examined by his general practitioner and sent to the Department of infectious diseases in Ostrava because of malaria suspicion.

First hospitalisation

After admission malaria was excluded, and hepatosplenomegaly was proved by ultrasonography. Laboratory analyses showed increased C-reactive protein (109 mg/l), and alanine aminotransferase (ALT) was elevated (100.2 U/l). Widal test was repeatedly negative during hospitalisation. On 3 December *Salmonella* sp. was found in blood culture and in stool, and on the next day *Salmonella typhi* (*S. typhi*) was identified.

The patient was first treated by cefotaxime in a dose of 6 g per day. As fever continued, after five days of cefotaxime, ciprofloxacin of 800 mg per day was added. Although fever gradually dropped, the temperature stayed at 38.5°C for 10 days and at 37.5°C for next five days. Laboratory results were subsequently improving (a decline of C-reactive protein and ALT). Cefotaxime was administered for a total of 19 days, ciprofloxacin for a total of 15 days. The patient was discharged on 22 December 2008 after 21 days of hospitalisation and after seven days without fever.

Second hospitalisation

At home the patient was feeling weak but his condition was gradually improving. On 31 December (nine days after leaving hospital), the patient had a new episode of fever (temperature 38.5°C) and on 1 January 2009 he was hospitalised again with the temperature of 39.5°C, fatigue and sweat. Malaria was excluded again. Ciprofloxacin was used in the therapy. As treatment showed no effect on the third day ciprofloxacin was replaced by meropenem, however, despite therapy change the patient's temperature continued to peak daily at 39.5°C. Laboratory analyses showed increasing C-reactive protein (from 42 mg/l to 96 mg/l) and decreasing platelet count (from 195 to 83 x 10⁹/l). Hepatosplenomegaly was proved by ultrasonography again. When *S. typhi* was detected in blood culture again on 5 January 2009 the patient was administered intravenous chloramphenicol in dose of 6 g per day for 17 days. Finally his temperature dropped within 36 hours and the patient started to feel better without further complications. Laboratory results were gradually improving. He was discharged home after 22 days.

Discussion

In endemic areas typhoid fever occurs as asymptomatic or mild illness. According to the World Health Organization the case-fatality rates were 10-20% during the pre-antibiotic era, and can be reduced to less than 1%, with prompt and appropriate antibiotics therapy [1]. Fluoroquinolones had previously been very effective in the treatment of typhoid fever but in the past decade, progressive increase in the minimum inhibitory concentration (MIC) of ciprofloxacin and high incidence of clinical failures to quinolones have been described [2]. The third generation cephalosporins are now being increasingly used but they are associated with a long time of defervescence and high rates of relapses [2].

The annual incidence of typhoid fever in India is 493.5 per 100,000 inhabitants, and quinolones treatment failure is common there [3]. In India there have also been sporadic reports of high-level resistance to ceftriaxone in *S. typhi* and return of sensitivity to chloramphenicol [1,3]. Multi-drug resistance was seen in 32% of strains [4]. There are reports of the emergence of fluoroquinolone-resistant isolates in various part of Asia and descriptions of resistance to third-generation cephalosporins in the same region. However, many of these reports are coupled with evidence of re-

emergence of sensitive isolates in the same region [1]. In South America incidence of fluoroquinolone-resistant strains is low [5].

In the case described in this paper, sensitivity tests performed during the first hospitalisation showed that *S. typhi* had MIC of cefotaxime equal to 0.016 mg/l, of ciprofloxacin 0.250 mg/l and of meropenem 0.016 mg/l. *S. typhi* was sensitive to chloramphenicol, but MIC was not assessed. During the second hospitalisation *S. typhi* had MIC of cefotaxime 0.016 mg/l, of meropenem 0.016 mg/l, of ciprofloxacin 1.000 mg/l, of ampicillin >128.0 mg/l and of cotrimoxazol > 64.0 mg/l. MIC of 0.250 mg/l has been described as resistance to ciprofloxacin [6,7].

In our patient typhoid fever therapy with ciprofloxacin plus cefotaxime showed to be ineffective, despite of adequate dose, duration of therapy and susceptibility to cefotaxime in vitro. Even though the results of blood tests were improving, the temperature declined very slowly and a relapse of typhoid fever appeared two weeks after stopping the treatment. In spite of good sensitivity to meropenem, this agent was also ineffective. Only traditional chloramphenicol actually showed to be effective.

In typhoid fever diagnostics Widal test is very commonly used but has very variable sensitivity and specificity and problems in interpretation [2]. In our patient Widal test was repeatedly negative.

Conclusion

The 2003 World Health Organization guidelines recommend treatment with fluoroquinolones for both complicated and uncomplicated cases of typhoid fever. However, sensitivity profiles of *S. typhi* vary geographically, so the initial antibiotic choice for typhoid fever treatment should be based on the sensitivity data of the area in which the infection was acquired [5]. In a patient returning from India *S. typhi* resistance to quinolones has to be presumed. The third generation cephalosporins represent treatment alternative, although resistance to these drugs is gradually increasing [3]. Chloramphenicol can be an option of antibiotic choice for typhoid fever treatment when another therapy fails.

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