Partie IV

Documentation clinique

IV A: Etudes de bioéquivalence

SCHERING SA

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SOMMAIRE

Partie I.A : étude de bioéquivalence

ANDROCUR 100

Page

Rapport de recherche N°8772

Etude randomisée en cross-over comparant d'1 comprimé d'Androcur 100 versus 2 comprimés d'Androcur 50 chez 17 volontaires sains. 1

Rapport de recherche N°9705

Etude de bioéquivalence d'une administration orale d'un comprimé d'Androcur 100 versus 2 comprimés d'Androcur 50 chez 36 volontaires 33

Rapport de recherche N°8772

Etude randomisée en cross-over comparant d'1 comprimé d'Androcur 100 versus 2 comprimés d'Androcur 50 che 17 volontaires sains

Pharma-Forschung
Pharmaceutical Research

SCHERING

Pharma Forschungsbericht
Pharma Research Report

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☐ Pharma Qualitätssicherung ☐ Chem.-mikrobiol. Entwicklung ☐ Pharmazeutische Entwicklung ☒ Physikochemie und Informatik	☐ Pharma Forschung ☒ Vorklinische Entwicklung ☒ Klinische Forschung ☐	Bericht Nr. / Report No. 8772 Datum / Date 08.03.1990	Seite / Page 1 IV / 001 Umfang, Seiten / Total No. of pages 32

Titel des Berichtes / Title of Report

Study on the bioequivalence of a new pharmaceutical preparation containing 100 mg cyproterone acetate (Androcur 100) and 2 tablets of Androcur® 50 in a randomized, intraindividual cross-over design with 17 healthy male test subjects.

Segment Endocrine Therapy	Versuche bzw. Prüfungen wurden durchgeführt / Studies were carried out von / from April 89 bis / to February 90
Kennzeichnung der biol. Wirkung / Characteristic biological effect - Antiandrogenic - Progestogenic - Antiestrogenic	Klinische Prüfphase / Clinical trial phase I
ZK-Nr. / ZK No. 9 471	Versuchs-/Prüf-Nr. / Study-No. # 89 034 KI 89 049
Generic name Cyproterone Acetate	SH-Nr. / SH No. 8.0714/50 mg T 548 A

Problemstellung / Purpose of Study

Cyproterone acetate (CPA) is a well known sex steroid being widely used in various gynecological and endocrine indications. Its antiandrogenic properties are used to treat patients with prostate carcinoma. The marketed preparation (Androcur 50®) contains 50 mg CPA/unit. Daily therapeutic doses are in the range of 100 - 200 mg (castrated patients) or 200 - 300 mg (not castrated patients). In order to facilitate treatment and to increase compliance a new preparation containing 100 mg CPA/unit had been developed. The present study in 17 male volunteers (randomized, cross-over) was carried out in order to test the bioequivalence of both preparations (Androcur 50, Androcur 100).

Formular Nr. 1694.2

Deckblatt 2/Fly Sheet 2	Bericht Nr./Report No. 8772	Seite/Page 2 IV / 002

Kurzfassung des Berichtes / Summary of Report

Summary

1. Aim, Material and Methods

The aim of the present in vitro and in vivo studies was to investigate whether the new preparation Androcur 100 is equivalent to two tablets Androcur 50.

The batches used in the clinical study were analysed for their in vitro dissolution profile (USP paddle method) about 2 months before. The clinical study was carried out as an open, randomized, single dose, cross-over trial in 17 healthy male volunteers. Both treatments, either 2 tablets of Androcur 50 or 1 tablet of Androcur 100, were separated by a wash-out period of 3 weeks.

The clinical study had been approved by an Ethical Committee.

Urine-analysis, blood biochemistry, hematology and a physical examination by an internist and spermiograms were performed before the study. With the exeption of the spermiogram all tests were also done after the completion of the study. Blood was drawn and serum prepared before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours and 2, 3, 4, 5, 7 days after each treatment. Serum was kept deep frozen at -18°C until analysis by means of an HPLC based assay (UV detection with a limit of quantification of 50 ng CPA/ml).

Target variables to test bioequivalence were C_{max}, t_{max} and the area under the curve up to 24 hours.

In addition to CPA serum levels, the levels of the main metabolite in serum, 15β-hydroxy-CPA, had been quantified (same limit of quantification as with CPA: 50 ng/ml). Student's t-Test was used on the difference between periods 1 and 2 to compare the two treatment sequences with respect to the above variables.

2. Results

The in vitro dissolution rates were slightly different between both preparations. However, specifications were met for both the preparations as more than 75 % of CPA had been dissolved from two tablets of Androcur 50 and one tablet of Androcur 100 within 30 minutes.

In agreement with these in vitro data, in the the clinical study, no statistically significant difference was found between both formulations in any of the target variables. No hang-over effect of the first treatment was found. In detail, the following results were obtained:

Deckblatt 2/Fly Sheet 2	Bericht Nr./Report No. 8772	Seite/Page 3 IV / 003

Kurzfassung des Berichtes / Summary of Report

Preparation n =	Androcur 50 (2 tablets) 17	Androcur 100 (1 tablet) 17	p-value (α = 0.05, β = 0.1)
Parameter			
C_{max} (ng/ml)	168 ± 76	131 ± 34	0.074
t_{max} (h)	2.5± 0.7	2.8 ± 1.8	0.442
AUC ($ng \cdot h \cdot ml^{-1}$)	1501 ± 717	1556 ± 917	0.831

All values as means ± S.D.

The treatments were well tolerated and no drug related side effects were reported.

Conclusion

As demonstrated by the present clinical study Androcur 100 can be regarded as bioequivalent to two tablets of Androcur 50.

Records pertaining to this study are in the archives of HD Pharmacokinetics and HD Human Pharmacology.

Pharma-Forschung
Pharmaceutical Research

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Deckblatt 3/Fly Sheet 3

Bericht Nr. / Report No. 8772

IV/ 004

Fachgebiet / Research Department	Hauptdepartment / Main Department	Hauptdepartment / Main Department
Q Development	Pharmacokinetics	Human Pharmacology
Leiter / Head	Leiter / Head	Leiter / Head
Unterschrift, Datum / Signature, date 12.3.90	Unterschrift, Datum / Signature, date .90	Unterschrift, Datum / Signature, date 8.3.90
Labor / Laboratory	**Department / Department**	**Department / Department**
		Human Pharmacol. I
Leiter / Head	Leiter / Head	Leiter / Head
Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date 8.3.90
Berichter, Author	**Sektion / Section** Pharmacokinetics C	**Sektion / Section** Pharmacokinetics
Unterschrift, Datum / Signature, date	Leiter / Head	Leiter / Head
	Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date 8.3.90
Verantwortlich für / Responsible for Dissolution Profiles		
Name	Versuchsleiter / Study Director	Berichter / Author
Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date
Verantwortlich für / Responsible for	Verantwortlich für / Responsible for Report	Verantwortlich für / Responsible for Clinical part
Name		Name 8.3.90
Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date 8.3.90
Verantwortlich für / Responsible for HD Biometry	Verantwortlich für / Responsible for Analyses	Verantwortlich für / Responsible for
Name		Name
Unterschrift, Datum / Signature, date 12.3.90	Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date
Verantwortlich für / Responsible for Section Biostatistics	Verantwortlich für / Responsible for	Verantwortlich für / Responsible for
Name	Name	Name
Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date
Verantwortlich für / Responsible for Statistical Analysis	Verantwortlich für / Responsible for	Verantwortlich für / Responsible for
Name	Name	Name
Unterschrift, Datum / Signature, date 8.3.90	Unterschrift, Datum / Signature, date	Unterschrift, Datum / Signature, date
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Formular-Nr.: 1696-3

Deckblatt 4 / Fly Sheet 4	Bericht Nr. / Report No. 8772	Seite / Page 5 IV / 005

Angaben zu Prüfsubstanz(en) und -präparat(en) / Data on test article(s) and formulation(s)

Chargen-Nr. und Stabilität der Prüfsubstanz(en) und der geprüften Formulierung(en)
Batch No. and stability of test article(s) and the tested formulation(s)

Substanz / Substance	Formulierung / Formulation
Batch No. ZK 9 471 I II	Batch No. U-No.

Hersteller der Prüfsubstanz(en) / Manufacturer of test article(s)

Schering AG

Hersteller der Formulierung der Prüfsubstanz(en) / Manufacturer of formulation of test article(s)

Schering AG, Pharmaceutical development

Galenische Formulierung (bei Anwendung von SH-Formulierungen SH-Nr. angeben)
Formulation (if SH formulations are used, state SH No.)

I SH 8.0714 (ANDROCUR) one tablet contains 50 mg ZK 9 471

II SH T 548 A (ANDROCUR-100) one tablet contains 100 mg ZK 9 471

Angaben zu Referenzsubstanz(en) und -präparat(en) / Data on control article(s) and -preparation(s)

Generic name, ZK-Nr. und Stabilität von Referenzsubstanz(en) und/oder Handelspräparat(en)
Generic name, ZK No. and stability of control article(s) and/or commercial preparation(s)

Hersteller der Referenzsubstanz(en) / Manufacturer of control article(s)

Hersteller der Formulierung der Referenzsubstanz(en) / Manufacturer of formulation of control article(s)

Galenische Formulierung (bei Anwendung von Handelspräparaten Name angeben)
Formulation (if commercial preparations are used, state name)

Deckblatt 5 / Fly Sheet 5	Bericht Nr. / Report No.	Seite / Page 6
	8772	IV / 006

Chem. Bez. / Chemical name (Iupac)

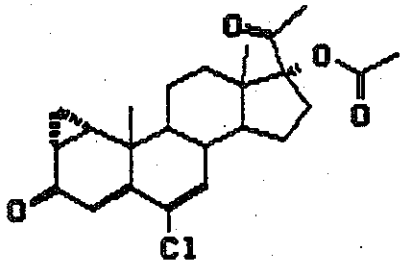
17-Acetoxy-6-chloro-1α,2α-methylene-4,6-pregnadiene-3,20-dione ✓

Generic name

Cyproterone acetate ✓

ZK-Nr. / ZK No.

9 471



Strukturformel / structural formula

Chem. Bez. / Chemical name (Iupac)

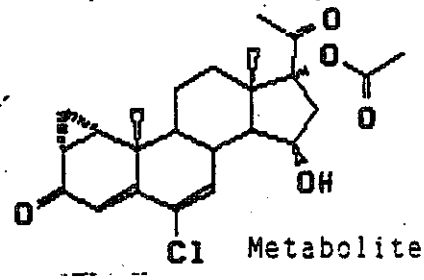
17-Acetoxy-6-chloro-15β-hydroxy-1α,2α-methylene-4,6-pregnadiene-3,20-dione ✓

Generic name

15ß-Hydroxy-Cyproterone Acetate ✓

ZK-Nr. / ZK No.

51 306



Metabolite

Strukturformel / structural formula

Chem. Bez. / Chemical name (Iupac)

Generic name

ZK-Nr. / ZK No.

Strukturformel / structural formula

Chem. Bez. / Chemical name (Iupac)

Generic name

ZK-Nr. / ZK No.

Strukturformel / structural formula

Table of contents

		Page
I.	Introduction	8
II.	Material and Methods	8
	II.1 Study design	8
	II.2 Pharmaceutical preparation	12
	II.3 Bioanalytics	13
	II.4 Evaluations	14
III.	Results	14
	III.1 Tolerance and side effects	14
	III.2 Dissolution profiles of tablets	15
	III.3 Bioanalytics	15
	III.4 Statistical analysis	17
IV.	Discussion	17

I. INTRODUCTION

Cyproterone acetate (CPA) is a well known sex steroid being widely used in various gynecological and endocrine indications. Its antiandrogenic properties are used to treat patients with prostate carcinoma. The marketed preparation (Androcur 50^{R}) contains 50 mg CPA/unit. Daily therapeutic doses are in the range of 100 - 200 mg (castrated patients) or 200 - 300 mg (not castrated patients). In order to facilitate treatment and to increase compliance a new preparation containing 100 mg CPA/unit has been developed. The present study in 17 male volunteers (randomized, cross-over) was carried out in order to test the bioequivalence of both preparations (Androcur 50, Androcur 100).

II. MATERIALS AND METHODS

II.1 Study design

The study was an open, randomized, cross-over single dose study in 18 healthy male volunteers. Test subject 4 was excluded from the study by reasons not related to the first treatment and therefore 17 volunteers were evaluated. The range in age was 24 - 44 years, in height 170 - 197 cm and in weight 62 - 85 kg. Table 1 gives the individual data of volunteers and means with standard deviations (S.D.)

Table 1: Biological data of the test subjects and sequence of treatment

Subject	Initials	Age (years)	Height (cm)	Weight (kg)	Sequence of treatment	
1		26	177	69.0	B	A
2		32	175	80.0	B	A
3		33	176	73.0	A	B
5		27	184	74.0	B	A
6		37	170	73.0	B	A
7		27	189	77.0	A	B
8		29	179	69.0	B	A
9		42	180	70.0	A	B
10		35	180	70.0	A	B
11		25	186	75.0	B	A
12		29	179	62.0	A	B
13		24	190	80.0	A	B
14		44	182	85.0	A	B
15		27	185	74.0	A	B
16		30	183	66.0	B	A
17		26	197	81.0	B	A
18		26	181	80.0	B	A
Mean ± SD	-	31 ± 6	182 ± 6	74 ± 6	-	

A = 2 tablets of Androcur 50
B = 1 tablet of Androcur 100
Volunteer 4 not evaluated (drop out)

The volunteers met both the criteria for exclusion from and inclusion into the study as there are:

Main criteria for exclusion from the study:

- Previous study within last 3 months
- Extensive varicosis
- History of thromboembolic events
- More than 20 cigarettes/day
- Indications for hormonal diseases
- Drug or alcohol abuse
- Postive hepatitis B or HIV test
- Intake of enzyme inducing agents within the last 2 weeks
- Severe illness within last month
- Physical stress within last 2 weeks
- Deviations from normal diet

Main criteria for inclusion into the study:

- Male sex
- Good physical condition as determined by a general medical check and lab tests
- Fast metabolizer

One week before the start of the study, test subjects were examined for normal blood and urine biochemistry, hematology and spermiogram. Except sperm analysis all tests were repeated one week after the end of the study. In addition, a drug abuse screen was carried out on these occasions.

Physical examinations were done before (at least 3 months before the start of the study) and after the end of the trial.

Test subjects were randomly allocated to one of the following treatment sequences:

Androcur 50 (A) followed by Androcur 100 (B)
Androcur 100 (B) followed by Androcur 50 (A)

Both treatments were separated by a wash-out period of 3 weeks. Each treatment was followed by an observation period of 7 days during which blood samples were taken.

The tablets (1 tablet of Androcur 100 or 2 tablets of Androcur 50) were administered together with 100 ml of mineral water without CO_2 under controlled conditions in the morning before breakfast (8 - 8.30 a.m.). The last meal was to be before 10 p.m. the previous day. Standardized meals were served:

breakfast: 2 hours
lunch: 5 hours
dinner: 11 hours after drug ingestion.

Test subjects remained in the clinical facility up to 8 p.m. of the test day and then returned at home. According to the sampling schedule, they had additional short-term visits the following days.

Five minutes before and at specified times after ingestion of one tablet Androcur 100 or two tablets Androcur 50, 5 ml blood were drawn from a peripheral vein. Blood was allowed to clot at room temperature for 30 minutes and centrifuged at low speed. The resulting serum was transferred into a polypropylene tube and kept frozen at -18°C until analysis.

Blood samples were taken at -5 minutes, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 168 hours after ingestion. The time of administration was defined as time zero.

During the entire study (two parts within 5 weeks) there was a blood loss of 200 ml, which includes samples for blood biochemistry and hematology.

All volunteers who participated in the study were verbally informed about aim of the study, study related restrictions and possible risks in nontechnical form. Subsequently they received the written information for test subjects and gave their written informed consent. The procedure is in

accordance with the declaration of Helsinki and the amendment of Venice (1983). The study protocol was approved by an Institutional Review Board (IRB) on March 10, 1989.

II.2 Pharmaceutical preparations

The pharmaceutical preparations tested were Androcur^{R}50 (marketed preparation, batch No [redacted] and the new preparation Androcur 100 (SH T 548 A, batch No. [redacted] Each test subject received 100 mg of CPA two times, either as one tablet Androcur 100 or two tablets Androcur 50.

Specifications of preparations are:

a) Ingredients

	Androcur 50	Androcur 100
	50 mg	100 mg
CPA	[redacted]	
Lactose x 1 H_2O		
Corn starch		
PVP 25.000		
Aerosil		
Mg-stearate		
Total weight	225 mg	400 mg

b) Dissolution profile

The dissolution <u>in vitro</u> of CPA from both the preparations had been determined according to the USP paddle method. Dissolution medium was 900 ml of 0.1 N HCl containing 0.1 % (w/v) of SDS (sodium dodecylsulfate).

The dissolution test was carried out with those batches of tablets used in the clinical trial. These tests were conducted about 2 months prior to the start of the clinical trial.

II.3 Bioanalytics

To follow CPA serum levels a reversed phase HPLC method coupled with UV detection was used. The system applied has been published previously (1). In short, 0.2 ml of serum was injected on a pre-column (Lichrosorb RP 18), the column was washed with 10 % (v/v) methanol in water and then switched to an eluent consisting of 55 % water and 45 % acetonitrile (v/v). Separation of ZK 9471 and its main metabolite in serum, ZK 51 306, was achieved by an ODS-Hypersil column (5 µm, i.d. = 4.6 mm, l = 125 mm). The eluent passed a UV detector (Spectroflow 773, Kratos) and the absorption at 282 nm was recorded. The system was run automatically (Perkin-Elmer-Autosampler ISS 100) using a column switching device (Gynkotek). HPLC equipment of Messr. Knauer (FRG) was used. Serum samples from each test subject were analysed by means of a separate standard curve containing 0, 50, 100, 250, 500 and 1000 ng of ZK 9471 as well as of ZK 51 306 per ml of blank serum. Control samples, spiked with 100 and 500 ng ZK 9471 and ZK 51 306/ml serum, were analysed after about every 5 - 6 unknown samples. Control samples were spiked independently from standard curves. Standard curves and control samples were determined in duplicate whereas unknown samples were analysed singularly per standard curve. The above procedure was duplicated for samples of each volunteer and therefore each sample was determined in duplicate. Two standard curves and about 10 - 12 controls were run for the analysis of all samples of one volunteer. The results of serum concentrations of ZK 9471 and 51 306 represent the mean of two independent measurements.

The retention time of ZK 51 306 was around 3.4 min and that of ZK 9471 was around 8.9 min. Total time of analysis was 15 minutes. Peak areas were used for evaluation. The limit of quantification was 50 ng/ml for both substances evaluated.

II.4 Evaluations

Parameters of tolerability, blood chemistry, urine analysis, hematology and results of sperm-analysis were evaluated by the responsible clinical investigator as an inspection for pre/post-treatment deviations or deviations from normal values.

Pharmacokinetic evaluations were C_{max}, t_{max} and $AUC_{0-24\ h}$. The time of maximum drug level (t_{max}) and its concentration (C_{max}) were taken from individual concentration versus time curves.

When more than one maximum occured the first was chosen. Values were considered alike if they did not differ by more than 10 % (see CV interassay III.3).

The area under the curve was calculated according to the trapezoidal rule. Samples with concentrations of below 50 ng/ml were set to zero.

For the pharmacokinetic parameters means and standard deviations were calculated. Student's t-test was used to test the equality of the two treatment sequences with respect to the sum of the parameters for both formulations of each test subject as a test for the equality of the hangover effect. To test the bioequivalence of Androcur 100 against Androcur 50 the t-test was used to test the equality of the two treatment sequences with respect to the difference between the parameters at period 1 and period 2.

III. RESULTS

III.1 Tolerance and side effects

Volunteer 4 finished the study by personal reasons not related to the study or first drug medication.

No drug related side effects were reported by any of the test subjects. Volunteer 17 reported about headache, starting 2 hours after treatment of 2 tablets of Androcur 50 and lasting for about 3.5 hours. No deviations from normal values were found in any parameter of pre/post-examinations.

Therefore, the treatments were tolerated by all volunteers without subjective complains or objective changes in parameters evaluated.

III.2 Dissolution profiles of tablets

Both preparations were investigated for in vitro dissolution of CPA according to the USP method.

Results are given in Table 2 and shown in Fig. 1. Obviously both preparations were equivalent as far as in vitro liberation of CPA is concerned. More than 75 % of dose had been dissolved within 30 minutes (see dotted line in Fig. 1). The statement on equivalence is in agreement with USP XXII (1990).

III.3 Bioanalytics

Assay quality (CPA)

In total 60 standard curves were run in duplicate to evaluate all samples. Altogether about 130 control samples were analyzed.

Assay parameters of variability were evaluated in 11 assays in which the 100 ng/ml control samples were analysed at least four fold. Coefficients of intraassay variance ranged from 2.3 % to 21.7 % with an average of 9.7 %. The coefficient of interassay variance was 10.6 %. On an average of all 11 assays evaluated, the content of control sample was 103.4 ± 11 ng/ml.

Assay quality (OH-CPA)

The number of assays and control samples run were essentially identical to the analysis of CPA. Assay prameters of variability were evaluated in 12 assays in which the 500 ng/ml control samples were analyzed at least four fold. Coefficients of intraassay variance ranged from 1.5 % to 16.7 % with an average of 6.7 %. The coefficient of interassay variance was 7.1 %. On an average of all 12 assays evaluated the content of control sample was 504 ± 36 ng/ml.

Serum CPA levels

Individual CPA serum levels found after oral administration of 2 tablets of Androcur 50 (1 tablet of Androcur 100) are given in Table 3 (Table 4). Mean values are shown in Figures 2 and 3. Derived pharmacokinetic parameters are summarised in Table 7. After ingestion of 2 tablets Androcur 50 individual maximum serum levels of 168 ± 76 ng/ml were found at 2.5 ± 0.7 h. Thereafter CPA levels decreased and dropped below the limit of quantification of 50 ng/ml in 9 of 17 volunteers. The $AUC_{0-24\ h}$ accounted for 1501 ± 717 $ng \cdot h \cdot ml^{-1}$.

Following oral administration of 1 tablet of Androcur 100 on an average a C_{max} of 131 ± 34 ng/ml was found at 2.8 ± 1.8 h. Thereafter drug levels decreased and reached 31 ± 10 ng/ml (SEM) at 24 hours. In 10 of 17 volunteers the 24 hours drug level was below 50 ng/ml (limit of quantification). The $AUC_{0-24\ h}$ accounted for 1556 ± 917 $ng \cdot h \cdot ml^{-1}$.

Serum levels of OH-CPA

15β-hydroxy-CPA (OH-CPA) is the main serum metabolite of CPA and therefore had been quantified also.

Individual and mean (± SEM) serum levels are given in Tables 5 and 6. Figures 4 and 5 show the mean values.

Time courses of serum OH-CPA levels show a typical profile of metabolites with a delayed increase, no sharp maximum and a slow decrease.

Following oral ingestion of 2 tablets of Androcur 50 (1 tablet of Androcur 100) individual maximum serum levels of OH-CPA averaged to 154 ± 45 ng/ml (149 ± 51 ng/ml) at 6.2 ± 3.3 h (6.9 ± 5.5 h). $AUC_{0-24\ h}$ was calculated to 3981 ± 2156 $ng \cdot h \cdot ml^{-1}$ (2 tablets Androcur 50) or 3656 ± 1827 $ng \cdot h \cdot ml^{-1}$ (1 tablet Androcur 100). The ratio of individual $AUC_{0-24\ h}$ (OH-CPA/CPA) was 3.56 ± 2.25 in case of Androcur 50 and 3.43 ± 3.59 in case of Androcur 100.

III.4 Statistical analysis

No hangover effect was observed with respect to C_{max}, t_{max} and $AUC_{0-24\ h}$ ($p > 0.05$). Bioequivalence was observed with respect to the above variables ($p > 0.05$). Therefore, the in vivo bioequivalence study on Androcur 50 and Androcur 100 revealed that both preparations are bioequivalent (Table 8).

IV. DISCUSSION

The aim of the present study was to investigate whether the newly produced preparation Androcur 100 is equivalent to the marketed tablet Androcur 50. The in vitro dissolution data (method USP paddle) could show the equivalence of those batches of tablets used in the clinical study. Equivalence is defined as the dissolution of more than 75 % of dose within 30 minutes.

In addition to the in vitro study a clinical study had been performed with 17 healthy male volunteers. The analytical method used to quantify CPA and OH-CPA in serum was an HPLC assay with UV-detection. The pharmacokinetics of CPA had been extensively investigated by means of a radioimmunoassay. This system has the advantage of a high sensitivity but is not totally specific for CPA. An about 20 - 30 % cross reactivity with the main metabolite, OH-CPA, in human serum was reported. The HPLC assay, however, is specific for CPA but has the disadvantage of a low sensitivity. In this study the limit of quantification was 50 ng/ml. Therefore, in most cases serum levels could be followed for only 12 - 24 hours and the half-life of disposition of CPA from serum could not be estimated.

The main criterion for bioequivalence is the area under the curve, AUC, and the time and height of maximum serum levels (Fig. 6). No statistically significant differences were found between both formulations for any of the three parameters. In addition time courses of the main metabolite of CPA in serum (OH-CPA) were almost identical after ingestion of 100 mg CPA as Androcur 50 or Androcur 100 (Figure 7). Therefore, both the preparations, 2 x tablets of Androcur 50 and 1 tablet of Androcur 100 can be regarded as bioequivalent.

References:

1. Kuhnz W.: Automated high-performance liquid chromatographic assay for cyproterone acetate and 15β-hydroxy cyproterone acetate in plasma
J. Chromatography 420 (1987): 432 - 438

Table 2: In vitro dissolution profile of CPA from Androcur 50 and Androcur 100 as determined by the USP paddle method (900 ml 0.1 N HCl containing 0.1 % SDS). All values as % of CPA dissolved (n = 6).

time (min)		Androcur 50 % CPA	Androcur 100 % CPA
10	MV	75.0	66.8
	SD	0.9	2.1
	min	73.4	63.4
	max	75.8	68.4
20	MV	86.1	79.6
	SD	0.9	2.2
	min	84.7	76.8
	max	87.3	82.6
30	MV	91.1	82.8
	SD	0.7	1.2
	min	90.0	81.6
	max	91.7	84.5
45	MV	94.9	84.3
	SD	0.9	1.1
	min	93.5	83.0
	max	95.9	85.9
60	MV	96.5	86.1
	SD	0.5	1.0
	min	95.9	84.5
	max	97.1	87.1

MV = Mean value SD = Standard deviation
min = Minimum value max = Maximum value

* in vitro and in vivo tests were carried out with tablets from the same production batch. The last figure of the batch number only indicates different packages.

Table 3: Serum levels of CPA following ingestion of 2 tablet of Androcur 50 in 17 male volunteers. Individual concentrations and means ± SEM are given. Zero means a number of below 50 ng/ml, which was the limit of quantitation. All values are given as ng CPA/ml serum.

Vol. No.	1	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	MW ± SEM
time after adm. (h)																		
0.5	0	0	90	85	0	0	0	0	0	61	0	0	71	0	0	0	0	18 ± 8
1	72	0	202	164	98	83	62	78	0	201	118	0	103	0	0	57	0	73 ± 17
1.5	89	93	238	124	95	103	85	127	0	264	107	95	101	0	92	0	0	95 ± 18
2	118	117	256	118	112	145	103	126	86	336	171	150	153	74	114	97	0	134 ± 18
3	108	150	326	116	295	134	139	-	120	274	105	119	123	115	113	89	95	151 ± 19
4	91	135	154	78	210	93	120	162	114	191	87	102	85	88	95	72	97	116 ± 10
6	85	119	158	70	182	62	74	128	100	179	80	75	56	51	109	64	102	100 ± 10
8	91	150	119	77	115	58	61	116	82	88	75	60	70	0	87	76	96	84 ± 8
12	105	85	64	87	82	76	75	95	68	67	79	85	65	74	87	0	83	75 ± 5
24	0	0	63	0	0	56	0	72	51	57	62	60	0	0	54	0	0	31 ± 7

- sample not available

Table 4: Serum levels of CPA following ingestion of 1 tablets of Androcur 100 in 17 male volunteers. Individual concentrations and means ± SEM are given. Zero means a number of below 50 ng/ml, which was the limit of quantitation. All values are given as ng CPA/ml serum.

Vol. No.	1	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	MW ± SEM
time after adm. (h)																		
0.5	0	0	0	0	0	62	0	0	0	0	0	120	82	0	0	0	0	16 ± 9
1	0	0	0	92	80	112	111	69	0	0	0	101	153	0	0	0	0	42 ± 13
1.5	105	90	94	106	91	98	161	106	77	0	0	136	142	90	127	80	0	88 ± 12
2	146	46	83	96	85	107	178	96	82	128	69	109	156	125	155	80	68	106 ± 9
3	147	109	126	96	80	139	129	124	70	194	71	106	106	135	124	68	95	113 ± 8
4	81	91	71	76	83	102	117	98	85	185	64	76	104	102	87	67	80	92 ± 7
6	94	73	104	63	140	55	94	101	73	187	73	62	77	102	113	60	116	93 ± 8
8	117	116	98	50	134	50	71	101	78	132	0	55	76	100	90	62	168	88 ± 10
12	119	56	130	84	121	0	87	83	88	66	0	61	79	88	81	60	77	75 ± 9
24	91	0	83	0	0	0	53	0	65	0	0	0	0	87	84	60	0	31 ± 10

Table 5: Serum levels of 15β-hydroxy-CPA (OH-CPA) following ingestion of 2 tablet of Androcur 50 in 17 male volunteers. Individual concentrations and means ± SEM are given. Zero means a number of below 50 ng/ml, which was the limit of quantitation. All values are given as ng OH-CPA/ml serum.

Vol. No.	1	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	MW ± SEM
time after adm. (h)																		
0.5	0	0	0	79	0	0	0	0	0	0	0	0	0	0	0	0	0	5 ± 5
1	0	0	0	129	63	0	0	0	0	85	0	0	54	0	80	0	0	24 ± 10
1.5	86	66	87	179	73	0	64	68	0	136	93	59	86	0	173	0	0	69 ± 14
2	118	74	105	185	104	82	84	75	110	156	154	109	105	98	163	98	54	110 ± 9
3	139	99	124	181	224	101	105	-	112	210	132	101	88	133	176	136	93	135 ± 11
4	126	109	100	152	215	93	118	99	134	180	163	111	70	115	167	120	127	129 ± 9
6	142	94	127	134	228	89	106	108	151	264	125	103	83	96	203	145	113	136 ± 12
8	123	105	110	146	184	85	114	93	161	149	126	74	89	106	189	100	143	123 ± 8
12	164	92	148	156	159	127	108	82	155	142	106	99	85	129	152	132	142	128 ± 7
24	101	73	90	132	117	55	0	65	148	81	107	74	0	122	139	99	115	89 ± 10

- sample not available

Table 6: Serum levels of 15β-hydroxy-CPA (OH-CPA) following ingestion of 1 tablets of Androcur 100 in 17 male volunteers. Individual concentrations and means ± SEM are given. Zero means a number of below 50 ng/ml, which was the limit of quantitation. All values are given as ng OH-CPA/ml serum.

Vol. No.	1	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	MW ± SEM
time after adm. (h)																		
0.5	0	0	0	0	0	0	0	0	0	0	0	75	63	0	0	0	0	8 ± 6
1	0	0	66	69	64	0	67	0	0	0	0	95	82	76	57	0	0	34 ± 9
1.5	56	0	77	105	79	89	103	0	110	39	64	140	101	94	139	79	55	78 ± 10
2	94	0	102	106	81	96	149	102	151	112	95	128	115	101	181	83	64	104 ± 10
3	89	62	123	121	67	125	124	67	165	173	111	133	79	118	165	86	109	113 ± 8
4	68	58	103	114	84	110	126	125	177	163	109	105	69	103	214	65	124	113 ± 10
6	67	53	135	115	187	103	115	120	138	197	99	96	77	98	193	78	155	119 ± 11
8	82	68	98	152	154	89	98	128	153	178	102	107	98	114	168	91	286	127 ± 13
12	102	59	90	116	156	70	101	54	140	166	104	104	86	121	159	119	224	116 ± 11
24	97	55	83	66	102	99	102	0	155	92	108	71	74	103	148	128	92	93 ± 9

Table 7: Pharmacokinetic parameters taken from serum CPA and OH-CPA levels determined after single oral ingestion of 100 mg CPA in form of 2 tablets of Androcur 50 or 1 tablet of Androcur 100 in 17 healthy male test subjects (open, randomized, single dose, cross-over study design).

Preparation	ANDROCUR 50 100 (2 tablets)						ANDROCUR 100 100 (1 tablet)					
Dose (mg)												
Measured	CPA			OH-CPA			CPA			OH-CPA		
Parameter	C_{max}	t_{max}	AUC_{0-24h}	C_{max}	t_{max}	AUC_{0-24h}	C_{max}	t_{max}	AUC_{0-24h}	C_{max}	t_{max}	AUC_{0-24h}
	(ng/ml)	(h)	(ng h ml^{-1})	(ng/ml)	(h)	(ng h ml^{-1})	(ng/ml)	(h)	(ng h ml^{-1})	(ng/ml)	(h)	(ng h ml^{-1})
1	118	2	3122	164	12	4885	147	3	2438	102	12	3948
2	150	3	1321	109	4	2011	109	3	908	68	8	1235
3	326	3	1547	148	12	2677	126	3	2356	135	6	1138
5	164	1	1031	185	2	6377	106	1.5	801	152	8	2451
6	295	3	1639	228	6	6061	140	6.0	1258	187	6	5291
7	145	2	1691	127	12	2060	139	3	653	125	3	4150
8	139	3	934	118	4	1132	178	2	1963	149	2	4356
9	162	4	2356	108	6	3245	124	3	2222	128	8	1083
10	120	3	916	161	8	5754	82	2	1749	177	4	6919
11	336	2	2565	264	6	5021	194	3	1275	197	6	3310
12	171	2	1831	163	4	4899	69	2	275	111	3	4374
13	150	2	1773	111	4	2031	136	1.5	862	140	1.5	2293
14	153	2	938	105	2	929	153	1	1084	115	2	1956
15	115	3	709	133	3	5548	125	2	4117	121	12	4896
16	114	2	1867	203	6	1906	155	2	2050	214	4	6388
17	97	2	528	145	6	4688	80	1.5	1390	128	24	2741
18	95	3	754	143	8	8463	168	8	1058	286	8	5623
Mean	168	2.5	1501	154	6.2	3981	131	2.8	1556	149	6.9	3656
S.D.	76	0.7	717	45	3.3	2156	34	1.8	937	51	5.5	1827

Table 8: Results of statistical analysis: Test on the bioequivalence of Androcur 100 as compared to two tablets of Androcur 50

	Period 1		Period 2	
Parameter	Mean	S.D.	Mean	S.D.
AUC_{0-24h} ($ng \cdot h \cdot ml^{-1}$)				
A100/A50	1460	563	1529	865
A50/A100	1470	565	1665	1239
C_{max} (ng/ml)				
A100/A50	142	37	168	88
A50/A100	168	67	119	29
t_{max} (h)				
A100/A50	3.33	2.22	2.33	0.71
A50/A100	2.63	0.74	2.19	0.75

A100 means Androcur 100 (1 tablet)
A50 means Androcur 50 (2 tablets)

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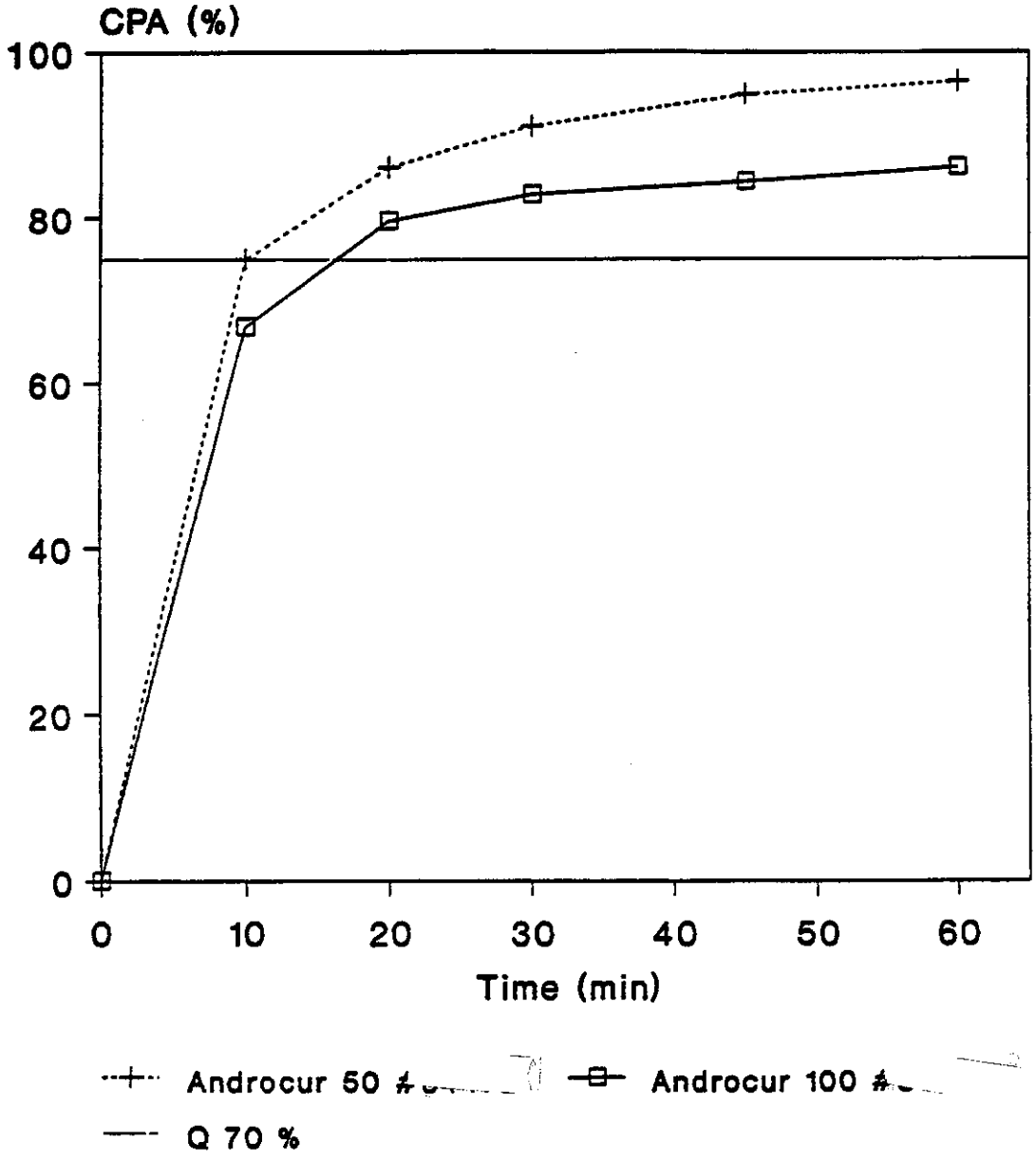

Fig. 1: Dissolution rate of 2 x Androcur 50 vs. 1 x Androcur 100 tablets
Q 70 % means that each individual test gives a dissolution of more than 75 %.

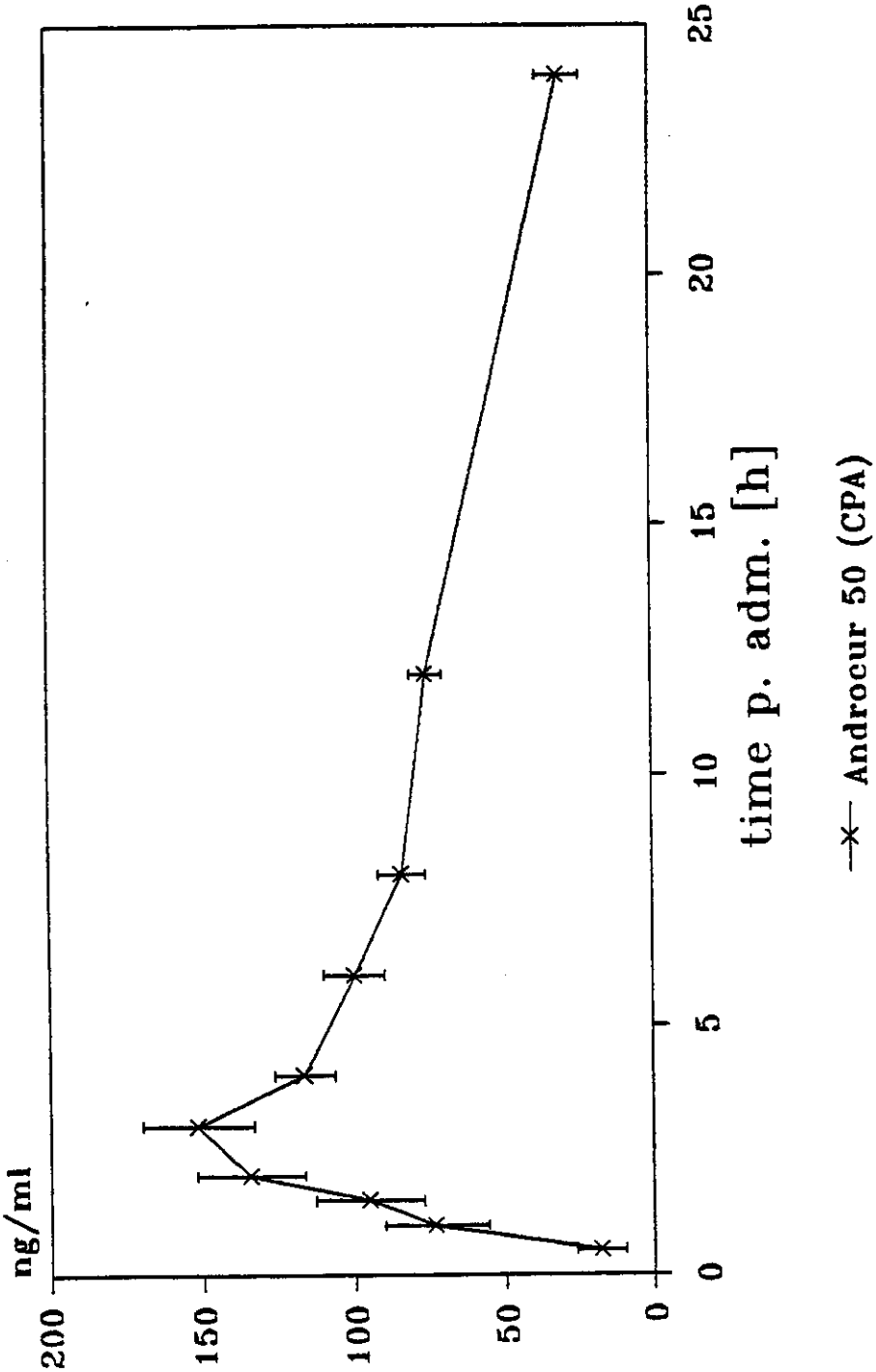

Fig. 2: Serum CPA levels (mean ± SEM) following single oral ingestion of 2 tablets of Androcur 50 in 17 healthy male volunteers.

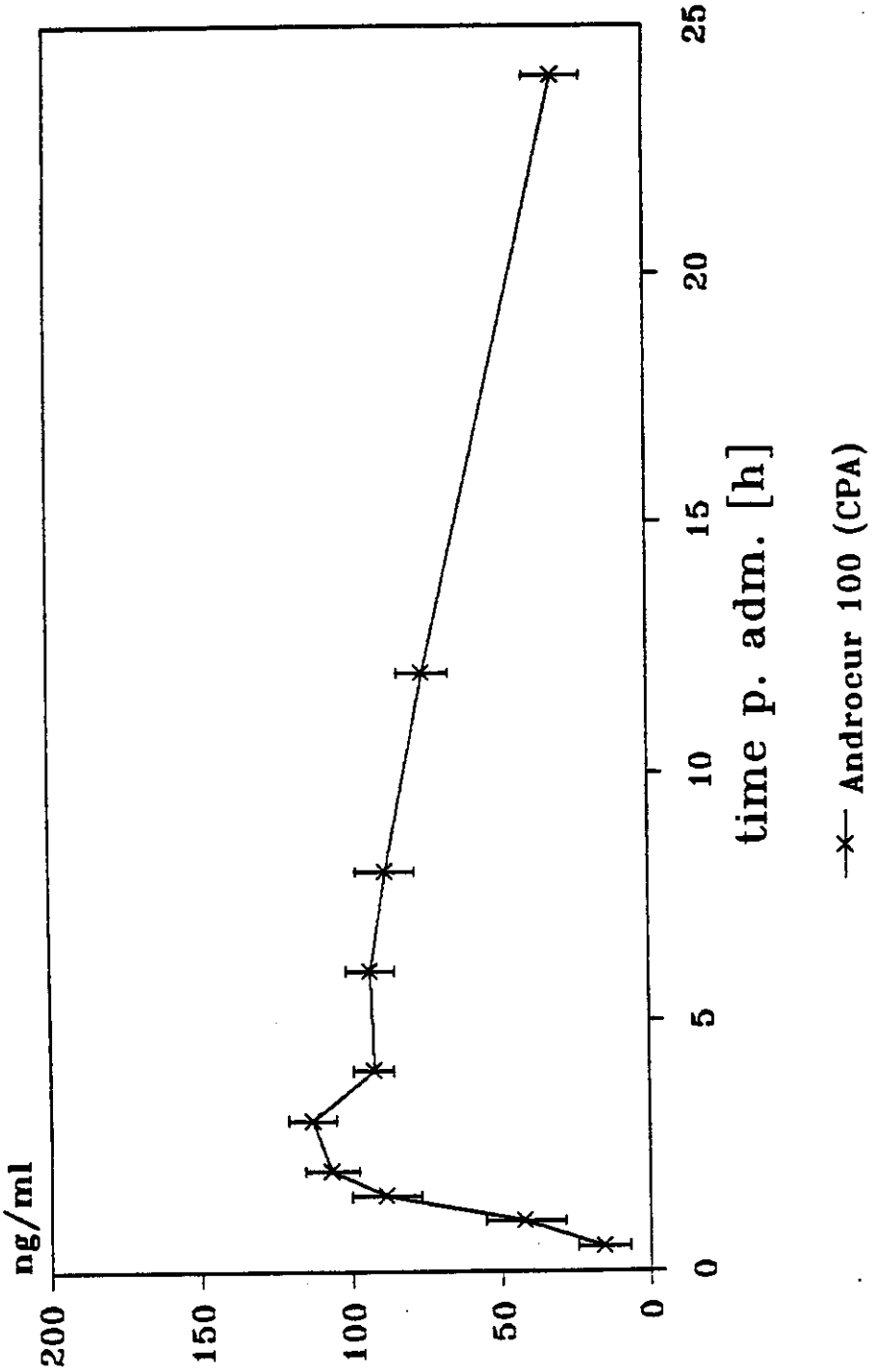

Fig. 3: Serum CPA levels (mean ± SEM) following single oral ingestion of 1 tablet of Androcur 100 in 17 healthy male volunteers.

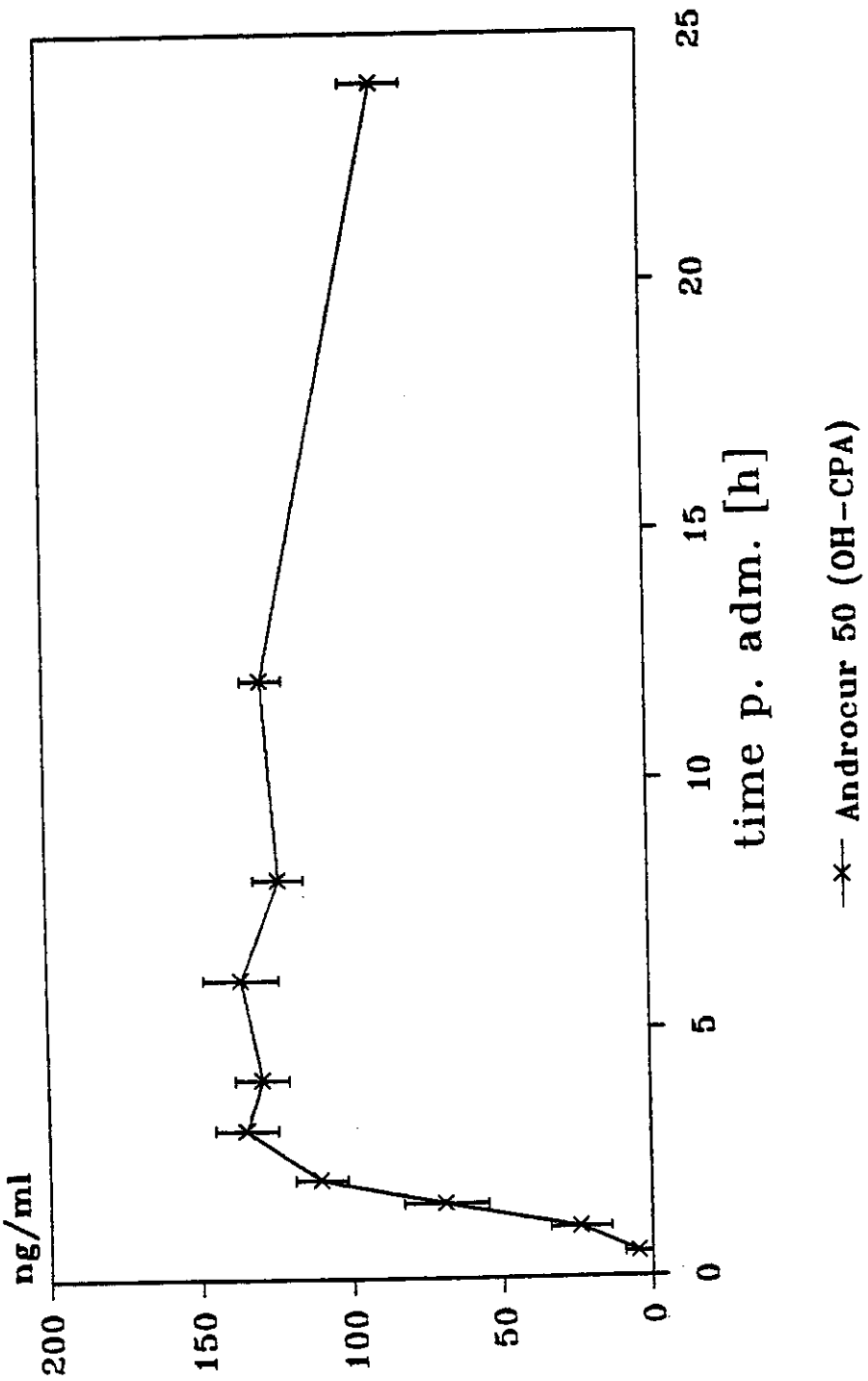

Fig. 4: Serum levels of 15β-hydroxy cyproterone acetate following single oral administration of 100 mg CPA (2 tablets of Androcur 50) in 17 healthy male volunteers (means ± SEM).

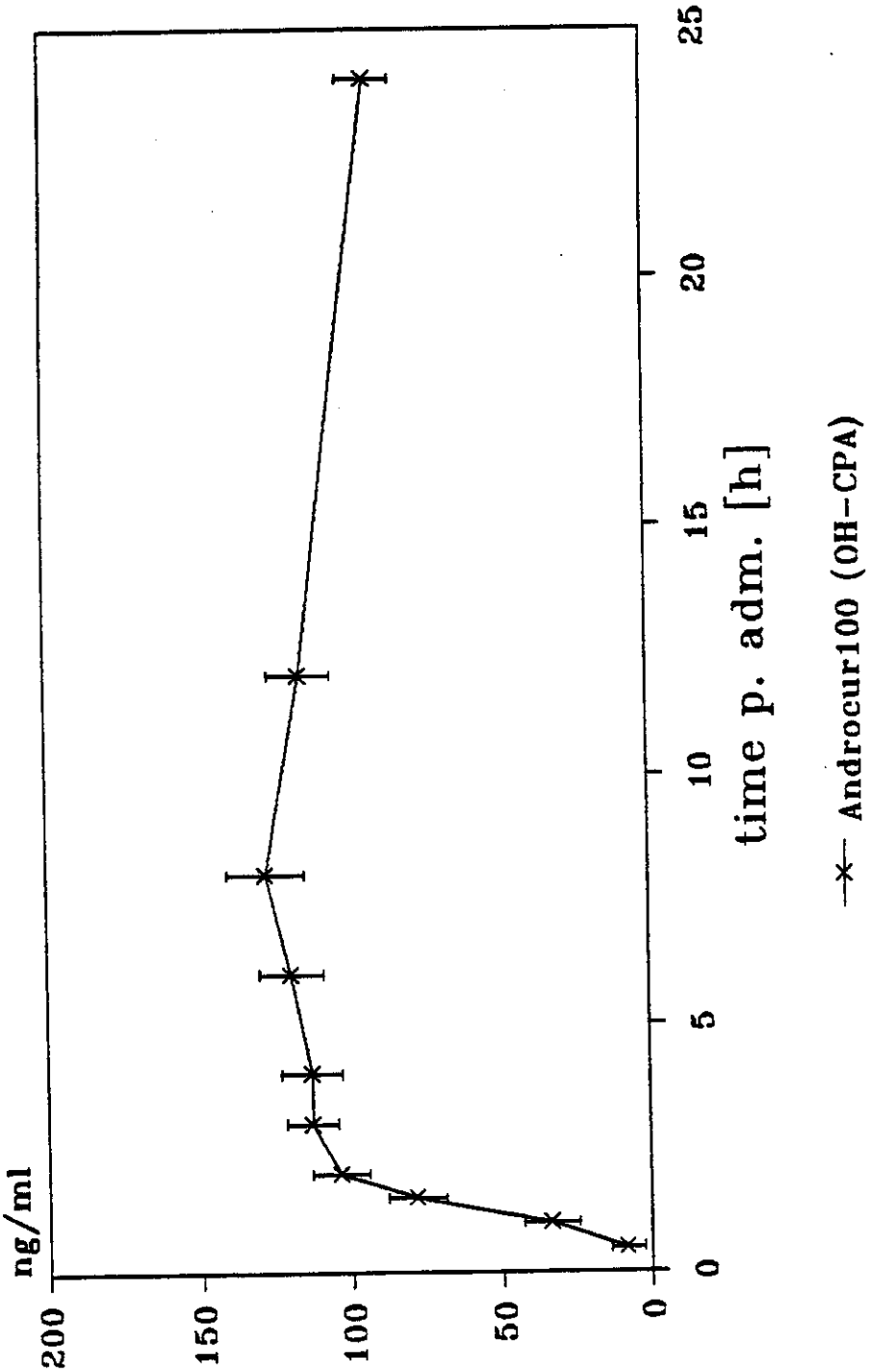

Fig. 5: Serum levels of 15β-hydroxy cyproterone acetate following single oral administration of 100 mg CPA (1 tablet of Androcur 100) in 17 healthy male volunteers (means ± SEM).

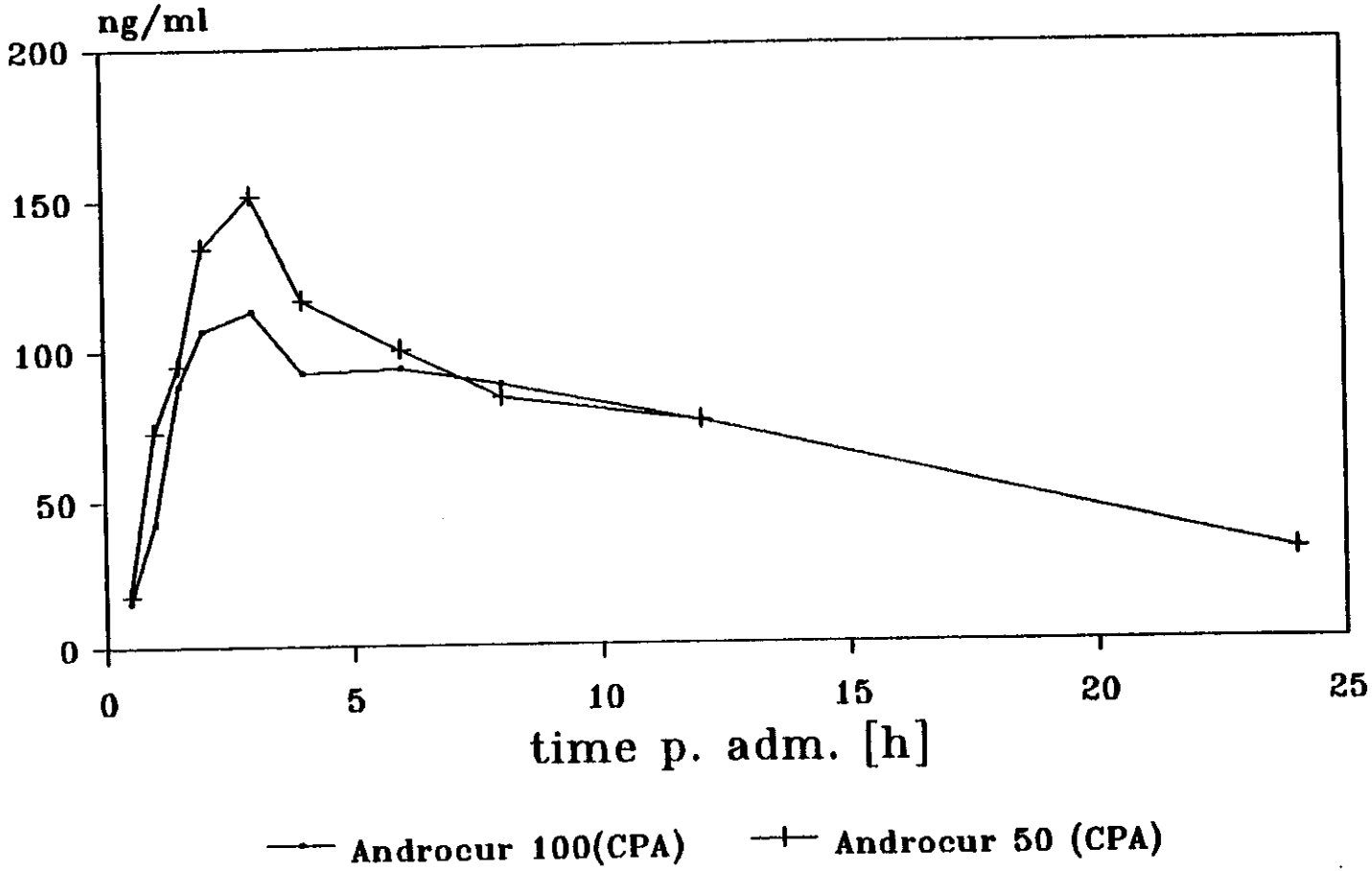

Fig. 6: Serum CPA levels following single oral administration of 100 mg as 2 tablets of Androcur 50 or 1 tablet of Androcur 100 in 17 healthy male volunteers (randomised, cross-over study); mean values, for SEM see tables.

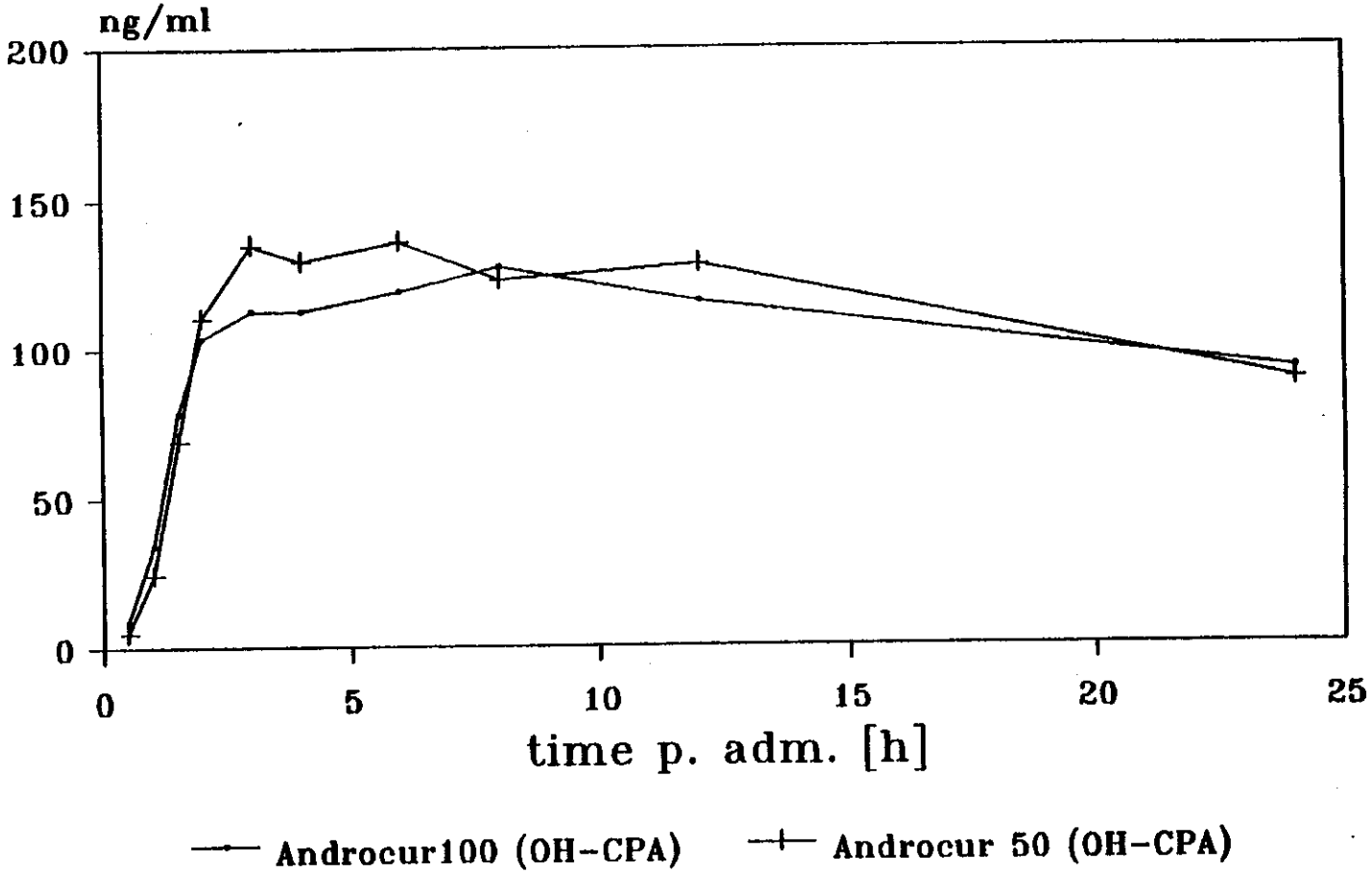

Fig. 7: Serum levels of 15β-hydroxy cyproterone acetate following single oral administration of 100 mg as 2 tablets of Androcur 50 or 1 tablet of Androcur 100 in 17 healthy male volunteers (randomised, cross-over study); mean values, for SEM see tables