Brief reports

Eradication of non-typhoid salmonellae in acute enteritis after therapy with ofloxacin for 5 or 10 days

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Eradication of non-typhoid salmonellae was evaluated in a randomized, double-blinded study of 49 patients with acute enteritis after therapy with ofloxacin 400 mg once daily for 5 or 10 days. Early eradication of salmonellae was found in 57\% of patients in the 5 day therapy group and in 74\% of patients in the 10 day therapy group. This difference was larger among severely ill patients. Together with our previous study of ofloxacin therapy for 3 days or placebo, this shows that early eradication of non-typhoid salmonellae increases with duration of ofloxacin therapy without an increase in persistence of salmonellae in stools or development of resistant strains.

\section*{Introduction}

Antimicrobial therapy of acute bacterial enteritis remains controversial.\textsuperscript{1} Although they have high activity against enteropathogenic bacteria \textit{in vitro}, a number of antimicrobial agents have little or no effect on eradication \textit{in vivo}.\textsuperscript{2,3} The quinolones, with high activity and favourable bioavailability, may offer a better opportunity for treatment of acute bacterial enteritis.\textsuperscript{4} The clinical efficacy of these agents in acute salmonella enteritis has been demonstrated in placebo-controlled studies,\textsuperscript{5,6} but bacteriological efficacy has been disappointing.\textsuperscript{7} Prolonged persistence of non-typhoid salmonellae in stools after quinolone therapy has been reported.\textsuperscript{7}

In an earlier study,\textsuperscript{5} 39 patients with acute salmonella enteritis were randomized to receive either the quinolone ofloxacin 400 mg od for 3 days or placebo. The ofloxacin group showed clinical improvement earlier than the placebo group, but at the end of therapy the eradication of salmonellae from stools was similar in the two groups. The aim of the present study was to examine the effect of ofloxacin 400 mg od for 5 or 10 days on eradication of non-typhoid salmonellae.

\section*{Materials and methods}

\subsection*{Patients}

The recorded clinical history included age and gender, country of salmonella acquisition, duration of illness, maximum body temperature, presence of shivering, maximum number of loose stools per day, blood in stools and abdominal pain during the illness. The study was approved by the Regional Committee for Ethics in Medical Research; informed consent was given by all patients before therapy.

\subsection*{Inclusion and exclusion criteria}

Patients aged \geq18 years with acute enteritis and three or more unformed stools per day on inclusion were recruited. Forty-nine patients with non-typhoid salmonellae isolated from stools were included for ofloxacin therapy, follow-up and final evaluation. During the week before inclusion they had received no antimicrobial therapy. None of the patients recruited had to be excluded from the study because of lack of follow-up, contraindication of quinolones or other medical reasons.

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Study design

Thirty and 19 patients were randomized, double blinded, to 400 mg ofloxacin od for 5 days (ofloxacin for 5 days followed by placebo for 5 days) or 10 days, respectively. Stool samples were collected at the beginning of therapy, on days 7, 12, 19, 26 and 40 (all ±1 day) after initiation of therapy and weekly thereafter until salmonellae were absent from three subsequent samples. Except for two missing samples in the 5 day therapy group, all samples were available for culture. The patients received no other antimicrobial therapy during the follow-up period.

Bacteriological studies

Salmonella isolates were identified by routine bacteriological methods and serotyped using antisera from Behring Diagnostics, Frankfurt, Germany. Susceptibility to ofloxacin was determined by the Etest (AB Biodisk, Solna, Sweden).8 Isolates with MICs of ≤0.5 mg/L were recorded as susceptible, those with MICs between >0.5 and <8.0 mg/L as intermediate and those with MICs of ≥8.0 mg/L as resistant.9

Evaluation criteria

The outcome was defined as ‘early eradication’ when no salmonellae were isolated from stool samples at the end of therapy or at subsequent follow-up examinations. The outcome was defined as ‘failure’ if salmonellae were found in stools at the end of therapy or at subsequent follow-up examinations.

Statistical analysis

Fisher’s exact test (two-tailed) was applied for statistical analysis; $P$ values ≤0.05 were regarded as significant.

Table. Eradication of non-typhoid salmonellae related to duration of ofloxacin therapy and pretherapy symptoms, and persistence of salmonellae at 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
<th>5 days of therapy ($n = 30$)</th>
<th>10 days of therapy ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early eradication of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>salmonellae (all)</td>
<td></td>
<td>17/30 (57)</td>
<td>14/19 (74)</td>
</tr>
<tr>
<td><em>Salmonella enteritidis</em></td>
<td></td>
<td>9/19 (47)</td>
<td>5/8 (63)</td>
</tr>
<tr>
<td>other salmonella serotypes</td>
<td></td>
<td>8/11 (73)</td>
<td>9/11 (82)</td>
</tr>
<tr>
<td>Eradication related to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abdominal pain</td>
<td></td>
<td>9/20 (45)</td>
<td>10/11 (91)</td>
</tr>
<tr>
<td>maximum 3–9 stools/day</td>
<td></td>
<td>8/11 (73)</td>
<td>4/6 (63)</td>
</tr>
<tr>
<td>maximum ≥10 stools/day</td>
<td></td>
<td>9/20 (45)</td>
<td>10/12 (83)</td>
</tr>
<tr>
<td>Persistence of salmonellae at 6 weeks</td>
<td></td>
<td>5/28a (18)</td>
<td>2/19 (11)</td>
</tr>
</tbody>
</table>

*For two patients there was no stool sample at 6 weeks.
had severe diarrhoea (>10 stools/day) and 31 (63%) had abdominal pain. In the patients with abdominal pain, early eradication of salmonella was achieved in 45% (9/20) and 91% (10/11) of those treated for 5 and 10 days, respectively \( (P = 0.02) \). Patients with >10 stools per day experienced 45% (9/20) and 83% (10/12) eradication when treated for 5 and 10 days, respectively \( (P = 0.06) \) (Table).

The main reasons for clinicians not initiating antimicrobial therapy in acute salmonella enteritis have been: the low clinical and bacteriological efficacy; the prolongation of salmonella carriage after therapy; and the fear of development of drug resistance.\(^1\) In our study, the persistence of salmonella isolated from stools 6 weeks after the start of therapy was not significantly different between the groups: 18% (5/28) in the 5 day therapy group and 11% (2/19) in the 10 day therapy group \( (P = 0.68) \). All these patients were followed weekly until three subsequent negative cultures were obtained, the last one being 18 weeks after the start of therapy.

All but two strains isolated before, during and after therapy were fully susceptible to ofloxacin. These two strains were immediately susceptible; one isolate with intermediate susceptibility was eradicated at the end of therapy. The other strain persisted; the MIC of this isolate was 1.0 mg/L initially and 6.0 mg/L after 5 days of therapy; four subsequent isolates had MICs of 0.75–1.5 mg/L. Except for this, the susceptibility of isolates after therapy was the same as that before therapy in both therapy groups. S. enteritidis had susceptibility patterns similar to those of the other salmonella strains. Resistance of salmonella to quinolones can develop during treatment. Therefore, we recommend that every post-therapy isolate should be monitored for changes in MIC. Salmonella typhimurium DT104, which is often resistant to quinolones, was not observed in the present study.

Although acute salmonella enteritis may, for some patients, cause great inconvenience and disability, it is usually a self-limited disease in otherwise healthy individuals, and the use of antimicrobial therapy is controversial. Accordingly, such therapy should be based on age, presence of underlying diseases, severity of clinical symptoms and the objective of therapy: whether to avoid serious complications of infection (septicaemia or even death), to achieve early relief of clinical symptoms or to shorten shedding and spread of salmonella.\(^1\) Our previous study\(^5\) and the present one demonstrate that early eradication of non-typhoid salmonelae increases with duration of ofloxacin therapy without a concomitant increase in the persistence of salmonelae in stools or development of resistant strains. Severely ill patients seem to benefit more from 10 days of ofloxacin therapy than from 5 days of therapy.

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References


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