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A PHARMACOKINETIC STUDY OF CETIRIZINE AFTER ADMINISTRATION OF A SINGLE ORAL DOSE OF 5 MG (10 DROPS OF A DRINKABLE SOLUTION CONTAINING 10 MG/ML) TO CHILDREN BETWEEN 2 AND 6 YEARS OF AGE

Principal Investigator : Prof. C. HARVENGT, MD, PhD,
Laboratory of Pharmacotherapy
Avenue E. Mounier, 53
B-1200 Brussels
Belgium

Co-Investigators : J.P. DESAGER, Ph.D.
Laboratory of Pharmacotherapy
Avenue E. Mounier, 53
B-1200 Brussels
Belgium

I. DAB, MD, PhD,
Department of Pediatrics
AZ-VUB
Laarbeeklaan, 101
B-1090 Brussels
Belgium
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I. SUMMARY

To study the plasma kinetics of a pediatric preparation of cetirizine in the form of drops for small children (between 2 and 6 years of age), we conducted a study using a single oral dose of 5 mg cetirizine. This was an open study in 8 children (5 boys and 3 girls) between 2.5 and 3.8 years of age.

Plasma kinetics and urinary excretion were assessed over a 24-h period during hospitalization for a chronic respiratory infection or allergic condition. The mean values (± standard deviations) of the pharmacokinetic parameters in these 8 subjects were: $C_{\text{m}}$: $660 \pm 191$ ng/ml; $T_{\text{m}}$: $1.44 \pm 1.12$ h; $T-1/2\beta$: $4.91 \pm 0.6$ h; AUC 0.5→∞: $4009 \pm 867$ ngml$^{-1}$lh; Cl/F: $1.48 \pm 0.41$ ml/min/kg; VD/F: $0.63 \pm 0.18$ l/kg. The urinary excretion was $37.8 \pm 5.2$ % of the administered dose.

Comparing our results in these young children with those obtained from previous studies, it would appear that in older children the $t-1/2\beta$ is similar but that the apparent oral clearance is somewhat lower. In young adults, the $t-1/2\beta$ is greater and the apparent oral clearance is lower.
II. INTRODUCTION

Cetirizine, an active metabolite of hydroxyzine, is commercially available for adult use in the form of 10 mg tablets in the EEC countries. It is a powerful and specific (1) H₁ antihistamine with a weak sedative effect (2).

Pharmacokinetic studies in adults show that cetirizine is rapidly absorbed after a single oral dose of 10 mg; the peak plasma concentration of approximately 350 ng/ml is reached, on average, 1 h later (3). There is a biphasic clearance from the plasma with a t₁/₂β of 10 h on average. The mean total plasma clearance is 0.6 ml/min/kg and the volume of distribution is approximately 40 l. Excretion from the body is closely related to the renal function; 60 % of the administered dose is found unchanged in the urine; small quantities of an inactive de-alkylated metabolite are also found (4).

In children between 6 and 12 years of age, a single dose of 5 mg cetirizine gives a similar plasma peak (275 ng/ml), but the plasma clearance is more rapid (mean t₁/₂β of 6 h). This is due to a higher total plasma clearance (0.9 ml/min/kg), as the distribution volume/kg remains comparable. Approximately 70 % of the administered dose is found unchanged in the urine (5,6).

To date, there is no pharmacokinetic data available on the behaviour of cetirizine in young children (i.e. between 2 and 6 years of age). Such information is necessary before cetirizine can be developed for use in this age group.
The aim of this study was to measure the pharmacokinetic parameters of cetirizine in children between 2 and 6 years of age, so as to determine whether they are different from the data available for older children. The study was conducted after the administration of a single oral dose of 5 mg cetirizine in the form of drops containing 10 mg/ml (batch No. 76), a preparation shown to be bioequivalent to tablets containing 10 mg (7).

III. METHODS

a) Study plan

This was a single-dose, open study. Eight children were included in the study (envisaged: 6 to 8) after ensuring that they met the criteria of eligibility and checking their laboratory results. A drip was set up in all children to keep an intravenous line open. The fasted children were given 10 drops of the test solution of cetirizine (5 mg). Nine blood samples of between 3 and 4 ml were drawn in heparin tubes at the following times: 30 min, 1 h, 1 h 30, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h after the oral dose. The urine was collected as accurately as possible in each child. During this period, special attention was paid to recording any adverse effects.

The study protocol was approved by the Medical Ethics Committee of the St-Luc University Clinic (UCL-Woluwe) and Vrije Universiteit in Brussels. The parents gave written consent for their children to participate in the study.

b) Selection of children

The boys and girls expected to satisfy the selection criteria were hospitalized for a work-up of their chronic respiratory infections or other conditions for which an allergic origin was suspected.

The children did not receive a direct benefit from the test product, but could later be candidates for treatment with cetirizine.

c) Treatments

At about 8 a.m., the children, fasted overnight (8 p.m.), were given 5 mg cetirizine in the form of drops (10 drops of a solution containing 10 mg/ml of active principle, 20 drops = 1 ml) administered in a small quantity of water. The drugs necessary for the main condition for which the children were suffering were continued and are described in each file. Among the drugs used, only valproic acid (Depakine®) could have influenced the plasma kinetics of cetirizine because of its strong binding to the plasma proteins (subject DEL/006).
d) **Samples for pharmacokinetic measurements and description of the parameters calculated**

Blood samples were taken, as described in paragraph a) above, and sent immediately to the medical biochemistry laboratory of the AZ-VUB.
The peak plasma concentration (Cₘₐₓ) and the time to attain this (Tₘₐₓ) are the observed values. Because of the small number of experimental points, the plasma excretion half-life was calculated by log/lin regression of the points on the last slope. The area under the curve (AUC) was calculated between 0.5 and 24 h by the trapezoidal rule and extrapolated to infinity using the formula

\[ \text{AUC}_{\infty} = \text{AUC}_{24} + \frac{C_{24}}{\beta} \]

in which \( C_{24} \) h is the concentration measured at 24 hours and \( \beta \) the last slope.

The apparent oral clearance was calculated by dividing the dose by the \( \text{AUC}_{\infty} \). Finally, the apparent volume of distribution is the result of dividing the apparent oral clearance by the last slope (\( \beta \)).

e) Compliance

The dose of cetirizine was administered by a doctor or nurse who ensured that the child ingested the entire dose.
IV. RESULTS

a) Demography

Eight children (5 boys and 3 girls) from 2.5 to 3.8 years of age participated in the study. Their demographic data are shown in Table I.
b) Pharmacokinetic parameters
parameters. The observed $C_{\infty}$ was $660 \pm 191$ ng/ml (extremes: 410-962) and reached in $1.44 \pm 1.12$ h (extremes: 0.5-4). The plasma elimination half-life was $4.91 \pm 0.6$ h (extremes: 4.1-6). The area under the curve, extrapolated to infinity, was $4009 \pm 867$ ng/ml·h (extremes: 2942-5296).

The apparent oral clearance was $1.48 \pm 0.41$ ml/min/kg (extremes: 1.02-2.3) and the apparent volume of distribution was $0.63 \pm 0.18$ l/kg (extremes: 0.42-0.94). As one subject (DEL/006) had plasma kinetic values which were completely different from those of the other subjects, the means were calculated without including the values from this subject (see Table III (n=7)).
collection and concentrations measured. Urinary excretion represented 37.8 ± 5.2 % of the oral dose (extremes : 31.2-44.6).
c) Safety

No adverse effects were reported during the study.
V. DISCUSSION

The group of subjects in the study was homogeneous in age (2.5 to 3.8 years). All had a condition for which cetirizine could have been indicated. The protocol was respected, and we consider that we may draw some pertinent conclusions from our results.

We compared our pharmacokinetic results with those obtained in the studies by Uden (5) (14 children between 7 and 12 years of age), Baltes (6) (urinary excretion in 12 children between 10 and 12 years of age), Watson (9) (19 children between 5 and 12 years of age) and Harvengt (7) (16 young adults between 21 and 35 years of age).

Table V summarizes the main data (means ± standard deviations and extremes). This comparison shows that plasma kinetics of cetirizine in very young children are characterized by a shorter plasma elimination half-life and a higher apparent oral clearance than in older children (5,9) and adults (7). The apparent volume of distribution in the younger children was higher than that of older children in the study by Uden (5), but similar to that found by Watson (9). In contrast, the Tₘₙ was longer than in adults (7).

The urinary excretion of cetirizine proved to be low, as in the study by Watson (9), although there is no difference between children (6) and adults (7). It should, however, be pointed out that it is difficult to obtain a complete urinary collection in small children, and we can also not be sure that the bladder was emptied at the 24th hour. In the 5 urinary collections judged to be complete, the maximum excretion was 44.6 %. By contrast, in older children (6) and adults (7) these values were higher, with one exception (32.5 %).

VI. CONCLUSIONS

This pharmacokinetic study in young children given a single dose of 5 mg cetirizine (in the form of drops) shows that the drug is more rapidly excreted in these children than in older ones. The plasma excretion half-life was shorter, and the apparent oral clearance higher than in older children (7-12 years of age) or young adults. It might therefore be appropriate to adjust the dose in very young subjects according to their clinical responses, as the pharmacodynamic effect of the drug was not evaluated in this study.
VII. REFERENCES

1. SNYDER S.H., SNOWMAN A.M.
   Receptor effects of cetirizine.

2. RIHOUX J.P., DUPONT P.
   Comparative study of the peripheral and central effects of
terfenadine and cetirizine .2HCl.

3. BALTES E.
   ucb P071 - Summary of metabolic and pharmacokinetic data.
   Internal report UCB-LE87E151.

4. WOOD S.G., JOHN A.B., CHASSEAUD L.F., YEH J., CHUNG M.
   The metabolism and pharmacokinetics of "C-cetirizine in
   humans.
   Ann. Allergy, 1987, 59 (part II) : 31-34.

5. UDEN D.
   Clinical pharmacokinetics of cetirizine 5 mg po in pediatric
   patients with allergic rhinitis.

6. BALTES E., BAEILDE Y., COUPEZ R.
   ucb P071 - Urinary excretion after administration of a single
   oral dose to children.
   Internal report UCB-LE87B021.

7. HARVENGT C., DESAGER J.P.
   Etude de bioéquivalence d’une forme gouttes vis-à-vis des
   comprimés de cetirizine chez le sujet adulte sain.
   Internal report UCB-DF90E101.

8. BALTES E., COUPEZ R., BROUWERS L., GOBERT J.
   Gas chromatographic method for the determination of
   cetirizine in plasma.

   Cetirizine: a pharmacokinetic and pharmacodynamic evaluation
   in children with seasonal allergic rhinitis.
Signed,

Prof. Dr. C. Harvengt                                      J.P. Desager Ph.D.

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