PHARMACOKINETIC STUDY OF CETIRIZINE AS A SINGLE DOSE
OF 5 mg (ORAL SOLUTION OF 10 mg/ml)
IN CHILDREN AGED 2–6 YEARS

(Translated from RRCF92F1502)

STUDY A 176 - PROTOCOL RPCF91A0701

REPORT (final version)

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SUMMARY

Cetirizine, the principal metabolite of hydroxyzine, is a potent and specific antihistamine H₁ (1) with little sedative action (2). A study was performed in the Saint Vincent de Paul Hospital (Anaesthesiology Department of Prof. C. SAINT-MAURICE, Dr. I. MURAT; Clinical Pharmacology Department of Prof. G. Olive, Prof. G. Pons) to determine the pharmacokinetic parameters of cetirizine in children aged 2 years or more and not more than 6 years. Cetirizine in the form of a solution at 10 mg.ml⁻¹ was administered orally on an empty stomach as a single dose of 5 mg or 0.32 ± 0.07 mg.kg⁻¹ (mean ± standard deviation (SD) of the variable) as premedication before a simple surgical intervention (mean duration ± SD: 0.90 ± 0.25 hours), given a mean of 1.73 ± 0.64 hours before anaesthesia in 8 children aged 3.84 ± 1.17 years between July 1991 and January 1992. Seven specimens of 1.5 ml blood were obtained in dry heparinized tubes via a catheter inserted for anaesthesia and left in place after surgery; these specimens were collected before and 0.5, 1.5, 4, 8, 12 and 24 hours after the cetirizine dose. Control urine and urine produced during 24 hours after cetirizine administration were collected and frozen at -18°C. Plasma and urinary cetirizine concentrations were measured by high-pressure liquid chromatography. The results for the plasma (n = 8) and urinary (n = 4) kinetic parameters are presented in the following tables:
### Pharmacokinetics of cetirizine

**Plasma data**

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>Mean ± SD (Range)</th>
<th>Total n = 8</th>
<th>95 % confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg.l$^{-1}$)</td>
<td>606.5 ± 231.3 (196.3 - 856.9)</td>
<td></td>
<td>413 - 800</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>1.93 ± 1.39 (0.50 - 4.08)</td>
<td></td>
<td>0.77 - 3.09</td>
</tr>
<tr>
<td>AUC(0-t) (μg.l$^{-1}$.h)</td>
<td>4506.3 ± 1251.1 (2013.56 - 5741.92)</td>
<td></td>
<td>3460 - 5550</td>
</tr>
<tr>
<td>$\lambda_{\text{e}}$ (h$^{-1}$)</td>
<td>0.128 ± 0.020 (0.090 - 0.159)</td>
<td></td>
<td>0.111 - 0.145</td>
</tr>
<tr>
<td>$C_{\text{ss}}$ (μg.l$^{-1}$)</td>
<td>644.8 ± 226.7 (382.39 - 1086.72)</td>
<td></td>
<td>455 - 834</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>5.55 ± 0.98 (4.37 - 7.69)</td>
<td></td>
<td>4.73 - 6.37</td>
</tr>
<tr>
<td>AUC(0-∞) (μg.l$^{-1}$.h)</td>
<td>4772.05 ± 1318.4 (2155.93 - 6107.83)</td>
<td></td>
<td>3670 - 5870</td>
</tr>
<tr>
<td>MRT or $t$ (h)</td>
<td>8.13 ± 1.31 (6.89 - 10.39)</td>
<td></td>
<td>7.03 - 9.23</td>
</tr>
<tr>
<td>$\text{*Cl}_{\text{app}}$ (ml.min$^{-1}$.kg$^{-1}$)</td>
<td>1.27 ± 0.80 (0.79 - 3.22)</td>
<td></td>
<td>0.59 - 1.93</td>
</tr>
<tr>
<td>$\text{*Vd}_{\text{app}}$ (l.kg$^{-1}$)</td>
<td>0.60 ± 0.38 (0.37 - 1.52)</td>
<td></td>
<td>0.29 - 0.91</td>
</tr>
<tr>
<td>$C_{\text{max}}$ normalized (μg/l$^{-1}$)</td>
<td>599.3 ± 237 (141.3 - 957.6)</td>
<td></td>
<td>401 - 797</td>
</tr>
<tr>
<td>AUC normalized (0-t) (μg.l$^{-1}$.h)</td>
<td>4464 ± 1420 (1449.76 - 6089.28)</td>
<td></td>
<td>3270 - 5650</td>
</tr>
<tr>
<td>AUC normalized (0-∞) (μg.l$^{-1}$.h)</td>
<td>4729 ± 1513 (1552.27 - 6361.57)</td>
<td></td>
<td>3470 - 5990</td>
</tr>
</tbody>
</table>

**SD** : standard deviation of the variable

* values for clearance and volume of distribution assuming complete absorption
Urinary data: mean values, n = 4 (cases 1, 4, 5, 6)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ae (24) (µg)</th>
<th>Urinary excretion (% of the dose)</th>
<th>Renal Cl (ml.min⁻¹.kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD (range)</td>
<td>1922.5 ± 494.6</td>
<td>38.4 ± 9.9</td>
<td>0.42 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>(1348.5 - 2456.2)</td>
<td>(27.0 - 49.1)</td>
<td>(0.33 - 0.55)</td>
</tr>
<tr>
<td>95% confidence interval of the mean</td>
<td>1135 - 2709</td>
<td>22.6 - 54.2</td>
<td>0.26 - 0.58</td>
</tr>
</tbody>
</table>

SD: standard deviation of the variable

A correlation between the kinetic parameters and age was sought for. Only the correlation between MRT and age was significant (p<0.05).

In conclusion:

- The mean elimination half-life in children aged 2-6 years is half that in adults. The mean apparent elimination clearance is twice as great as in adults.

- There seemed to be no influence of age on the pharmacokinetic parameters of cetirizine in the group of children aged 2-6 years.

- A mean of at least 38.4% of the administered cetirizine dose were recovered in unchanged form in the 24-hour urine, i.e. less than in adults.

- Cetirizine was well tolerated.
I. INTRODUCTION

Cetirizine, the principal metabolite of hydroxyzine, as a potent and specific antihistamine H₁ (1) with little sedative action (2).

In adults there is rapid absorption after the oral administration of a tablet of 10 mg, with a mean t_{max} of one hour and a peak concentration (C_{max}) of about 350 µg.l⁻¹ (3). The plasma decrease is biphasic and has a mean elimination half-life t_{1/2h} of 10 h. The mean apparent plasma clearance is 0.6 ml.min⁻¹.kg⁻¹ and the apparent volume of distribution is about 40 litres. Elimination is highly dependent on kidney function. Indeed, 60% of the administered cetirizine are recovered unchanged in the urine; small amounts of an inactive O-dealkylated metabolite (4).

In children aged 6-12 years, a single oral dose of 5 mg cetirizine provides a peak concentration (C_{max}) close to that in adults (275 µg.l⁻¹), with a faster fall (mean t_{1/2h} of 6 h), a larger apparent plasma clearance (0.9 ml.min⁻¹.kg⁻¹) and a comparable apparent volume of distribution/kg. About 70% of an oral dose are recovered in the urine in unchanged form (5, 6).

II. PURPOSE OF THE STUDY

The purpose of this study was to determine the pharmacokinetic parameters of cetirizine in children aged 2 years or more and 6 years or less having to undergo a simple surgical intervention. This study was performed after the oral administration of a single dose of 5 mg cetirizine as a solution of 10 mg.ml⁻¹ in premedication for surgery, 90 minutes before anaesthesia.

III. MATERIALS AND METHODS

III.1. Clinical investigators
This study was performed at the St. Vincent de Paul Hospital (Paris), in Prof. C. Saint-Maurice's Department of Anaesthesiology under the supervision of Dr. I. Murat, and in Prof. G. Olive's Department of Clinical Pharmacology under the supervision of Prof. G. Pons.
b) Administration:

The single dose of 5 mg, i.e. 0.5 ml of cetirizine was taken with a syringe and the volume was administered either directly into the mouth via the syringe or diluted in 10-20 ml of water. The product was administered on an empty stomach as premedication for surgery, about 90 minutes before anaesthesia.

III.3. Subjects

Eight children aged 2-6 years were enrolled in this study. As stated in the protocol, they were divided into 4 age groups (group 1: aged 2 years or more and 3 years or less; group 2: aged 3 years or more and 4 years or less; group 3: aged 4 years or more and 5 years or less; group 4: aged 5 years or more and 6 years or less).

These children underwent a simple surgical intervention (with a mean duration ± standard deviation of 0.90 ± 0.25 hours).

After obtaining the written consent of the parents or guardians, the children were enrolled if they complied with the following inclusion criteria:

- Children of both sexes.
- Aged 2-6 years.
- Hospitalized and requiring a simple surgical intervention (predicted duration of 60 to a maximum of 90 minutes),

and did not present any of the following exclusion criteria:

- Known allergy to antihistamines H1.
- Concomitant disease:
  - impaired kidney function, defined by a blood creatinine value greater than the mean + 2 standard deviations for age (Annexe C of the protocol),
  - impaired liver function, defined by a Quick time of less than 70% and/or transaminase more than twice the upper normal limit,
  - known heart failure,
  - poor nutritional status,
  - known digestive malabsorption.

- Children with a body weight more than the mean + 2 standard deviations for age (see growth curves in Annexe D of the protocol).

- Children taking the following concomitant medicines:
  - within the month prior to the study and during the study:
    - enzyme inducers (rifampicin, or antiepileptics such as pheno-barbital, carbamazepine and phenytoin),
    - enzyme inhibitors (valproic acid, anti-H₂, erythromycin, TAO, imidazole fungicides),
  - within the 2 days prior to the study and during the study:
    - antihistamines.

- Participation in a clinical study during the 3 months prior to this study.

The following drugs were permitted during the study:
- Anaesthetic drugs:
  - thiopental, 5-10 mg/kg i.v.
  - isoflurane, 1-3% by mask
  - vecuronium bromide (Norcuron), 70-100 µg/kg
  - fentanyl, 2-5 µg/kg
  - nitrous oxide/oxygen
  - flunitrazepam, solution at 0.04 mg/kg, intra-rectal.

- Local anaesthetics:
  - 0.25% bupivacaine, for spinal or trans-sacral anaesthesia.

- Paracetamol as required, at the usual doses.

- Any other drug administered during the study had to be reported in the case report forms.
The following additional examinations were performed in a single laboratory within a maximum of 8 days before the administration of cetirizine:
- differential blood cell count, platelets
- bilirubin
- SGOT, SGPT
- creatinine
- Quick time

III.4. Study design
One hour before inserting the catheter, the skin at the puncture site was smeared with EMLA cream and covered with an occlusive dressing. About 90 minutes before anaesthesia, the fasting child ingested 0.5 ml of cetirizine solution, introduced directly into the mouth by means of a syringe or diluted with 10-20 ml of water.

The 7 specimens of 1.5 ml blood were obtained at times t0 hour, t0.5 hour, t1.5 hours, t4 hours, t8 hours, t12 hours and t24 hours after the cetirizine dose. They were collected in dry heparinized tubes via the catheter inserted for anaesthesia and left in place after the operation.

The tubes were centrifuged at 3000 rpm for 10 minutes in the pharmacology laboratory and the supernatant plasma was frozen at -18 °C.

As far as possible, a specimen of control urine and the urine produced during 24 hours following cetirizine administration were collected. After measuring its volume, an aliquot was frozen at -18 °C in the pharmacology laboratory.

III.5. Analytical methods
The assays were performed under the supervision of Mrs. Rey, head of the drugs assay unit (Prof. G. Olive's department).

The plasma and urinary concentrations of cetirizine were measured by high-pressure liquid chromatography within 20 min incubation with ethyl acetate at pH 5.
III.6. Data analysis
The data were recorded in a VICTOR VPC II computer and processed by the TRIOMPHE program. This program was developed by Ph. d'Athis in the Pharmacology Laboratory of the St. Vincent de Paul Hospital and was used to calculate the pharmacokinetic parameters in a "model-independent" manner.
2. Statistical calculations

a) Plasma data

The plasma concentrations found at each measurement time were described in such a way as to obtain a curve of mean concentrations for the entire study population.

The descriptive analysis of the pharmacokinetic parameters was completed by calculation of Student's 95% confidence interval.
Spearman's correlation coefficient was calculated between each pharmacokinetic parameter and age, and was then tested against zero. Since this test is non-parametric, there was no need to confirm normal distribution. The relationship between each kinetic parameter and age was analyzed by linear regression.

b) **Urinary data**

The descriptive analysis of urinary elimination was completed by calculating the 95% confidence interval. Spearman's correlation coefficient was calculated between the amount of drug recovered from the urine ($AE_{(24)}$) and age, and was then tested against zero.

The mean and standard deviation of $Ae$, renal clearance and urinary excretion were calculated.

**IV. RESULTS**

The eight children were enrolled between July 1991 and January 1992.

**IV.1. Deviations from the protocol**

a) **Administration of the product**

* Method of administration: Although the protocol planned the administration of 10 drops of cetirizine solution by dropper, the corresponding volume of 0.5 ml was measured with a
IV.2. Presentation of the results

The clinical characteristics of each subject on enrolment are presented together with the mean, standard deviation and range for all these data in Table I (Annexe II).

a) Plasma parameters

* The plasma concentrations versus time, the real sampling times and the individual curves are presented in Annexe III.

* The individual plasma concentration-time curves in semi-logarithmic coordinates and the table of $t_{1/2}$ calculations are presented in Annexe IV.

* The 8 individual curves of plasma concentration versus time are shown superimposed in Figure 1 (Annexe II).

* The mean plasma concentration-time curve for all subjects is presented in Figure 2 (Annexe II).

* The correlation between administered cetirizine dose in mg.kg$^{-1}$ and age is presented in Figure 3 (Annexe II).

* The correlations between the following kinetic parameters: $C_{max}$, $t_{1/2}$, $AUC_{0-\infty}$, MRT or $t'$, $Cl_{app}$, $Vd_{app}$, $C_{max}$ normalized for a dose of 0.3 mg.kg$^{-1}$, $AUC_{0-\infty}$ normalized for a dose of 0.3 mg.kg$^{-1}$, $AUC_{0-\infty}$ normalized for a dose of 0.3 mg.kg$^{-1}$, and age are presented in Figures 4a-4i (Annexe II).
* The plasma kinetic parameters: $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{0-\infty}$, 
lambda, $C_t$, $t_{1/2}$, $AUC_{0-\infty}$, MRT or $t$, $Cl_{\text{app}}$, $Vd_{\text{app}}$, $C_{\text{max}}$ normalized for a
dose of 0.3 mg.kg$^{-1}$, $AUC_{0-\infty}$ normalized for a dose of
0.3 mg.kg$^{-1}$, and $AUC_{0-\infty}$ normalized for a dose of 0.3
mg.kg$^{-1}$ are presented in Table II (Annexe II) as
means and standard deviations, range and confidence
interval of the mean for the entire study
population. Individual values are presented in
Annexe V.

b) Urinary parameters
* The individual urinary cetirizine concentrations
(n = 6) are presented in Annexe VI. The urinary
concentrations were not determined in the 2 cases
(Nos. 2 and 8) with incomplete collection.

* Renal clearance was calculated in 6 cases (Nos. 1,
3, 4, 5, 6, 7).

* The amount of drug recovered from the urine ($AE_{124}$)
and urinary excretion as a percentage of dose were
determined in 4 cases (Nos. 1, 4, 5, 6) with
collection periods close to 24 hours (collection
period varying from 19 to 25 hours after the
cetirizine dose).

* The individual urinary parameters, $AE_{124}$, urinary
excretion and renal clearance are presented in
Table III (Annexe II).

* The mean, standard deviation, range and confidence
interval of the mean (n = 4) of $AE_{124}$, urinary
excretion and renal clearance are presented in
Table IV (Annexe II).

* The individual cumulative urinary excretion versus
time curves are presented in Annexe VII.

* The correlation between the amount of drug
recovered from the urine ($AE_{124}$ and age is presented
in Figure 5 (Annexe II), and that between renal
clearance and age is presented in Figure 6 (Annexe
II).

IV.3. Statistical comparisons

a) Plasma parameters
No significant correlations ($p < 0.05$) were found
between the following kinetic parameters and age:
$C_{\text{max}}$, $t_{1/2}$, $AUC_{0-\infty}$, $Cl_{\text{app}}$, $Vd_{\text{app}}$, normalized $AUC_{0-\infty}$ and
normalized $C_{\text{max}}$, and age (Figures 4a, b, c, e, f,
g, i) (Annexe II).
In contrast, a significant correlation (p<0.05) was found between MRT (or $T_{1/2}$) and age. It should be noted that the mean MRT decreased with age in the study population (n = 8; Figure 4d, Annexe II).

b) Urinary parameters
Considering the small number of complete urine collection, the means and standard deviations of the parameters were calculated only for the whole group and not per age range.

No significant correlation was found between the amount of drug recovered from the urine ($Ae_{24}$) and age, nor between renal clearance and age.

IV.4. Safety
The drug was well tolerated by all the enrolled children. Indeed, no adverse effects were reported during the 24 hours following the administration of cetirizine.

V. DISCUSSION
After discussing some methodological points, our results will be compared with those of the literature in order to deduce practical consequences for the prescription of cetirizine in young children.

V.1. Methods

a) Concomitant treatments

* Anaesthesia :
For ethical and practical reasons, this kinetic study was performed in children under general anaesthesia. Indeed, laboratory tests and repeated venous punctures without therapeutic benefit cannot be imposed on children. The anaesthetic protocol (products, doses, duration of intervention, time between administration and the onset of anaesthesia) was standardized. The drugs planned in the anaesthetic protocol modified neither cardiac output nor hepatic blood flow at the doses used. Their influence on the measured pharmacokinetic parameters is thus limited, and the conclusions can be extrapolated to non-anaesthetized children.

* Other treatments :
Similarly, any other concomitant treatment might modify the kinetics of the product. Only one child (case No. 6) received a suppository of 150 mg paracetamol for analgesic purposes.
b) **Division into 4 age ranges**
The protocol planned to include 8 children divided into 4 age ranges of 2 children. However, only the results for the whole group \((n = 8)\) have been adopted for several reasons:

- the purpose of this subdivision was to ensure an even distribution of ages between 2 and 6 years,
- the population per age range is very small \((n = 2)\).

c) **Dose of cetirizine administered**
The kinetic study was performed after the administration of 0.5 ml of 1% cetirizine solution to 8 children. The dose in mg.kg\(^{-1}\) thus varied according to the weight of each child (mean dose 0.32 ± 0.07 mg.kg\(^{-1}\)). This is why a normalized peak concentration and a normalized area under the curve were calculated for each child. It should be noted that the mean values for these normalized parameters are not very different from the untreated values (Table II, Annexe II).
e) Urinary parameters
There are only a few renal clearance values available (n = 4) for calculating a mean. Indeed, the individual renal clearance was determined in 6 children but the mean was calculated with just 4 values since the clearance had been evaluated in 2 cases with urine collected only for about 12 hours.

V.2. Effect of age
In this group of 8 children aged 2-6 years there was no effect of age on any of the studied kinetic parameters except MRT (or T) (p < 0.05). MRT is a general kinetic parameter which takes both absorption, distribution and elimination phenomena into account. In addition, after excluding subject No. 2, the correlation between MRT and age was no longer significant. This significant correlation is thus to be considered with great reservation.

V.3. Comparison of our results with those of other studies
Results are available for kinetic studies performed in elderly subjects (10-mg tablet; CB87A101), in adults (20-mg capsule and 10-mg tablet; LE87E151), children aged 10-12 years (5-mg tablet) and children aged 6-12 years (5-mg capsule; DE88A202). The relative bioavailability data suggest that the oral cetirizine formulations used are bioequivalent.

a) Plasma parameters
The means and standard deviations of the kinetic parameters obtained in the various studies are presented in Table VI (Annexe II).

It seems that in the studied group of children aged 2-6 years:

- the mean Cmax relative to administered dose in mg.kg\(^{-1}\) is in the same order of size as that in adults and elderly subjects;

- the mean tmax observed is greater than the mean values observed in the other studied groups, although marked interindividual variability is also noted.

- the mean t\(_{1/2a}\) is half that of adults and elderly subjects, but is in the same order of size as in children aged 6-12 years.

- apparent clearance is twice as great as the mean value in adults (capsule of 10 or 20 mg).
- the mean apparent Vd is equivalent to the mean value in adults (10-mg tablet) and in children aged 6-12 years (5-mg capsule).

b) **Urinary parameters**
At 24 hours, urinary excretion (as a percentage of dose) was:
- at least 38.4 ± 9.9 % in the studied group
- 70 % in children aged 6-12 years
- 63.7 % in children aged 10-12 years
- 56.3 % (10-mg dose) and 50.0% (20-mg dose) in adults, and
- 41.9 % in elderly subjects.

It therefore seems that urinary excretion in unchanged form is less in children aged 2-6 years, but:

- there is uncertainty regarding the time at which the urine pouch was fitted. In some cases the pouch could not be applied immediately after the cetirizine dose (intervention involving the urinary system),

- this parameter was calculated in a small sample (n = 4). The mean is 38.4 % with marked interindividual variability (standard deviation 9.9 %; range 27.0 % - 49.1 %).

V.4. **Practical consequences**

The plasma kinetics results obtained in children aged 2-6 years suggest that, considering the elimination half-life which is half that in adults and the apparent clearance which is twice that in adults, the dose in mg.kg⁻¹.day⁻¹ should be multiplied by 2 and that this should be administered in 2 divided doses instead of the single daily dose used for adults. However, the value of dosage adjustment in children in relation to these pharmacokinetic features is subject to the demonstration of a potential correlation between plasma concentration and the desired effect, and between plasma concentration and side effects.
VI. CONCLUSION

The mean elimination half-life in children aged 2-6 years is half that in adults. The mean apparent elimination clearance is twice that in adults.

There seems to be no influence of age on the pharmacokinetic parameters of cetirizine in the group of children aged 2-6 years.

A mean of at least 38.4% of the administered cetirizine dose is recovered in unchanged form from the 24-hour urine, i.e. less than in adults.

Cetirizine is well tolerated.
VII. REFERENCES

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