Effect of fluoroquinolones on body temperature of mice

Shuichi Miyazaki1*, Fumio Ishikawa2, Saburo Matsuo3 and Keizo Yamaguchi1

1Department of Microbiology and Infectious Disease, Toho University Faculty of Medicine School of Medicine, Tokyo, Japan; 2Immunology, Toho University Faculty of Medicine School of Medicine, Tokyo, Japan; 3Laboratory of Toxicology, Course of Veterinary Science, Graduate School of Life and Environmental Biosciences, Osaka Prefecture University, 1-1 Gakuen-cho, Nakaku, Sakai, Japan

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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 result was still statistically significant, which could not be attributed to higher dosage in the patients treated with moxifloxacin.4 Intention-to-treat analysis showed that the duration of intravenous treatment was 4.02 ± 1.78 days in patients treated with moxifloxacin and 4.81 ± 2.07 days for patients treated with a comparator regimen.4 The cure rate based on body temperature was higher in patients treated with fluoroquinolones than in those treated with cephems and macrolides.5 Analysis using the definition of apyrexia as a temperature of <37°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

*Corresponding author. Tel: +81-3-3762-4151, ext. 2395; Fax: +81-3-5493-5415; E-mail: shuichi@med.toho-u.ac.jp

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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>
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<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>Ceftidoren 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 < 0.01 versus other points at 0, 1, 2, 14 days after starting oral administration of the same drug at the corresponding dose.
#
P < 0.05 versus other points at 0, 1, 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

Table 1 shows that gatifloxacin, ciprofloxacin and levofloxacin all caused significant hypothermia in mice at 4 days after starting agent administration. Body temperature began to normalize after 8 days. In contrast, ceftidoren pivoxil and cefcapene pivoxil caused no change in body temperature during the experimental period of 14 days. No significant changes in body weight were recorded in any group.

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

Table 2 shows the findings at 6 days after infection. The viable count was less than the detectable limit in the tissues of mice treated with 1 or 10 mg/kg gatifloxacin. The viable count was significantly lower compared with the infected control group in mice treated with 1 mg/kg ceftidoren pivoxil and significantly lower compared with the infected control group and the corresponding 1 mg/kg group in mice treated with 10 mg/kg ceftidoren pivoxil. The rectal temperature was significantly lower compared with the non-infected and infected control groups in infected mice treated with 1 or 10 mg/kg gatifloxacin and compared with mice treated with 1 or 10 mg/kg ceftidoren pivoxil. The rectal temperature tended to be higher compared with the infected control group in mice treated with ceftidoren pivoxil and was significantly higher compared with other infection groups in mice treated with 10 mg/kg ceftidoren pivoxil.

Body weight decreased significantly in the infected control group compared with the non-infected group. Body weight in mice treated with 1 or 10 mg/kg gatifloxacin was significantly lower compared with the non-infected control and with mice treated with ceftidoren pivoxil. Body weight increased significantly compared with the infected control in mice treated with 10 mg/kg ceftidoren pivoxil and compared with the other infected groups.

Discussion

The present study found that rectal temperature was significantly reduced by the administration of 10 mg/kg fluoroquinolones in mice.
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 390 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


