The pharmacokinetics and antihistaminic of the H₁ receptor antagonist hydroxyzine

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We studied the pharmacokinetics and the suppression of histamine-induced wheals, flares, and pruritus in the skin after administration of the histamine H₁ antagonist hydroxyzine to seven healthy adults. After a single oral dose of hydroxyzine, 0.7 mg/kg (mean dose 39.0 ± 5.4 mg) the mean maximum serum hydroxyzine concentration of 72.5 ± 11.1 ng/ml occurred at a mean time of 2.1 ± 0.4 hr. The mean elimination half-life calculated from the terminal linear portion of the serum hydroxyzine concentration vs. time curve was 20.0 ± 4.1 hr. The mean clearance rate was 9.78 ± 3.25 ml/min/kg and the mean volume of distribution was 16.0 ± 3.0 L/kg. The single dose of hydroxyzine suppressed pruritus at the wheal and flare sites from 1 to 36 hr. Maximal suppression of the wheals was 80% and maximal suppression of the flares was 92%. Significant suppression of the wheals and flares persisted for 36 and 60 hr, respectively. Pharmacodynamic analysis of the wheal and flare suppression data and the mean serum hydroxyzine concentrations supports the prolonged terminal serum half-life value for the drug. (J ALLERGY CLIN IMMUNOL 73:69-75, 1984.)

Hydroxyzine hydrochloride, a member of the piperazine class of H₁ receptor antagonists is a strong antipruritic¹ and antiwhealing²-⁴ agent and is often recommended as the antihistamine of choice in the treatment of allergic skin disorders.⁵-⁷ It is also effective in the treatment of allergic rhinitis⁸,⁹ and has some bronchodilator properties when used alone or in combination with other bronchodilators.¹⁰-¹² Although its efficacy in allergic disorders is well documented, there is only one previously published study of the pharmacokinetics of hydroxyzine in humans¹³ and there are no studies in which serum hydroxyzine concentrations have been correlated with antihistaminic effects. Present recommendations about dose size and dosing interval with this drug are therefore empirical.¹⁴-¹⁶

We administered a single dose of hydroxyzine to healthy adults and studied its pharmacokinetics and antihistaminic effects as evidenced by suppression of histamine-induced wheals, flares, and pruritus in the skin. Serum hydroxyzine concentrations were determined by a sensitive and specific HPLC assay developed in our laboratory.

METHODS

All subjects gave informed, signed consent before entering the study, which was approved by the Faculty Committee on the Use of Human Subjects in Research of the University of Manitoba. A single oral dose of hydroxyzine, 0.7 mg/kg (Atarax Syrup) was administered with 2.50 ml of water at 0900 hr to seven healthy, fasting adults. Subjects were nonobese, had never smoked or required regular antihistamine treatment previously, and had not received any medications for 1 mo prior to study. They had documented normal renal and hepatic function. Blood samples were obtained at -0.1, 1, 2, 3, 4, 5, 6, 9, 12, 24, 36, 48, 60, and 72 hr after the dose. Intradermal tests with 0.01 ml of histamine phosphate, 0.1 mg/ml, were performed at the same times as blood samples were obtained. A different site on the volar surface of the forearms was used for each test and the sequence of the sites chosen was identical in all subjects. Wheal and flare circumferences were traced at 10 min with a felt-tip pen.

Abbreviation used

HPLC: High-performance liquid chromatography
TABLE I. Serum hydroxyzine concentrations in seven healthy adults given a 0.7 mg/kg oral dose of hydroxyzine

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
<th>6 hr</th>
<th>9 hr</th>
<th>12 hr</th>
<th>24 hr</th>
<th>36 hr</th>
<th>48 hr</th>
<th>60 hr</th>
<th>72 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.d.</td>
<td>0.6</td>
<td>58.6</td>
<td>56.5</td>
<td>46.1</td>
<td>40.4</td>
<td>35.7</td>
<td>24.9</td>
<td>18.4</td>
<td>10.1</td>
<td>10.0</td>
<td>5.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>n.d.</td>
<td>32.1</td>
<td>62.9</td>
<td>61.0</td>
<td>39.5</td>
<td>34.0</td>
<td>27.7</td>
<td>21.9</td>
<td>18.2</td>
<td>9.5</td>
<td>6.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>n.d.</td>
<td>50.9</td>
<td>82.0</td>
<td>69.9</td>
<td>42.3</td>
<td>32.3</td>
<td>25.1</td>
<td>16.7</td>
<td>13.3</td>
<td>6.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>n.d.</td>
<td>28.0</td>
<td>77.2</td>
<td>67.3</td>
<td>53.3</td>
<td>52.4</td>
<td>50.7</td>
<td>36.3</td>
<td>29.5</td>
<td>19.9</td>
<td>11.5</td>
<td>8.8</td>
<td>6.0</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>n.d.</td>
<td>58.1</td>
<td>62.3</td>
<td>61.2</td>
<td>41.9</td>
<td>39.0</td>
<td>35.4</td>
<td>21.8</td>
<td>16.7</td>
<td>10.2</td>
<td>5.7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>n.d.</td>
<td>74.4</td>
<td>89.4</td>
<td>84.2</td>
<td>64.1</td>
<td>43.8</td>
<td>39.9</td>
<td>31.3</td>
<td>25.7</td>
<td>20.5</td>
<td>10.1</td>
<td>7.5</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>7</td>
<td>n.d.</td>
<td>14.3</td>
<td>35.0</td>
<td>72.1</td>
<td>67.7</td>
<td>60.3</td>
<td>59.5</td>
<td>37.1</td>
<td>35.0</td>
<td>18.2</td>
<td>13.4</td>
<td>10.6</td>
<td>7.0</td>
<td>n.d</td>
</tr>
<tr>
<td>Mean</td>
<td>n.d.</td>
<td>42.6</td>
<td>70.0</td>
<td>67.5</td>
<td>52.5</td>
<td>43.2</td>
<td>39.2</td>
<td>27.0</td>
<td>22.4</td>
<td>13.6</td>
<td>9.6</td>
<td>7.4</td>
<td>5.6</td>
<td>3.9</td>
</tr>
<tr>
<td>±S.D.</td>
<td>20.2</td>
<td>12.9</td>
<td>9.2</td>
<td>11.6</td>
<td>10.0</td>
<td>12.3</td>
<td>8.0</td>
<td>7.9</td>
<td>5.7</td>
<td>2.9</td>
<td>2.4</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.d. = no hydroxyzine detected.
— = sample not collected.

HPLC analysis of hydroxyzine

**Extraction.** One milliliter of standard or test serum was pipetted into 16 by 100 mm test tubes and 100 µl of internal standard (1 µg/ml triprolidine) was added. To this, 250 µl of 10% potassium hydroxide and 5 ml of ether were added. Samples were extracted by mixing on a vortex mixer and centrifuging. The ether layer was transferred to concentrate tubes and 100 µl of 0.5% phosphoric acid was added. The samples were mixed by vortex mixer and centrifuged again. Most of the ether layer was aspirated and traces of remaining ether were removed by dry nitrogen at room temperature 25° C for 2 to 3 min. The total phosphoric acid layer was injected directly into the HPLC system.

**Instrument conditions.** The HPLC system used consisted of a U6K injector, a 6000A high-pressure pump, a radial compression module, a 441 absorbance detector with a fixed wavelength of 229 nm, and a 7000 data module (Waters Associates, Inc., Milford, Mass.). A CN reverse-phase radial compression column (Waters) was used, with a mobile phase of 27% acetonitrile in 0.075M phosphate buffer (pH 3.0) containing 0.02M dibutyl amine and 50 ng/ml triprolidine to block adsorption and act as a carrier. At a flow rate of 1.0 ml/min and operating pressures of 300 to 600 psi, the internal standard and hydroxyzine eluted at about 3.6 and 6.9 min, respectively.

**Data analysis**

Pharmacokinetic parameters were calculated by standard equations. The log of the serum hydroxyzine concentrations was plotted vs. time. The terminal linear portion of the curve was fitted to equation 1.

\[
\ln C_p = \ln C_p^\infty - Kt
\]

where \( C_p \) is the serum hydroxyzine concentration at any time \( t \), \( C_p^\infty \) is the serum concentration extrapolated to zero time \( (t_0) \), and \( K \) is the first-order elimination rate constant.

The elimination half-life \( t^{1/2} \) was calculated with equation 2.

\[
t^{1/2} = \frac{0.693}{K}
\]

Total body hydroxyzine clearance \( (Cl) \) was calculated with equation 3.

\[
Cl = \frac{\text{Dose}}{\int C_p dt}
\]

where \( \int C_p dt \) is the area under the serum hydroxyzine concentration vs. time curve calculated with the trapezoid rule to \( C_p^\infty \), to which the area \( C_p/ K \) was added to extrapolate to time infinity.

The apparent volume of distribution \( (V_d) \) was calculated with equation 4.

\[
V_d = \frac{Cl}{Kc}
\]

The mean residence time \( (MRT) \) was calculated with equation 5.35, 19
The histamine-induced wheal and flare areas were analyzed as absolute values and as percent reduction of predrug control values, by the two-way analysis of variance and Duncan's multiple range test. Pruritus scores were analyzed by the same tests.

RESULTS

HPLC analysis

Serum hydroxyzine concentrations were determined with no interference from endogenous substances or hydroxyzine metabolites, with this HPLC procedure. Calibration curves were linear over the range 0 to 100 ng/ml and the mean coefficient of variation over a 6 mo period was 10.6%. The limit of sensitivity with these specifications was 3 ng of hydroxyzine in 1 ml of serum.

Pharmacokinetics

Serum hydroxyzine concentrations from the seven healthy volunteers are listed in Table I and representative log serum hydroxyzine concentration vs. time plots are shown in Fig. 1. The 0.7 mg/kg oral dose of hydroxyzine produced a mean peak serum concentration of 72.5 ± 11.1 ng/ml at a mean time of 2.1 ± 0.4 hr. It was not possible to fit the serum hydroxyzine concentration vs. time data to a compartment model, since insufficient samples were collected in the absorption phase. A two-compartment model with first-order absorption may be required, as evidenced by visual inspection of the curves.

The pharmacokinetic data are given in Table II. The mean elimination half-life calculated from the terminal linear portion of the curves was 20.0 ± 4.1 hr. This was similar to the mean residence time value of 17.7 ± 5.2 hr calculated with the method of statistical moments. The mean clearance rate, 9.78 ± 3.25 ml/min/kg, and mean apparent volume of distribution, 16.0 ± 3.0 L/kg, were also calculated by nonparametric methods. These were not corrected for bioavailability, since no intravenous dose is available for hydroxyzine.

Wheal and flare

Three of the volunteers had intradermal histamine injections every 3 to 12 hr over a 48 hr period in the absence of hydroxyzine. By the two-way analysis of variance, the absolute wheal or flare areas obtained were not significantly different (p = 0.01) from subject to subject at any time [wheal F = 2.22, flare F = 5.30 (F0.0.99 [2,12] = 6.93)] or at the various times within the same subject [wheal F = 3.13, flare = F 4.82, (F0.0.99 [6,12] = 4.82)].

In the seven healthy volunteers who received hydroxyzine, the wheal area values obtained at any given time were not significantly different (p = 0.01) from subject to subject: [F = 1.90 (F0.0.99 [6,78] = 3.12)] but there was a significant difference between the values obtained at the various times within the same subject [F = 6.91 (F0.0.99 [13,78] = 2.50)]. The flare area values obtained from the different subjects at any time (F = 11.10) and also at the various times within the same subject (F = 13.51) were significantly different. Thus there is more intersubject variability in the flare data than the wheal data.
FIG. 2. Mean + S.E.M. histamine-induced wheal and flare areas before and after administration of a 0.7 mg/kg oral dose of hydroxyzine.

Log mean percent reduction of control wheal and flare areas were plotted vs. time (Fig. 3), resulting in curves similar to the log serum hydroxyzine concentration vs. time plots. However, peak mean percent reduction of the wheal occurred much later, at 6 to 12 hr after the dose, and peak mean percent reduction of the flare occurred from 5 to 9 hr after the dose. Half-life values of 22.0 hr for wheal data and 46.5 hr for flare data were calculated. These results support the prolonged mean hydroxyzine serum half-life value of 20.0 ± 4.1 hr.

Pruritus

Clinically and statistically significant suppression of pruritus at the wheal and flare sites (p ≤ 0.025) occurred from 1 to 12 hr after the dose, when mean serum hydroxyzine concentrations ranged from 70.0 ± 12.9 ng/ml to 22.4 ± 7.9, and at 36 hr, when the mean serum hydroxyzine concentration was 9.6 ± 2.9 ng/ml (Fig. 4).

Adverse effects

Transient dry mouth, drowsiness, and light-headedness occurred in five of seven subjects from 1 to 6 hr after the dose, when mean serum hydroxyzine concentrations were greater than 39.2 ± 12.3 ng/ml.

DISCUSSION

Pharmacokinetics

In a study of the disposition of tritiated hydroxyzine in rats, 40% to 42% of the radioactivity was excreted within 24 hr, largely in the feces via the bile and in the urine. Hydroxyzine was rapidly distributed to all organs studied, with the highest activity being found in the lungs, fat, liver, spleen, and kidneys. The drug appeared to be completely metabolized, since less than 2% of the radioactivity as unchanged drug was recovered in the urine or feces. About 16% of the dose of radioactivity was recovered in urine over 5 days. Of this, 7% was identified as p-chlorobenzophenone, p-chlorobenzhydrol, and p-chloro-p'-hydroxybenzophenone, 15% as p-chlorobenzhydrol and p-chloro-p'-hydroxybenzophenone glucuronides, and 5% as piperazine and 2-[2-(1-piperazinyl)-ethoxy]ethanol.

In a previous pharmacokinetic study in humans, hydroxyzine given to four adults in a dose of 1.1 to 1.4 mg/kg appeared to be well absorbed, giving a peak concentration of about 80 ng/ml 3 hr after administration. The mean elimination half-life was about 3 hr in this study, in which hydroxyzine concentrations were measured by a gas-liquid chromatography mass spectrometry technique. Serum concentrations were monitored for 24 hr but only those at 1, 2, 4, 6, and 8 hr were determined quantitatively. In our patients, who had serum concentrations quantitated for at least 60 hr, we found a much longer mean terminal half-life value of 20.0 ± 4.1 hr, slow total body clearance rates, and large volumes of distribution. In order to confirm these results, the disposition of hydroxyzine in humans must be determined in multiple-dose studies in a carefully monitored population.

Wheal and flare

The histamine-induced wheal and flare is a safe, well-studied, quantitative bioassay. The dose-related response to intradermally injected histamine is similar in normal and in asthmatic subjects. Wheal formation and reabsorption take place over about 80 min, with the wheal edge being sharpest 10 min after injection of histamine. When the test is performed in a carefully controlled manner by a skilled injector, the day-to-day variation of wheal and flare size is minimal for tests performed at the same time of day over several days. This reproducibility was confirmed in the three untreated subjects in our study who were tested over a 48 hr period. We did not find circadian variation in wheal and flare sizes in our untreated subjects. Where this has been shown, wheals and flares were larger at 2300 hr than at 0700 to 1100 hr.
In our hydroxyzine-treated subjects, wheals and flares were maximally suppressed in the evening. Since the maximum suppression of the wheals occurred 6 to 12 hr after the dose and 4 to 10 hr after peak serum hydroxyzine concentrations were achieved, maximum distribution into the skin receptor sites presumably required many hours after dose administration. This provides rational pharmacokinetic support for the clinical dictum that antihistamines should be given before an anticipated allergic reaction rather than after, in order to exert a maximal effect.

Hydroxyzine results in more lasting suppression of the histamine-induced wheal-and-flare response than diphenhydramine, tripelennamine, chlorpheniramine, or promethazine. A 25 mg dose of hydroxyzine four times daily for 3 days resulted in 60% suppression of the wheal 1 hr after the last dose of the drug. In our study, a single dose of hydroxyzine profoundly suppressed the wheal and flare in all subjects. Maximal suppression was 80% for the wheal and 92% for the flare. This was found 6 to 12 hr and 5 to 9 hr after the dose, respectively, at a time of day when, in the absence of hydroxyzine, wheal and flare might be expected to be largest.

Pruritus

Hydroxyzine, 25 mg, increases the threshold for itching from the histamine-induced wheal and flare by 750-fold in normal subjects and is superior to that of diphenhydramine, tripelennamine, chlorpheniramine, or promethazine. A 25 mg dose of hydroxyzine four times daily for 3 days resulted in 60% suppression of the wheal 1 hr after the last dose of the drug. In our study, a single dose of hydroxyzine profoundly suppressed the wheal and flare in all subjects. Maximal suppression was 80% for the wheal and 92% for the flare. This was found 6 to 12 hr and 5 to 9 hr after the dose, respectively, at a time of day when, in the absence of hydroxyzine, wheal and flare might be expected to be largest.

Adverse effects

The drowsiness and dry mouth noted by some of the subjects in our study are not surprising consider-
ing that none of them had ever received antihista-
mamines previously. These adverse effects occurred
when serum hydroxyzine concentrations were high-
est. In the only previous report in which adverse ef-
From hydroxyzine have been correlated with
fects from hydroxyzine have been correlated with
sion of wheals, flares, and associated pruritus per-
FIG. 4. Mean + S.E.M. histamine-induced pruritus scores
before and after administration of a 0.7 mg/kg oral dose of
hydroxyzine.

**Conclusion**

Data from the present study suggest that hydroxy-
zine may exert its antihistaminic actions effectively
when given once or twice daily to adults, instead of
three or four times daily as presently recommended.
In general, doses of a drug should ideally be given
half-life to maintain stable serum concentra-
tion. In every subject, suppression of wheals,
flares, and associated pruritus persisted even when serum hydroxyzine concentrations were low.

Hydroxyzine is frequently used in clinical research
as a prototype histamine $H_1$ receptor antagonist. The
information from the present single dose study will be
useful in designing future systematic investigations of
this drug.

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