Effects of Isolation Housing and Timing of Drug Administration on Theophylline Kinetics in Mice

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ABSTRACT—ICR mice were grouped according to 1) housing environment: individual (I) or aggregated (A) and 2) timing of drug administration: midnight (L) or middark (D), i.e. I-L, I-D, A-L, A-D groups. Theophylline was orally administered at midnight or middark. The results showed that both social environment and timing of drug administration exerted significant influence on the pharmacokinetics of theophylline. These data may suggest the importance of considering many non-drug factors in toxicological studies with experimental animals.

Keywords: Social isolation, Timing of drug administration, Theophylline

In recent years, numerous investigations have shown the importance of psychosocial factors in the development, relapse or prognoses of many diseases (1, 2). After social isolation, humans or animals would show biochemical (3–6), physiological and even structural changes (7). Social isolation is a situation often experienced by hospitalized patients (8) and chronically ill patients (9). It has been reported that the effects of drugs can change according to housing conditions (10). Furthermore, circadian rhythmical changes in both drug effects and drug disposition have also been reported (11–13). In the present study, we used a factorial design to investigate the effects of social isolation housing and timing of drug administration on theophylline kinetics.

Forty male ICR mice, aged 5 weeks, were randomly assigned into 4 different groups according to 1) housing condition: individual (I) or aggregated (A) and 2) timing of drug administration: midnight (L) or middark (D), i.e. I-L, I-D, A-L, A-D groups. In the I groups, the mice were individually raised in cages (16 × 16 × 25 cm³ in size) with food and water ad libitum and a light-dark (12:12 hr) cycle (light phase 07:00–19:00). The room temperature was 25 ± 1°C. In the A groups, the mice were raised under the same conditions as used for the I groups except there were 10 mice per cage. Theophylline dissolved in physiologic saline was orally administered at a dose of 30 mg/kg at midnight (13:00) or middark (01:00) after 4 weeks of housing under the above conditions. Blood sampling was from the orbital sinus, using heparinized micropipette aspirator tubes, at 0.25, 0.5, 1, 2, 3 hr after drug administration. Plasma theophylline concentrations were measured by enzyme immunoassay (EMIT). Kinetic parameters were calculated using a one-compartment open model and the data were analyzed by 2-way ANOVA. The observed T_max values were analyzed by the Mann-Whitney U-test.

The results showed that there were no differences in body weight between socially isolated and aggregated groups both before (30.23 ± 13.16 vs. 31.82 ± 3.40 g, n = 40) and after 4 weeks of raising the mice under the above conditions (36.78 ± 3.26 vs. 38.20 ± 3.25 g, n = 40). The time-concentration curve of theophylline and the kinetic parameters are shown in Fig. 1 and Table 1, respectively. Two-way ANOVA showed that the housing conditions had significant effects on theophylline clearance/F (CL/F, P < 0.05), half-life (T½, P < 0.001), and area under the concentration versus time curve (AUC, P < 0.01). Timing of drug administration had significant effects on theophylline apparent volume of distribution/F (Vd/F), CL/F, peak concentration (C_max) and AUC (each P < 0.001). No factorial interactions were found.

Psychosocial factors have great effects on health and development, relapse and prognoses of disease (1, 2). Under social isolation, diseases would relapse easily, develop easily and have poor prognoses. It has been reported that social isolation can cause physiological or biochemical and even structural changes in animals or humans (3–7). Under social isolation, cerebral spinal
fluid monoamine metabolism can change in monkeys and humans, and brain catecholamines, plasma corticosterone, hypothalamic serotonin metabolism can change in rats. Recently, social isolation has become a problem in the care or management of patients. Under hospitalization, the patients would feel lonely, socially isolated, which may lead to deterioration in their physical and mental health, and thus facilitating social communication including nursing intervention is advocated.

Fig. 1. Time-course of theophylline concentrations in plasma. I-L: - - - - - - , A-L: - - - - - - , I-D: - - - - - - , A-D: - - - - - - .

Table 1. Kinetic parameters of theophylline in each group (Mean ± S.D.)

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Housing condition for 4 weeks</th>
<th>Statistical significance (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolated</td>
<td>Aggregated</td>
</tr>
<tr>
<td></td>
<td>Midnight (n = 10)</td>
<td>Middark (n = 9)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</td>
<td>37.7 ± 8.6</td>
<td>23.0 ± 3.7</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>0.51 ± 0.12</td>
<td>0.57 ± 0.13</td>
</tr>
<tr>
<td>Vd/F (l/kg)</td>
<td>0.44 ± 0.12</td>
<td>0.70 ± 0.17</td>
</tr>
<tr>
<td>CL/F (l/hr/kg)</td>
<td>0.62 ± 0.15</td>
<td>0.86 ± 0.11</td>
</tr>
<tr>
<td>AUC (µg·hr/ml)</td>
<td>50.72 ± 11.41</td>
<td>35.46 ± 4.55</td>
</tr>
</tbody>
</table>


Experimental studies in mice have shown that under social isolation, the time of pentobarbital-induced sleep is longer (10) and haloperidol has a shorter half-life than under social condition (14). Besides, circadian variations of the response to and the kinetics of drugs have been reported in both humans (15) and animals (11–13). Circadian rhythms can also be affected by social environment (6). From the pharmacokinetic point of view, we used a factorial design to investigate the effects of social environment and timing of drug administration on theophylline kinetics in mice. The results showed that both social environment and timing of drug administration had significant effects on theophylline kinetics. The CL/F was larger, T<sub>1/2</sub> shorter, AUC smaller in the I groups than in the A groups; and Vd/F was larger, CL/F larger, C<sub>max</sub> lower and AUC smaller when theophylline was administered at middark than at midlight. The observed T<sub>max</sub> values (Table 2) showed that these values were occurred earlier in the I groups than in the A groups (P < 0.05) but not different between L and D groups. These results may suggest that the first-pass effect of theophylline is larger, the metabo-
lism is more rapid in the dark phase when the mice are active or under social isolation than in the light phase when the mice are silent or under a social condition, respectively; and the rate of absorption of theophylline can be affected by social condition. However, the change in the bioavailability of theophylline due to housing conditions and diet schedule cannot be excluded. Although the mechanism requires further study, this study may suggest that non-drug factors should be considered in toxicological studies with experimental animals.

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