Effect of fluoroquinolones on body temperature of mice

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Objectives: The purpose of this study was to assess the effect of fluoroquinolones on rectal temperature of infected and non-infected mice.

Methods: The effect of fluoroquinolone administration on rectal temperature was investigated in a mouse model with and without infection.

Results: Hypothermia was induced by administration of gatifloxacin at doses of 1 and 10 mg/kg in non-infected mice, but not by cefditoren pivoxil. In addition, the rectal temperature was decreased in infected mice administered fluoroquinolones or cephems, a greater decrease being noted in animals receiving the former agents.

Conclusions: This study shows that fluoroquinolones decrease the rectal temperature of mice regardless of infections.

Keywords: hypothermic effect, mouse model, CAP, community-acquired pneumonia

Introduction

Community-acquired pneumonia (CAP) is an important disease, with as many as 50 000 patients admitted to hospitals in the UK every year.1 The response of the patients to treatment is generally monitored by daily measurement of the body temperature, heart rate, respiratory rate and blood pressure until discharge from the hospital or the end of treatment.2,3 Monitoring of body temperature as a vital sign in patients with CAP has produced two interesting observations. First, the mean time to normalization of body temperature was shorter in patients treated with moxifloxacin than in patients treated with amoxicillin/clavulanic acid or clarithromycin, irrespective of the disease severity, suggesting a direct effect of moxifloxacin on the shorter time to resolution of fever.4 Analysis using the definition of apyrexia as a temperature of <37.5°C showed that 50% of patients recovered after 3 days in those treated with levofloxacin, but after 3.5 and 4 days in patients treated with cephems and macrolides, respectively.5 Such observations suggest that fluoroquinolones may have a hypothermic action in addition to antibiotic action, which may affect the use of body temperature measurement as a method for monitoring fever resolution. The observations may also reflect the possibility that fluoroquinolones are more effective antimicrobial agents.

The present study investigated whether administration of fluoroquinolones induces hypothermia in mice.

Materials and methods

Bacteria and animals

β-Lactamase-negative ampicillin-resistant Haemophilus influenzae strain TUM267 was isolated from patients with bronchopneumonia admitted to our hospital. Three-week-old Crlj:CD1 male mice, which are immunodeficient, were obtained from Japanese Charles River (Atsugi, Kanagawa, Japan) and divided into groups of seven animals. The experimental protocol was approved by the Ethics
Table 1. Rectal temperature in non-infected mice after oral administration of antimicrobial agents

<table>
<thead>
<tr>
<th>Antimicrobial agent (10 mg/kg)</th>
<th>Time after commencing administration of antimicrobial agent (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>36.2±0.3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>36.3±0.3</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>36.3±0.4</td>
</tr>
<tr>
<td>Cefditoren pivoxil</td>
<td>36.9±0.4</td>
</tr>
<tr>
<td>Cefcapene pivoxil</td>
<td>36.9±0.4</td>
</tr>
</tbody>
</table>

Data are means ± SD. Each group contained seven animals.
*P < 0.01 versus other points at 0, 1 and 14 days after starting oral administration of the same drug at the corresponding dose.
#P < 0.05 versus other points at 0, 1, 2, 3, 8 and 14 days after starting oral administration of the same drug at the corresponding dose.

Results

Effect of antimicrobial agents on body temperature in non-infected mice

Non-infected mice were administered agents at 10 mg/kg twice a day for 3 days. Rectal temperature was measured using an automated temperature apparatus (Digital Thermometer type: SK1250MC; Sato Keiryokiki Co., Tokyo, Japan) and was recorded daily for 14 days beginning immediately after starting agent administration.

Effect of antimicrobial agents on body temperature in mice with bronchopneumonia caused by H. influenzae

The following antimicrobial agents were used in this study: gatifloxacin (Kyorin Pharmaceutical Co., Tokyo, Japan); levofloxacin (Daichi-Sankyo Co., Tokyo, Japan); ciprofloxacin (Bayer Yakuhin, Osaka, Japan); cefditoren and cefcapene pivoxil (Meiji Seika Co., Tokyo, Japan); and cefcapene pivoxil (Shionogi & Co., Osaka, Japan). The MIC for H. influenzae TUM267 was determined by the broth microdilution method using Haemophilus test medium as 0.016 mg/L for gatifloxacin and 0.03 mg/L for cefditoren. The recommended dose and frequency of administration in humans are gatifloxacin 200 mg twice a day and cefditoren pivoxil 100 mg three times a day. Therefore, we determined the dose ratio as 1 to 1. Bronchopneumonia caused by H. influenzae strain TUM267 was induced in mice, as described previously. The antimicrobial agent was administered at 1 or 10 mg/kg twice a day for 3 days starting at 40 h after infection. The rectal temperature and body weight were recorded in the infected mice also starting at 40 h after infection. Tissues from the treated mice were obtained 16 h after the last administration, and viable counts in the infected tissues were assayed as described previously. The bacterial count in samples under the detection limit was set at 1 × 10³ cfu/tissue.

Statistical analysis

All data are expressed as means ± SD. Differences between the bacterial number and rectal temperature were analysed by the Mann–Whitney U-test.

Discussion

The present study found that rectal temperature was significantly reduced by the administration of 10 mg/kg fluoroquinolones in
Effect of fluoroquinolones on body temperature

Table 2. Effects of gatifloxacin and cefditoren pivoxil in infected mice

<table>
<thead>
<tr>
<th>Group</th>
<th>viable organisms (log₁₀ cfu/lung)</th>
<th>rectal temperature (°C)</th>
<th>body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infected control</td>
<td>–</td>
<td>36.51 ± 1.56</td>
<td>22.5 ± 1.1</td>
</tr>
<tr>
<td>Infected control</td>
<td>7.17 ± 0.25</td>
<td>28.94 ± 1.94</td>
<td>16.5 ± 1.3a</td>
</tr>
<tr>
<td>With infection and treatment of gatifloxacin (1 mg/kg)</td>
<td>&lt;2</td>
<td>25.50 ± 0.76***</td>
<td>15.4 ± 1.4a##</td>
</tr>
<tr>
<td>With infection and treatment of gatifloxacin (10 mg/kg)</td>
<td>&lt;2</td>
<td>16 ± 0.50***</td>
<td>14.8 ± 1.6a##</td>
</tr>
<tr>
<td>With infection and treatment of cefditoren pivoxil (1 mg/kg)</td>
<td>3.40 ± 0.43a*</td>
<td>30.10 ± 1.03</td>
<td>17.4 ± 1.1</td>
</tr>
<tr>
<td>With infection and treatment of cefditoren pivoxil (10 mg/kg)</td>
<td>2.80 ± 0.52**</td>
<td>32.09 ± 0.78****</td>
<td>19.5 ± 1.3a##</td>
</tr>
</tbody>
</table>

Data are means ± SD.
Each group contained seven animals.
*P < 0.01 versus infected control.
**P < 0.05 versus infected control and administration of cefditoren pivoxil (1 mg/kg).
***P < 0.05 versus other infection groups.
****P < 0.05 versus infected control and administration of cefditoren pivoxil (1 mg/kg).
####P < 0.05 versus other infection groups.
####P < 0.05 versus other infection groups.

non-infected mice, beginning at 4 days and persisting until 7 days after starting a 3 day course. This effect was not observed in non-infected mice administered 1 mg/kg fluoroquinolones (data not shown) or after administration of cefditoren pivoxil or cefcapene pivoxil. Infection with *H. influenzae* TUM267 caused a significant decrease in rectal temperature compared with that in non-infected mice. The rectal temperature was significantly lower in infected mice treated with gatifloxacin compared with infected mice, although the causative organisms were eliminated from the tissues. In contrast, the rectal temperature tended to be higher in mice treated with 1 mg/kg cefditoren pivoxil compared with both infected mice and in mice treated with gatifloxacin, although viable counts were significantly greater than in mice treated with gatifloxacin. Moreover, the rectal temperature was significantly higher in mice treated with 10 mg/kg cefditoren pivoxil than other infection groups, but the viable count was almost the same as in mice treated with gatifloxacin. Body weight decreased in infected mice, but not in non-infected mice with administration of fluoroquinolones, indicating that the decrease in body weight is not associated with the administration of fluoroquinolones, but may be associated with loss of appetite.

Hypothermia has been recognized in models of pneumococcal pneumonia and may be beneficial to the host as pneumococci cannot multiply as quickly at hypothermic temperatures as at 37°C, both in vivo and in vitro. Therefore, transient hypothermia in BALB/c mice might resolve the inflammation before damage occurs. The initiation of hypothermia in BALB/c and CBA/Ca mice occurred rapidly after peak pulmonary inflammation. This suggests that the temperature changes in infected mice may involve one or more of the inflammatory mediators. We previously found that levels of tumour necrosis factor-α, interleukin (IL)-6 and IL-1β in mouse serum were 380, 220 and 821 pg/mL, respectively, at 3 days after infection, and IL-6 increased to 590 pg/mL but the other two cytokines were not detected at 5 days after infection. These values are lower than those previous studies of low body temperature in mice.

The findings of the present study indicate that fluoroquinolones have a hypothermic effect in the mouse separate from any effect of infection resolution. The mechanism is difficult to elucidate, but may involve the inflammatory response. This finding may have implications for fluoroquinolone administration in patients with CAP.

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Transparency declarations
None to declare.

References

