Bioavailability of Oral Ivermectin in Dog
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Ivermectin, a broad-spectrum antiparastic agent [1], is a mixture of homologues, not less
80% B1a and not more than 20% B1b. Although
the both components are active, the B1b is
generally metabolized more rapidly than the B1a,
so that the plasma concentrations of B1b are
always less than the B1a. In the present study, the
pharmacokinetics of ivermectin after oral admini-
stration in dogs were examined by determining of
B1a in plasma. Bioequivalence test of two kind of
tablets, containing 23 or 46 µg ivermectin, was
also a subject of the study.

The ivermectin products used in the present
experiment were 23 and 46 µg tablets (Cardomec®,
Merck Sharp and Dohme Research Laboratories,
New Jersey, USA). The formula for 23 µg tablet is given below:

**Ivermectin** 0.023mg

Hydrogenated castor oil 1.348mg

Hydroxypropyl cellulose 0.193mg

Microcrystalline cellulose 71.787mg

Propylene glycol 3.265mg

Magnesium stearate 0.385mg

The formula for 46 µg tablet is twice that of 23
µg tablet. Ten healthy male beagle dogs from 9.8
to 13.4 kg body weight were divided into two
groups, and a 2×2 Latin square design was
employed for 23 and 46 µg tablets. Blood
samples (approx. 7 ml) were taken from cephalic
vein into glass tubes containing heparin prior to
and at 1, 2, 3, 5, 7, 9, 24 and 48 hours after
administration. They were centrifuged immediately
to separate the plasma and stored at
−20°C until analysis. Plasma samples were
assayed for B1a using HPLC method [2]. The
plasma B1a concentration-time data for two kind
of tablets were fitted to a two-compartment open
model with first-order absorption process by the
equation:

\[ C_p = A_1 e^{-\alpha t} + A_2 e^{-\beta t} - A_3 e^{-K mt} \]

where \( C_p \) is the plasma drug concentration at
time \( t \) following drug administration; \( \alpha \) and \( \beta \) are the
fast and slow elimination rate constants, respectively; \( K_m \) is the absorption rate constant;
\( A_1, A_2, \) and \( A_3 \) are the constants of exponential
terms.

Pharmacokinetic analysis were carried out by
computer fitting of the observed data to the
two-compartment open model. For the computer
analysis, initial estimates of the kinetic paramet-
erd were obtained graphically. The half-lives
(\( t_{1/2e} \) and \( t_{1/2K_m} \)) for two kind of tablets were
calculated by multiplying the reciprocal values of
each rate constant by 0.693. The area under the
plasma drug concentration-time curve from 0 to
48 hours, AUC0–48hr, was calculated by
trapezoidal method. The Cmax, Tmax and
AUC0–48hr were obtained from the individual
plasma drug concentration-time data.

After oral administration of tablets to beagle
dogs, the B1a were rapidly absorbed. The plasma
concentration of B1a at each time were best fitted
by a two-compartment open model with first-
order absorption process adding the lag time.
The pharmacokinetic parameters are presented
in Table 1. The absorption rate constants of the
B1a were very similar between two kind of
tablets. The absorption half-lives of the B1a were
1.17±0.25 and 0.92±0.07 hours for 23 and 46 µg
tablets.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Estimate</th>
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<tbody>
<tr>
<td></td>
<td>23 µg tablet</td>
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<tr>
<td>( K_m (hr^{-1}) )</td>
<td>0.78±0.13(^a)</td>
</tr>
<tr>
<td>( \beta (hr^{-1}) )</td>
<td>0.029±0.004</td>
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<tr>
<td>( t_{1/2K_m} (hr) )</td>
<td>1.17±0.25</td>
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<tr>
<td>( t_{1/2g} (hr) )</td>
<td>31.1±6.67</td>
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<tr>
<td>Cmax (ng/ml)</td>
<td>17.24±1.42</td>
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<tr>
<td>Tmax (hr)</td>
<td>2.30±0.21</td>
</tr>
<tr>
<td>AUC (ng·hr/ml)</td>
<td>262.5±21.9</td>
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</table>

\(^a\) Mean ± S.E. of 10 beagle dogs.
Fig. 1. Mean plasma concentration time profiles of the B_{1a} after oral administration of 23 and 46 μg tablets to beagle dogs. ○—○: 23 μg tablet; ●—●: 46 μg tablet. Each point represents the mean ±S. E. for 10 beagle dogs.

tablets, respectively. The absorption lag time was ~0.9 hours for two kind of tablets. The half-lives of β (second phase) were 31.1±6.67 and 33.8±6.33 hours for 23 and 46 μg tablets, respectively. These t_{1/2β} values are comparable with the published values of terminal half-life after intravenous administration of ivermectin to dogs [3]. The C_{max}, T_{max} and AUC_{0-48hr} for these two kind of tablets are also presented in the Table 1. The differences in the mean values of these pharmacokinetic parameters were <20% between two tablets and that time profiles of mean plasma concentration, as indicated in Fig. 1, were comparable between these two kind of tablets. The analysis of variance, according to the Latin square method [4] of plasma concentration at each time, C_{max}, T_{max} and AUC_{0-48hr}, were not significant difference in variances due to the tablet. The results of this study demonstrate that following a single oral 276 μg does, two kind of tablets are bioequivalent.

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REFERENCES


要約

犬における経口イベルメクチンの薬動力学（短報）：児島健次・山本和克・片江宏已1）・中西 豊（大日本製薬（株）製品研究所、1）薬東試験場）——経口投与イベルメクチンの薬動力学的パラメータは静注動態と類似し、イベルメクチン 23 μg あるいは 46 μg を含有する錠剤は同等であった。