

Widal agglutination test was reactive only to *S. typhi* H with a titre of 1/160 on

discharge. A follow-up stool culture one month later failed to grow any Salmo-

nella microorganisms.

Commentary

As far as this case is concerned, several aspects of typhoid fever treatment with ciprofloxacin require comment. The first point is the treatment failure causing an early relapse. After finishing one week of treatment this patient, who was initially only readmitted to the hospital for upper gastrointestinal pain after switching from IV to oral ciprofloxacin, began experiencing chills at night and had a slightly increased body temperature. Although, on readmission, his CRP was near normal and no antimicrobial was administered due to the adverse gastrointestinal reaction, the next day his CRP was markedly elevated indicating a possible clinical relapse of typhoid fever. The *S. typhi* IgM test was positive and the antimicrobial treatment was switched from ciprofloxacin to levofloxacin. Intravenous levofloxacin was administered since from previous experience IV ciprofloxacin did not cause any adverse gastrointestinal effects. His blood biochemistry results also showed increased transaminases and an increased total bilirubin. A comment will be made on this finding after discussing the clinical failure of treating typhoid fever with ciprofloxacin. Two points need to be taken into consideration. Firstly, the relapse occurred because of the interrupted administration of ciprofloxacin due to the severe gastrointestinal problems that the patient experienced and, secondly, this relapse occurred early and probably was due to reduced sensitivity of *S. typhi* to ciprofloxacin. Following many years of ciprofloxacin use, it is well known that the sensitivity of *S. typhi* to ciprofloxacin gradually declined. Also, in our randomized multicenter study comparing the clinical efficacy of levofloxacin with ciprofloxacin (11), it was found that in the cases that were finally diagnosed as typhoid fever, in the ciprofloxacin group it took on average five days until normalization of body temperature while in the levofloxacin group, it took only 3 days (Table 1). After initial administration of IV levofloxacin, 500 mg, and following resolution of his gastrointestinal complaints by the third day, a switch was made to oral administration. Following this treatment, the patient made an excellent recovery. There were no aggravating gastrointesti-

nal complaints during his course of treatment with oral levofloxacin. The *S. typhi* IgM that became negative was re-confirmed by a PCR test for *S. typhi* which showed that his typhoid infection had been completely cured. Levofloxacin is also very effective against the whole spectrum of Gram-negative microorganisms and it also exhibits excellent pharmacokinetic and pharmacodynamic properties (12, 13).

The second aspect for discussion is the adverse reaction the patient experienced during ciprofloxacin treatment which was the main cause of his readmission to hospital. The patient described his epigastric distress as a feeling of compression from all sides of his stomach preventing him eating properly because he readily vomited any food he managed to swallow. The possibility of a *H. pylori* infection was ruled out because of negative results for both *H. pylori* IgG and IgM. Previously, he had never had any stomach problems. The ciprofloxacin was discontinued on his readmission and, as his CRP was nearly normal, no other antimicrobials were given. This gastrointesti-

nal type of adverse reaction to ciprofloxacin has been recorded ever since its first clinical use and has occasionally prompted its discontinuation. The results of a randomized single-blind multicenter study (11) comparing safety and efficacy in patients with uncomplicated typhoid fever in Indonesia showed that there was a significantly lower number of gastrointestinal reactions in the levofloxacin-treated patients compared to those receiving ciprofloxacin. There were also cases where ciprofloxacin treatment needed to be stopped suddenly compared with no cases in the levofloxacin group where treatment for this kind of condition was surprisingly well tolerated. As typhoid fever is a gastrointestinal infection, drugs causing adverse reactions in the gastrointestinal tract may result in the interruption of treatment because of aggravation of intestinal complaints. This is actually what happened to cases in this large study comparing ciprofloxacin with levofloxacin for uncomplicated typhoid fever (Table 2). From the findings already described regarding the treatment of typhoid fever, levofloxacin may be a bet-

Table 1. A randomized single-blind multicenter study comparing the clinical efficacy of levofloxacin with ciprofloxacin for the treatment of typhoid fever

Clinical efficacy	No. of patients	
	Levofloxacin (n=53)	Ciprofloxacin (n=54)
Average defervescence (days)	3	5
Fever-free at day 7 (%)	100	77.8
Clinical relapse	1	1
Others (relapse)	0	1

Presented at the 55th Annual Meeting of the ASTMH, Atlanta, USA, November 2006. Adapted from reference (11).

Table 2. Comparison of adverse reactions in a randomized multicenter study comparing levofloxacin with ciprofloxacin for the treatment of typhoid fever

Adverse reaction	No. of patients	
	Levofloxacin (n=54)	Ciprofloxacin (n=56)
Nausea	5	4
Vomiting	1	2
Nausea + vomiting	0	4
Epigastric pain	0	2
Insomnia	4	2
Cephalgia	0	1

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ter choice than ciprofloxacin because of its excellent proven clinical efficacy and lower incidence of adverse gastrointestinal reactions in this kind of infection. An analysis of the toxicity profile of fluoroquinolones supports this finding (14).

The third aspect of interest this case was the fact that although the patient became afebrile the increased liver transaminase SGPT on admission did not return to normal but increased slightly after his temperature returned to normal. Subsequently, when the patient was readmitted, his SGPT increased to over 10 times the upper limit of normal and his bilirubin also increased. This event may be a possible dual reaction that caused hepatic insufficiency due to both an adverse reaction to ciprofloxacin and a possible complication involving the hepato-biliary system due to typhoid fever. However, as has been reported by Aggarwal et al, the possibility of cholestasis caused by ciprofloxacin should be considered (15). This third aspect of hepatic problems is very interesting and it would be useful to discuss it more in depth. However, no hard evidence is currently available on the performance of ciprofloxacin in cases where hepatic problems are present. As reported by Parry et al, the levels of liver enzymes in typhoid fever are usually two to three times the upper limit of normal (16). This was exactly what happened in the case of our patient when he was admitted. Although his condition improved, his SGPT was still slightly elevated on his discharge on day 6. In addition, a very interesting result emerged from the study comparing the treatment of uncomplicated typhoid fever with either ciprofloxacin or levofloxacin. In the group of typhoid fever patients treated with ciprofloxacin there was a significantly higher number of patients with increased liver transaminases compared with those treat-

Table 3. Laboratory reactions in a comparative study of levofloxacin vs. ciprofloxacin for the treatment of uncomplicated typhoid fever

Laboratory reaction	No. of patients	
	Levofloxacin (n=54)	Ciprofloxacin (n=56)
Hematologic	None	None
Renal	None	None
Hepatic (> 3 fold increase in SGPT)	2	6

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Adapted from reference (11).

ed with levofloxacin (6 vs. 2, Table 3). Typhoid fever itself may cause hepatic complications that will be marked by an increase in bilirubin with liver transaminases that are only slightly increased. In 10 cases of typhoid hepatitis reported by Khosla SN, the total serum bilirubin ranged from 2.0 to 7.2 mg while the SGPT was between 80–186 IU (17). In the present case, a complication of typhoid fever may have occurred after the failure of ciprofloxacin to completely eradicate *S. typhi*. However, looking at the very high SGPT, it seems more likely that an adverse hepatic reaction occurred. After the infection was neutralized by levofloxacin, the bilirubin values slowly returned to normal as did the liver transaminases which prolonged the hospitalization of the patient. Whether this could have been avoided by initial immediate institution of levofloxacin treatment is a very good point for discussion. The findings of Harding and Simpson regarding the low potential of levofloxacin to cause adverse hepatobiliary reactions should be stressed in this kind of situation (18). As already reported, the efficacy of levofloxacin for the treatment of typhoid fever is excellent, and in 2 trials involving an open study and a comparative study with ciprofloxacin, it was found that all the patients in the levofloxacin group were free of fever by day 6, averaging 3 days without any

post-treatment carrier state, and the relapse rate was no different from that in the ciprofloxacin group (11, 19). Also, no severe adverse gastrointestinal reactions were noted during the use of levofloxacin while, in the ciprofloxacin group, the number of adverse gastrointestinal reactions was significantly higher resulting in more withdrawals of treatment. Also, in the cases of liver insufficiency, there seems to be less chance of such problems in the levofloxacin group compared with the ciprofloxacin group. We have to remember that the typhoid fever cases may already have had liver function impairment when admitted to hospital. In the case presented above, all sero markers for hepatitis A, B and C were negative proving that the deterioration in liver function may not have been caused by a co-infection of hepatitis viruses but could possibly be attributed to the drug that was used together will possible late hepatic complications of typhoid fever.

It looks as if there is a bright future for the early use of levofloxacin in typhoid fever patients in general and, especially, in patients with impaired liver function. The chance of levofloxacin exacerbating this condition is significantly smaller compared with the use of ciprofloxacin while, at the same time, levofloxacin offers a very high level of clinical efficacy with a minimal number of adverse gastrointestinal reactions.

Summary

A case was presented describing the treatment failure of typhoid fever with ciprofloxacin, along with gastrointestinal and hepatic adverse reactions resulting in

prolonged morbidity and hospitalization. The case was finally treated with levofloxacin producing excellent results and rapid hospital discharge. It appears that typhoid fever can be better treated with

levofloxacin because of its dual features of high efficacy and lower rate of adverse reactions compared with ciprofloxacin especially in infections due to *S. typhi*.

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