Pharmacokinetics of Haloperidol Decanoate in Rats

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(Received May 17, 1991)

Plasma levels of haloperidol decanoate and haloperidol after intramuscular administration of haloperidol decanoate in rats showed good fits with a multi-compartment model which was constituted by combination of 2-compartment models for the disposition of haloperidol and for its ester decanoate through the process of hydrolysis of the ester. Calculated parameters indicated that most of intramuscularly administered haloperidol decanoate is absorbed in blood after hydrolysis to haloperidol and the absorption is rate-limiting. Regional lymph node levels suggested that the intramuscularly administered ester was absorbed via the lymphatic system where the hydrolysis to haloperidol probably occurred. Thus, slow entrance and hydrolysis of haloperidol decanoate in the lymphatic system was considered to be the cause of sustained plasma levels of the active principle after intramuscular administration of haloperidol decanoate.

Keywords — haloperidol decanoate; haloperidol; long-acting antipsychotic; pharmacokinetic; multi-compartment model; disposition; flip-flop; lymphatic absorption; hydrolysis; rat

Introduction

Our previous studies in rats\(^1\) revealed that a long-acting antipsychotic haloperidol decanoate (HD) was slowly absorbed via the lymphatic pathway from the intramuscularly (i.m.) injected sites. This absorption process was rate-limiting and thereby the sustained plasma level of haloperidol (H\(^\prime\)) in this paper, haloperidol derived from HD is abbreviated as this), active principle, was maintained for a long period. Although it was shown that enzymatic hydrolysis of HD was strongly inhibited by its binding to macromolecules in body fluids\(^2\) and possibly occurs in tissue cells,\(^3\) the following are still obscure: the ultimate rate-limiting step in the absorption and the site of production of H\(^\prime\) after i.m. administration of HD. In other words, it has not yet been determined whether HD is mainly hydrolyzed before, during or after absorption. The present pharmacokinetic studies aimed to elucidate the site of hydrolysis of HD given i.m. Compartment model analysis and subsequent measurement of lymphaden components revealed that i.m. administered HD slowly enters to be hydrolyzed mainly in the lymphatic system in the process of absorption.

Materials and Methods

Labeled Compounds — [Carbonyl-\(^{14}\)C]-haloperidol (H) and its decanoate were used in this study and were prepared as described.\(^4\) Their specific activities were 884 and 603 kBq/mg, respectively, and radiochemical purities were > 99\%. The labeled compounds were suitably diluted with the unlabeled compound in following animal experiments. The actual specific activities used are described in the legends of figures and tables in this paper.

Animals and Maintenance — Male Wistar rats (6 weeks old, around 200 g) were used and maintained as described previously.\(^5\)

Procedure — In this paper, the dose and concentration of HD are expressed as an equivalence to H base: i.e., 50 mg eq to H of its decanoate is equal to 70.5 mg of HD. \(^{14}\)C\)\)H was dissolved in 10% lactic acid and \(^{14}\)C\)\)HD was dissolved in ethanol for intravenous (i.v.) administration and in sesame oil containing 1.5\% benzyl alcohol for i.m. administration. For i.v. administration, \(^{14}\)C\)\)H and \(^{14}\)C\)\)HD were given in a saphenous vein of a hind limb or in a tail vein at the dose of 0.1 mg/0.27 ml/kg and 25 mg eq/0.18 ml/kg, respectively. For i.m. administration, \(^{14}\)C\)\)HD was injected at 1 site of each femoral muscle (therefore, 2 sites in total)
at the dose of 50 mg eq/0.25 ml/kg. Blood was collected from the tail vein of individual rats.

Measurement of Total Radioactivity, Haloperidol and Haloperidol Decanoate —

Plasma was mixed with AQUASOL-2 (New England Nuclear, Boston, MA, U.S.A.) for determination of radioactivity in a Tri-Carb liquid scintillation spectrometer model 2200CA (Packard Instruments, Inc., Downers Grove, IL, U.S.A.). For quantification of H, H' and HD, plasma was deproteinized with 5 volumes of ethanol and then precipitates were washed twice with the same volume of ethanol. Supernatants were combined, evaporated to dryness and dissolved in a small volume of 67% ethanol for thin layer chromatography (TLC). Recoveries of total radioactivity (TR), HD and H were practically 100%. TLC analysis was performed on plates precoated with 0.25 mm thick silica gel 60F254 (E. Merck, Dermstadt, Germany) with a solvent system of chloroform—methanol—ammonium hydroxide (85:15:1). Under these conditions, HD, H' and its metabolites were successfully separated as shown in Fig. 1. Developed TLC-plates were scanned in a TLC-Multi-Tracemaster LB285 (EG&G Berthold, Wildbad, Germany) for quantification. Radioactive compounds on TLC were identified by comparison with authentic substances under ultraviolet lamp.

Fig. 1. A Typical Radiochromatogram of a Rat Plasma 12 d after i.m. Administration of [14C]HD

BP, p-fluorobenzoylpropionic acid; PA, p-fluorophenylacetic acid; PHB, p-fluorophenyl-4-hydroxybutyric acid, which are metabolites of H'.

O, origin; F, solvent front.

Lymph nodes were subjected to measurement of TR, H, H' and HD as described previously.¹

Compartment Model Analysis — Plasma levels of H, H’ and HD were analyzed by fitting the data to compartment models using the computer program MULTI.⁶ Initial values of parameters were determined by the least square method.

Fig. 2. Disposition of H

a) Plasma levels of H after i.v. administration.

[¹⁴C]H was administered i.v. at 88.8 kBq/0.1 mg/kg. Points and bars are means of 3 animals ± S.E. Line is a calculated curve fitted to the following equation:

\[ C_P = A e^{-k_T T} + Ce^{-k_D T} \]

b) Two-compartment model and parameters for the disposition of H.
Disposition of Haloperidol Decanoate

Fig. 3. Disposition of HD

a) Plasma levels of HD after i.v. administration.

$[^{14}C]HD$ was administered i.v. at 21.3 MBq/25 mg eq/kg. Points and bars are means of 3 animals ± S.E. Line is a calculated curve fitted to the following equation:

$$Cp = Ae^{-bT} + Ce^{-dT}$$

b) Plasma levels of HD after i.m. administration.

$[^{14}C]HD$ was administered i.m. at 42.2 MBq/50 mg eq/kg. Points and bars are means of 3 animals ± S.E. Line is a calculated curve fitted to the following equation:

$$Cp = FKae^{-KaT}(A(1-e^{-E1T})/EI + C(1-e^{-E2T})/E2) \times \text{Dose (i.m.))/Dose (i.v.)}$$

$$EI = B - Ka, E2 = D - Ka$$

c) Two-compartment model and parameters for the disposition of HD.

good fit with 2-compartment model (Fig. 2a). Calculated parameters are presented in Fig. 2b.

Disposition of Haloperidol

Plasma levels of H after i.v. administration of $[^{14}C]H$ decreased biphasically and showed a

Fig. 4. Multi-Compartment Model for the Disposition of HD and H' after Administration of HD

Biphasic elimination of HD was observed after i.v. administration at 25 mg eq/kg (Fig. 3a) and apparently mono-exponential disposition, after i.m. route at 50 mg eq/kg (Fig. 3b).

The latter disposition can be expressed by a 2-compartment model defined by following simultaneous equations, which were corrected with doses assuming the linear disposition after i.v. route.

$$Cp(\text{i.v.}) = Ae^{-bT} + Ce^{-dT}$$

$$Cp(\text{i.m.}) = FKe^{-KaT}(A(1-e^{-E1T})/EI + C(1-e^{-E2T})/E2) \times \text{Dose(i.m.)/Dose(i.v.)}$$

$$EI = B - Ka, E2 = D - Ka$$

Here, $Cp(\text{i.v.})$ and $Cp(\text{i.m.})$ are plasma levels after i.v. and i.m. administration, respectively. $F$
and Ka are the fraction absorbed and absorption rate constant after i.m. administration, respectively. Plasma levels of HD for both administration routes showed good fits with above simultaneous equations as shown by curves in Fig. 3a and 3b.

Figure 3c shows the compartment model for the disposition of HD and calculated parameters. Elimination rate constant of the ester from compartment-1(HD), Ke(HD) = 1.67 d⁻¹, indicates a much slower elimination of HD than H.

Our previous studies showed that metabolites yielded from H' alone were excreted into urine after administration of HD, which suggested that HD was excreted from the body after complete conversion to H' and then to its subsequent metabolites. Therefore, it can be mentioned that the Ke(HD) represents the rate constant (Kh) of hydrolysis in vivo of HD to H' which was eliminated promptly as shown above. Absorption rate constant (Ka(HD)) of HD from the injection site and the fraction absorbed (F(HD)) were calculated to be 0.0524 d⁻¹ and 0.125, respectively, indicating the slow and partial absorption of HD administered i.m.

**Disposition of Haloperidol Derived from Haloperidol Decanoate**

Assuming that H' is formed from absorbed HD alone, a model for the disposition of H' can be described by combination of models for H (Fig. 2b) and HD (Fig. 3c) through the finding of Ke(HD) = Kh. In such a model (Fig. 4), H' and HD concentrations in each compartment after i.v. administration can be described in the following simultaneous differential equations:

\[
dCI(HD)/dT = -(K_{12}(HD) + Kh)C1(HD) + K_{12}(HD)C2(HD)
\]
\[
dC2(HD)/dT = K_{21}(HD)(C1(HD) - C2(HD))
\]
\[
dCI(H')/dT = KhC1(HD)V_1(HD)/V_1(H) - (K_{12}(H) + Ke(H))C1(H') + K_{12}(H)C2(H')
\]
\[
dC2(H')/dT = K_{21}(H)(C1(H') - C2(H'))
\]

And for i.m. administration:

\[
dx/dT = - Ka(HD)X
\]
\[
dCI(HD)/dT = F(HD)Ka(HD)X/V_1(HD) - (K_{12}(HD) + Kh)C1(HD) + K_{12}(HD)C2(HD)
\]
\[
dC2(HD)/dT = K_{21}(HD)(C1(HD) - C2(HD))
\]
\[
dCI(H')/dT = KhC1(HD)V_1(HD)/V_1(H) - (K_{12}(H) + Ke(H))C1(H') + K_{12}(H)C2(H')
\]
\[
dC2(H')/dT = K_{21}(H)(C1(H') - C2(H'))
\]

Here, C1(HD), C2(HD), C1(H') and C2(H') are drug concentrations in compartment-1(HD), -2(HD), -1(H) and -2(H), respectively, and X is the amount of HD at the administered site.
CI(H'), plasma level of H', is calculated by the solution of the above simultaneous differential equations with Runge-Kutta-Gill method\(^8\) by using parameters described in Fig. 2b and 3c. Calculated plasma levels of H' after i.v. administration of HD were close to the observed values (Fig. 5a), indicating that this model can represent the disposition of H' as well as HD as shown before in Fig. 3a; the model in Fig. 4 is satisfactory for H' given in the blood.

On the other hand, after i.m. administration, calculated and observed plasma levels of H' were quite different from each other (see the curve of broken line in Fig. 5b), which suggests that H' is not exclusively derived from absorbed HD alone. This would be due to the fact that HD given i.m. was only about 12.5% absorbed as shown above by F(HD) under the present condition. It was seen previously that 93% of injected radioactivity was excreted into urine and feces and 6% remained at the injection site even 91 d after i.m. administration of [\(^1^4\)C]HD in rats.\(^1\)

This fact indicates that HD in an infinite time period can be completely absorbed: F = 1. Therefore, we can note that a part (F(HD) = 0.125) of absorbed radioactivity was due to absorbed HD and the remainder (F - F(HD) = 0.875 = F(H')), to H'. Differences between calculated and observed plasma levels of H' shown in Fig. 5b are thus due to the latter fraction, which agreed with the two-compartment model with first-order absorption by using the F(H') and parameters for H described in Fig. 2b. In this case, the absorption rate constant of H' (K(H')) was calculated to be 0.0717 d\(^{-1}\). When the differences were alternatively fitted to the same model by using parameters in Fig. 2b alone, Ka(H') and F(H') were 0.0780 d\(^{-1}\) and 0.988, respectively, which agree with the above ones. Therefore, compartment model for the disposition of H' and HD after i.v. and i.m. administration of HD can be described by the model shown in Fig. 6.

Here, compartment-X may be the injection site, absorption site or both where hydrolysis of HD occurred before absorption. In this model, drug concentrations in each compartment after i.m. administration can be described by following differential equations:

\[
\begin{align*}
\frac{dX(HD)}{dT} &= -Ka(HD)X(HD) \\
&= -Ka(HD)F(HD)X \\
\frac{dX(H')}{dT} &= -Ka(H')X(H') \\
&= -Ka(H')F(H')X \\
\frac{dC1(HD)}{dT} &= Ka(HD)X(HD)/V_1(HD) \\
&= (K_{21}(HD) + Kh)C1(HD) \\
&+ K_{12}(HD)C2(HD) \\
\frac{dC2(HD)}{dT} &= K_{21}(HD)(C1(HD) - C2(HD)) \\
\frac{dC1(H')}{dT} &= Ka(H')X(H')/V_1(H) \\
&= KhC1(HD)V_1(H)/V_1(H) \\
&= (K_{12}(H) + Ke(H))C1(H') \\
&+ K_{12}(H)C2(H') \\
\frac{dC2(H')}{dT} &= K_{21}(H)(C1(H') - C2(H')) \\
\end{align*}
\]

X(HD) and X(H') are the amount of HD and H' in compartment-X, respectively.

By solving the above simultaneous differential equations, calculated plasma levels of H', CI(H'), were close to observed ones (see the curve of solid line in Fig. 5b), indicating this model satisfactorily represents the disposition of H' and its ester after administration of HD in either route.

**Lymph Node Levels after i.m. Administration of Haloperidol**

Levels of TR were similar to each other in all examined lymph nodes involving the regional ones of the i.m. injected site of [\(^1^4\)C]H, which declined rapidly as plasma levels decreased (Table I). Therefore, there was no evidence sup-
TABLE I. Plasma, Liver and Lymph Node Levels of TR, HD and H' after i.m. Administration of [14C]H or [14C]HD in Rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Time after administration of [14C]H (h)</th>
<th>Time after administration of [14C]HD (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td>0.49</td>
<td>0.20</td>
</tr>
<tr>
<td>± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>± 0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>± 0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HD</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>H'</td>
<td>± 0.01</td>
<td>± 0.00</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
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<td></td>
</tr>
<tr>
<td>TR</td>
<td>6.56</td>
<td>6.31</td>
</tr>
<tr>
<td>± 0.61</td>
<td>± 0.41</td>
<td>± 0.05</td>
</tr>
<tr>
<td>(6.5)</td>
<td>(5.2)</td>
<td>(1.7)</td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandibular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td>4.05</td>
<td>1.30</td>
</tr>
<tr>
<td>± 0.17</td>
<td>± 0.14</td>
<td>± 0.00</td>
</tr>
<tr>
<td>Mediastinal</td>
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<td></td>
</tr>
<tr>
<td>TR</td>
<td>4.21</td>
<td>1.18</td>
</tr>
<tr>
<td>± 0.59</td>
<td>± 0.15</td>
<td>± 0.04</td>
</tr>
<tr>
<td>Mesenteric</td>
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<td></td>
</tr>
<tr>
<td>TR</td>
<td>5.32</td>
<td>1.56</td>
</tr>
<tr>
<td>± 0.47</td>
<td>± 0.16</td>
<td>± 0.03</td>
</tr>
<tr>
<td>HD</td>
<td>± 0.08</td>
<td>± 0.04</td>
</tr>
<tr>
<td>H'</td>
<td>± 0.04</td>
<td>± 0.00</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td>3.45</td>
<td>1.27</td>
</tr>
<tr>
<td>± 0.39</td>
<td>± 0.31</td>
<td>± 0.04</td>
</tr>
<tr>
<td>Medial iliac and hypogastric sacral (a part of regional lymphaden)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>130</td>
<td>100</td>
</tr>
<tr>
<td>± 0.58</td>
<td>± 0.26</td>
<td>± 0.03</td>
</tr>
<tr>
<td>H'</td>
<td>± 0.60</td>
<td>± 0.30</td>
</tr>
<tr>
<td>(2.1)</td>
<td>(2.1)</td>
<td>(14.4)</td>
</tr>
<tr>
<td>(2.1)</td>
<td>(2.1)</td>
<td>(14.4)</td>
</tr>
</tbody>
</table>

Dose [14C]H, 2.75 MBq/74.4 μCi/5 mg/kg; [14C]HD, 25.9 MBq/700 μCi/50 mg eq/kg.
Values are means of 3 animals ± S.E., except for of 6 animals (<sup>a</sup>) ± S.E. or of 2 animals (<sup>b</sup>).
<sup>a</sup> Sample radioactivity was under reliable limit.
After injection of HD, average fraction of absorption per day can be calculated by Dose × 0.5/(0.693/Ka).
Preliminary results in this table were previously described in ref. 1.

porting the lymphatic absorption of H.

**Lymph Node Levels after i.m. Administration of Haloperidol Decanoate**

When [14C]HD was administered i.m. medial iliac and hypogastric sacral lymph nodes, a part of the regional nodes of the injection site, showed the highest levels of TR and HD in examined lymph nodes and plasma. Maximum level of TR in those lymph nodes was more than 20 000 and 1400 times as high as plasma and other lymph node levels, respectively, and those of HD, about 80 000 times the plasma level.
Thereafter, those lymph node levels declined as slowly as plasma levels. In addition, those regional lymph nodes contained high levels of $\text{H}^\prime$, whose maximum level was about 4,600 times as high as plasma level and >80 times as other lymph node levels in TR, and declined as gradually as plasma levels.

Recoveries of radioactivity to administered dose in examined tissues are also given in the table. $[^{14}\text{C}]\text{H}$ radioactivity gathered in the liver in a high degree. Recoveries of $[^{14}\text{C}]\text{HD}$ radioactivity were calculated as the percent of absorbed dose per day (see the footnote of the table). Note that regional lymph nodes contained higher recoveries than liver late after i.m. administration of HD.

**Discussion**

In the present study, a multi-compartment model in Fig. 6 for the disposition of HD and $\text{H}^\prime$ after i.m. administration of HD was constituted by combination of 2-compartment models for the disposition of $\text{H}$ and for HD through the process of hydrolysis of the ester.

Values for $F(\text{HD})$ and $F(\text{H}^\prime)$ in the model indicate that most of i.m. administered HD is absorbed in blood after hydrolysis to $\text{H}^\prime$ in compartment-X. It has been believed that esterified long-acting antipsychotics such as the ester of the present H, fluphenazine, flupenthixol and clopenthixol, are hydrolyzed by esterases to each of active principles after absorption from depot sites. Despite this, present analysis has indicated that the esterified $\text{H}$ administered i.m. was hydrolyzed mainly before absorption in compartment-X and the hydrolysis after absorption believed hitherto was minor. However, it should be noted that $F(\text{active principle})$ and $F(\text{its ester})$ would be variably dependent on the volume of the injection formula, volume mass of muscle where injection had been done and the dose of the ester.

In addition, $Ka(\text{HD})$ and $Ka(\text{H}^\prime)$ indicate that the absorption is rate-limiting: the disposition of HD and $\text{H}^\prime$ after i.m. administration of the ester followed typical flip-flop kinetics.

Relevant to compartment-X, lymph node levels of $\text{H}$, $\text{H}^\prime$ and HD after i.m. administration of $[^{14}\text{C}]\text{H}$ and $[^{14}\text{C}]\text{HD}$ were analyzed.

After administration of $\text{H}$, there was no evidence supporting the lymphatic absorption of $\text{H}$. In contrast, regional lymph nodes at the injection site after i.m. administration of HD contained quite high levels of $\text{H}^\prime$, suggesting that the hydrolysis of the ester occurred in the lymphatic system. Our previous studies in vitro indicated that enzymatic hydrolysis of HD scarcely occurred by binding to macromolecules in body fluids and the intracellular hydrolysis occurred after rapid incorporation into cells. Moreover, HD given i.m. remained at the injection site for a long period suggesting that hydrolysis of HD at the injection sites is unlikely. These previous findings and present ones suggest that hydrolysis of HD in the lymphatic system occurs in lymphocytes which constitute a major cell population in the system involving lymph nodes. In fact, lymphocytes hydrolyzed HD in vitro. Therefore, compartment-X in Fig. 6 is possibly responsible for the lymphatic system rather than the injection site.

The conclusion concerning lymphatic absorption and thereby the compartment-X would be further supported by the following. That is, the liver is conceivably the major organ for disposing $\text{H}$ since it concentrated $[^{14}\text{C}]\text{H}$ radioactivity in the highest extent in the body. This is also indicated by findings in Table I: liver contained recoveries as high as several percent of administered dose of $[^{14}\text{C}]\text{H}$ radioactivity. In this respect, after i.m. administration of $[^{14}\text{C}]\text{HD}$, radioactivity was also concentrated in liver in an extent similar to $[^{14}\text{C}]\text{H}^\prime$ radioactivity. This is compatible with the fact described before that most of i.m. given HD are absorbed as $\text{H}^\prime$ in the systemic circulation, which was mainly disposed in liver. In contrast, recoveries of $[^{14}\text{C}]\text{HD}$ radioactivity in medial iliac and gastric sacral lymph nodes are much higher than liver late after i.m. administration. This fact strongly supports our conclusion that HD was absorbed via the lymphatic system from i.m. injection sites.

By using values in Table I, the elimination rate constants of HD and $\text{H}^\prime$ from regional lymph nodes were estimated roughly by the least square method to be around 0.05 d$^{-1}$, which are simi-
lar to respective absorption rate constants, $K_a$(HD) and two $K_a(H^+)$s obtained in preceding pharmacokinetic calculations. The presence of HD in the injection site for a long time\textsuperscript{11} suggests that the rate-limiting step in compartment-X in Fig. 6 is the process of HD to enter the lymphatic system from the injection site. Therefore, absorption rate constants into blood, $K_a$(HD), two $K_a(H^+)$s and the elimination rate constants in lymph nodes, are considered to be essentially the same one, $K_a$, which is ultimately the rate constant of entrance into the lymphatic system from the injection site. $K_a$ can be estimated to be 0.0674 d$^{-1}$ as an average of $K_a$(HD) and two $K_a(H^+)$s.

In summary, present pharmacokinetic studies revealed that the disposition of $H^+$ and HD after administration of HD could be described satisfactorily by the multi-compartment model of Fig. 6 which was constituted by combination of 2-compartment models for the disposition of H and HD. Parameters in this model suggest that most of i.m. administered HD is absorbed in blood after hydrolysis to $H^+$ and the absorption is rate-limiting. Thus the disposition of HD and $H^+$ after i.m. administration of HD follows typical flip-flop kinetics, resulting in slow releasing of active principle after i.m. administration of HD. Analysis of lymph node levels indicated that i.m. administered ester was absorbed via the lymphatic system and the hydrolysis to $H^+$ probably occurred there. The ultimate rate-limiting step would be the entrance of HD from the injection site into the lymphatic system.

Acknowledgement We wish to thank Mr. A. Kagemoto for the supply of $^{14}$C-labeled drugs, and Messrs. N. Nomura, H. Furukawa and A. Ishiwata for their collaboration.

References


