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Case Report

Ciprofloxacin treatment failure in a case of typhoid fever caused by *Salmonella enterica* serotype Paratyphi A with reduced susceptibility to ciprofloxacin

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This report describes a case of ciprofloxacin treatment failure in a patient with enteric fever caused by *Salmonella enterica* serotype Paratyphi A. The organism was isolated from a blood culture from a patient who was treated with oral ciprofloxacin (500 mg every 12 h) for 13 days. The organism showed reduced susceptibility to ciprofloxacin (MIC 0.75 μg ml^{-1}) and was resistant to nalidixic acid. The patient was then placed on intravenous ceftriaxone (1 g every 12 h) and responded within 3 days. The patient was discharged after 9 days on ceftriaxone with no relapse on follow-up. This case adds to the increasing incidence of treatment failures with ciprofloxacin in typhoid fever caused by typhoid salmonellae with reduced susceptibility to ciprofloxacin. It also highlights the inadequacy of current laboratory methods for fluoroquinolone susceptibility testing in adequately predicting *in vivo* activity of ciprofloxacin against typhoid salmonellae and supports calls for new guidelines for fluoroquinolone susceptibility testing of these organisms.

Introduction

Typhoid fever is a major health concern in the developing world. More than 16 million new cases occur worldwide annually, resulting in approximately 600 000 deaths per year (Parry *et al.*, 2002). Previously, typhoid fever was successfully treated with chloramphenicol, co-trimoxazole and ampicillin; however, resistance to these agents has emerged in the last two decades, especially in South and Southeast Asia (Chandel *et al.*, 2000). These developments resulted in the use of fluoroquinolones as the antimicrobial agents of choice for the treatment of typhoid fever (Parry *et al.*, 2002). Subsequently, fluoroquinolone resistance has been reported in some parts of the world (Wain *et al.*, 1997; Threlfall & Ward, 2001; Hakanen *et al.*, 2001). We now report ciprofloxacin treatment failure in a case of enteric fever caused by *Salmonella enterica* serotype Paratyphi A (*Salmonella* Paratyphi A) in Kuwait in a traveller returning from South Asia.

Abbreviation: CLSI, Clinical and Laboratory Standards Institute.

Case report

An 18-year-old female returned to Kuwait from India on 19 May 2005. On 21 May 2005 she developed low-grade fever, mild abdominal discomfort and passed loose motions once or twice daily. She did not seek medical help until 1 June 2005, when she started to run a high temperature ($>38\,^{\circ}C$) and presented at the outpatient clinic of a Kuwaiti hospital. A provisional diagnosis of fever of unknown origin was made, and blood was taken for culture and sensitivity testing. The blood culture yielded growth of *S.* Paratyphi A. Antimicrobial susceptibility testing, performed by the disc diffusion method, reported the isolate as sensitive to ciprofloxacin. On 4 June 2005 the patient was prescribed oral ciprofloxacin in doses of 500 mg twice daily. The patient's clinical condition did not improve after 7 days on ciprofloxacin, and she was referred to the Infectious Diseases Hospital on 11 June 2005 for admission with a 10 day history of continuous fever ($>38\,^{\circ}C$), poorly localized abdominal discomfort, myalgia and hepatomegaly. Blood culture, total blood count, urinalysis, Widal test and blood film for malaria parasites were ordered on admission. Her total leucocyte count was $8.5\times10^{9}\,l^{-1}$. Urinalysis was normal, and thin and thick film examinations of the

peripheral blood were negative for malaria parasites. The Widal test showed a titre of 1 : 160 against O (somatic) antigen and 1 : 10 240 against H (flagella) antigen of *S.* Paratyphi A, and blood culture yielded growth of *S.* Paratyphi A.

The antimicrobial susceptibility of the isolate was tested by the Kirby–Bauer disc diffusion technique according to the criteria of the Clinical and Laboratory Standards Institute (CLSI), formerly the National Committee for Clinical Laboratory Standards (National Committee for Clinical Laboratory Standards, 2005). The antimicrobial agents tested were chloramphenicol (30 μg), co-trimoxazole (1.25/23.75 μg), ampicillin (10 μg), nalidixic acid (30 μg), ciprofloxacin (5 μg) and ceftriaxone (30 μg). The MIC of ciprofloxacin was determined by the E-test method, according to the manufacturer's instructions. The isolate was sensitive to ampicillin, chloramphenicol, co-trimoxazole, ciprofloxacin and ceftriaxone, and resistant to nalidixic acid by the disc diffusion method. It had a ciprofloxacin MIC of 0.75 μg ml^{-1}, which suggested reduced susceptibility to ciprofloxacin.

The patient remained febrile after 13 days of oral administration of 500 mg ciprofloxacin twice daily. Due to her failure to respond to treatment with ciprofloxacin, intravenous ceftriaxone (1 g every 12 h) was administered and the patient responded within 3 days. She was discharged after 9 days on ceftriaxone therapy. The patient did not relapse on follow-up.

Discussion

This case highlights two important points. The first is the increasing incidence of treatment failures due to infection with typhoid salmonellae with reduced susceptibility or resistance to the fluoroquinolones. The first case of ciprofloxacin-resistant typhoid fever was reported in 1992 in the United Kingdom (Umasankar *et al.*, 1992). Since then, similar cases have been reported from other countries (Wain *et al.*, 1997; Threlfall & Ward, 2001; Hakanen *et al.*, 2001). Although reduced susceptibility to ceftriaxone and ciprofloxacin has been reported previously for *Salmonella enterica* serotype Typhi and *S.* Paratyphi A isolated in Kuwait (Dimitrov *et al.*, 2005), this report describes a case of ciprofloxacin treatment failure in a patient with enteric fever who had recently returned to Kuwait from India. The isolate in this report is different from that reported previously because it is susceptible to ceftriaxone whereas the isolates reported previously expressed reduced susceptibility to ceftriaxone (Dimitrov *et al.*, 2005). Treatment failures with fluoroquinolones in patients infected with *S.* Typhi with reduced susceptibility to ciprofloxacin have also been reported from Cameroon in Africa (Nkemngu *et al.*, 2005) and Bangladesh in Asia (Asna *et al.*, 2003). As the fluoroquinolones are the most effective antimicrobial agents for treating enteric fevers (Parry *et al.*, 2002), emergence of resistance against them is of major concern. The spread of this resistance would leave only the less effective but more expensive third-generation cephalosporins for treatment of typhoid (Parry *et al.*, 2002; Wain *et al.*, 1997).

Second, this report highlights the inadequacy of current laboratory methods for the detection of clinically significant resistance of typhoid salmonellae to fluoroquinolones and their failure to adequately predict the *in vivo* activity of ciprofloxacin against typhoid salmonellae.

In our patient, clinical failure resulted from treatment with ciprofloxacin even though the MIC was 0.75 μg ml^{-1}, which is below the cut-off for resistance according to CLSI guidelines. Similar observations have been made in other countries (Wain *et al.*, 1997; Threlfall & Ward, 2001; Hakanen *et al.*, 2001). Considering the absence of correlation between the MICs of fluoroquinolones and the therapeutic response in typhoid fever, as demonstrated in this report, a revision of breakpoint MIC values of ciprofloxacin for typhoid salmonellae is urgently required. Although fluoroquinolone resistance can be caused by several mechanisms, including alterations in the target enzymes (DNA gyrase, composed of subunits encoded by *gyrA* and *gyrB*, and topoisomerase IV, composed of subunits encoded by *parC* and *parE*), an efflux mechanism and decrease in the drug's permeability, mutations in the subunit of DNA gyrase encoded by *gyrA* have been shown to play a major role in quinolone resistance in salmonellae (Piddock, 2002; Poutanen & Low, 2003). It has also been demonstrated that *Salmonella* isolates with reduced susceptibilities to ciprofloxacin (MIC $\geqslant$0.125–1 μg ml^{-1}) typically have single amino acid substitutions in the subunit of DNA gyrase encoded by *gyrA* and are almost always resistant to nalidixic acid with MIC $\geqslant$32 μg ml^{-1} (Hakanen *et al.*, 1999; Giraud *et al.*, 1999). Therefore the proposals by Hakanen *et al.* (1999) and Poutanen & Low (2003) to revise ciprofloxacin breakpoint values for typhoid salmonellae as follows should be considered: $<$0.125 μg ml^{-1} as susceptible; $\geqslant$0.125–1 μg ml^{-1} as reduced susceptibility (low-level resistance); and $>$1 μg ml^{-1} as resistant. Similarly, a new criterion for interpreting disc diffusion for ciprofloxacin for typhoid salmonellae is required. In this regard, some authors have reported a correlation between resistance to nalidixic acid and reduced susceptibility to ciprofloxacin and other fluoroquinolones (Wain *et al.*, 1997; Hakanen *et al.*, 1999). Therefore, routine testing of nalidixic acid susceptibility with a disc content of 30 μg can serve as a useful surrogate test for fluoroquinolone resistance (Hakanen *et al.*, 1999). Even with adoption of the new recommended MICs for fluoroquinolones against typhoid salmonellae, MICs would have to be correlated with inhibition zone sizes by the disc diffusion technique and the clinical response in infection with these organisms.

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