Salmonella Excretion after Cessation of Tosufloxacin Therapy in Acute Nontyphoid Salmonella Enterocolitis

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Symptomatic nontyphoid salmonella enterocolitis patients were treated with tosufloxacin (TFLX) at oral doses of 150 mg three times a day for 5 to 7 days, but bacterial relapse without symptoms occurred in 85% of the patients within 15 days after the cessation of therapy. Our study indicates that TFLX may not be an ideal drug against symptomatic salmonella enterocolitis from a bacteriological point of view.

Salmonella spp. (other than Salmonella enterica serovars Typhi and Paratyphi A), a group of intracellular bacteria that invade host cells and grow, are a very important concern in Japan since they cause many cases of enterocolitis, a few of which are fatal. Nontyphoid salmonella enterocolitis is now endemic in Japan and is considered an important problem both clinically and for public health in general. Antimicrobial treatment against nontyphoid salmonella enterocolitis has not been recommended, since it brings about little improvement in the clinical course of the infection and may in fact prolong the Salmonella carriage state (3, 6). However, the administration of ciprofloxacin (CIP), a fluoroquinolone, produced clinical improvement in salmonella enterocolitis in a double-blind randomized placebo-controlled trial (9), and norfloxacin and ofloxacin, two other fluoroquinolones, were also reported to be effective against the disease (4, 10).

Although mild acute nontyphoid salmonella enterocolitis is generally a self-limiting infectious disease and most patients with mild symptomatic salmonella enterocolitis do well without antimicrobial agents, patients with severe conditions are often treated with antimicrobial agents, mainly fluoroquinolones. Unfortunately, a high percentage of patients treated with antimicrobial agents have been noted to undergo bacterial relapse 1 to 3 weeks after completing the drug therapy (5, 9). Tosufloxacin (TFLX), a fluoroquinolone antimicrobial agent with an excellent MIC against Salmonella spp. in vitro (1, 7), came into wide use against salmonella enterocolitis in Japan after it was demonstrated to yield good clinical results against symptomatic nontyphoid salmonella enterocolitis when administered for 7 days (2). However, it remains unknown whether bacterial relapse occurs after the cessation of TFLX therapy, and it is important to answer this question, since many patients with salmonella enterocolitis are treated with TFLX. We treated patients with symptomatic nontyphoid salmonella enterocolitis with TFLX and examined their stool samples for Salmonella during and after the cessation of TFLX therapy. We describe here the details of our study.

Sixty-one Japanese patients with acute nontyphoid salmonella enterocolitis, all over 15 years old, were hospitalized at the Department of Infectious Diseases of the Tokyo Metropolitan Bokutoh General Hospital due to frequently watery diarrhea, abdominal pain, and/or fever from May 1991 to September 1999. All patients were diagnosed by confirming the presence of Salmonella spp. (other than Salmonella serovars Typhi and Paratyphi A) in their stool samples. Most of them were treated with TFLX administered orally. Of these patients, we were able to monitor 21 who were treated with TFLX at an oral dose of 150 mg three times a day for 5 to 7 days, i.e., a standard dose of this compound against nontyphoid salmonella enterocolitis in Japan. The patients were monitored bacteriologically by stool culturing every day during TFLX administration and once or twice during each of three 5-day periods after the cessation of drug administration, i.e., days 1 to 5, days 6 to 10, and days 11 to 15, at the outpatient clinic using the same culturing technique. Based on the stool culture results, the cumulative Salmonella relapse rate was calculated.

The characteristics of the 21 patients are shown in Table 1. Although 6 of these 21 patients had accompanying acute renal failure, their serum blood urea nitrogen and creatinine levels returned to within normal limits in a few days by dripped intravenous water transfusion. Ten of these 21 patients were examined by ultrasonography to determine whether they had cholelithiasis. One patient was excluded from this retrospective review because he continued to excrete Salmonella bacteria during and after the cessation of TFLX administration, with the reappearance of fever 4 days after the cessation of therapy. The symptoms of the other 20 patients disappeared during or soon after the cessation of TFLX therapy, and these 20 patients were free from symptoms at their visits to the outpatient clinic.

The stool cultures of these 20 patients became negative for Salmonella within 3 days (mean, 1.4 days) from the beginning of TFLX administration and remained negative throughout the administration period. Bacterial relapse without symptoms occurred in 85% of patients within 15 days after the cessation of TFLX administration. The results are shown in Fig. 1. Bacterial relapse was not associated with the serotype of Salmonella, and no significant difference for bacteriological relapse was found between patients with and without renal failure. None of the patients investigated by abdominal ultrasonography had cholelithiasis.

TFLX has been used to treat many infectious diseases caused by Enterobacteriaceae in Japan, and its excellent clinical...
effect against them has been proved (1). The potent anti-
Salmonella activity of TFLX has been shown to be due not only
to its high activity against Salmonella in vitro but also possibly
to its ability to penetrate into tissue culture cells of human origin. Antimicrob.
Agents Chemother.

Since bacterial relapse occurred within 3 weeks after the ces-
sation of CIP treatment in 4 of 16 nontyphoid salmonellosis
patients treated with TFLX for 5 to 7 days. The mechanism of asymp-
tomatic Salmonella relapse in stools is not known, and our
study did not deal with it. However, since the results of our
study indicate that the administration of TFLX for 5 to 7 days
is not an ideal antimicrobial treatment for symptomatic non-
typhoid salmonella enterocolitis bacteriologically, TFLX may
have only limited efficacy in eradicating Salmonella in stools.
Since bacterial relapse occurred within 3 weeks after the ces-
sation of CIP treatment in 4 of 16 nontyphoid salmonellosis
patients (9), patients treated with TFLX may have a stronger
tendency to become asymptomatic Salmonella carriers than
patients treated with CIP. However, further studies are needed
to examine this point.

Since no significant difference in bacteriological relapse was
found between patients with and without renal failure in our
study, Salmonella relapse may be unrelated to the severity of the
illness. Further studies on the association between disease
severity and bacteriological relapse rate should be done with
larger patient populations. Moreover, since it has been re-
ported that typhoid fever patients can be cured clinically and
bacteriologically by the administration of 150 mg of TFLX
orally 4 times daily for 14 days (8), we speculate that the high
relapse rate in our study may have been due to the low dose of
TFLX administered. Further investigation is needed to deter-
mine whether a higher dose of TFLX or a prolonged treatment
period can overcome nontyphoid Salmonella relapse.

REFERENCES
acute enteritis. Kansenshogakuzashi 63:593–605. (In Japanese with Eng-
lish abstract.)
(tosufloxacin tosylate) on Salmonella enteritis, and fecal drug concentra-
tion and change in the fecal microflora in the acute diarrheal patients. Kansens-
salmonellosis on the fecal excretion of salmonellae. N. Engl. J. Med. 281:
636–640.
1989. Norfloxacins vs. trimethoprim-sulfamethoxazole in the treatment of
5. Neil, A. M., S. M. Opal, J. Heelan, R. Giusti, J. E. Cassidy, R. White, and
K. H. Mayer. 1991. Failure of ciprofloxacin to eradicate convalescent fecal
excretion after acute salmonellosis: experience during an outbreak in health
ment of Salmonella gastroenteritis with ampicillin, amoxicillin, or placebo.
Intracellular activity of tosufloxacin (T-3262) against Salmonella enteritidis
and ability to penetrate into tissue culture cells of human origin. Antimicrob.
administration of fluoroquinolones in the treatment of typhoid fever and
82(Suppl. 4A):329–332.

TABLE 1. Characteristics of symptomatic nontyphoid salmonella
enterocolitis patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>12/9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>16–75 (mean, 45.6)</td>
</tr>
<tr>
<td>Serotype of Salmonellab</td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>4</td>
</tr>
<tr>
<td>07</td>
<td>4</td>
</tr>
<tr>
<td>08</td>
<td>1</td>
</tr>
<tr>
<td>04</td>
<td>1</td>
</tr>
<tr>
<td>016</td>
<td>1</td>
</tr>
<tr>
<td>Symptoms on admission</td>
<td></td>
</tr>
<tr>
<td>Watery diarrhea</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21</td>
</tr>
<tr>
<td>Fever (≥38°C)</td>
<td>18</td>
</tr>
<tr>
<td>Acute renal failurec</td>
<td>6</td>
</tr>
</tbody>
</table>

* Number of patients (n = 21), unless otherwise indicated.

b Other than Salmonella serovars Typhi and Paratyphi A.

c Serum levels of blood urea nitrogen of ≥40 mg/dl and of creatinine of ≥1.7
mg/dl.

FIG. 1. Cumulative Salmonella relapse rate after cessation of
TFLX administration.