J. steroid Biochem. Vol. 32, No. 1A, pp. 21–25, 1989
Printed in Great Britain.

0022-4731/89 $3.00 + 0.00

PHARMACOKINETICS OF THE ANTIPROGESTERONE RU 486 IN WOMEN DURING MULTIPLE DOSE ADMINISTRATION

OSKARI HEIKINHEIMO*
Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, Helsinki, Finland

(*Received* 31 *October* 1987; *received for publication* 4 *July* 1988)

Summary—Serum levels of RU 486 were measured by high performance liquid chromatography (HPLC) following oral intake of 12.5, 25, 50 and 100 mg twice daily (b.i.d.) for 4 days, 50 mg b.i.d. for 7 days, as well as a single dose of 200 mg of RU 486. The pharmacokinetics of RU 486 were not linear: when the daily dose of RU 486 was 100 mg or more, the serum levels were similar. The pharmacokinetic behaviour of RU 486 during the treatment period was similar between the study subjects, whereas the elimination phase pharmacokinetics showed wide individual variation. Also the mean elimination phase half-lifes ($t_{1/2}$) of RU 486 varied from 25.5 to 47.8 h in the groups of different regimen, yet the variation between different groups was not statistically significant. The areas under the concentration curves (AUC) were calculated. In the multiple dose study (mds) the $AUC_{0\to12h}$:s decreased when the administered dose of RU 486 was increased. The $AUC_{0\to12h}$ seen after administration of 100 mg b.i.d. × 4d. (mean ± SEM = 0.43 ± 0.04 μmol/l × h/mg) was significantly ($P < 0.05$) lower than the $AUC_{0\to12h}$:s obtained with administration of 12.5 mg b.i.d. × 4d. (1.49 ± 0.37 μmol/l × h/mg), 25 mg b.i.d. × 4d. (1.09 ± 0.15 μmol/l × h/mg), and 50 mg b.i.d. × 7d. (0.72 ± 0.11 μmol/l × h/mg). The $AUC_{0\to\infty}$ obtained by administration of a single dose of 200 mg of RU 486 (sds) was 0.67 ± 0.21 μmol/l × h/mg. It is concluded that if multiple dose administration of RU 486 is preferred, daily administration of relatively small doses of RU 486 over several days seem to be advantageous.

INTRODUCTION

In attempts to terminate early human pregnancy, various regimens of the antiprogesterone RU 486 have been used. In the studies published so far, the overall success rate with treatment periods of 2–7 days, and daily doses of RU 486 ranging from 50 to 400 mg, has varied from 60 to 85% [1–6]. However, no clear dose–response correlation with clinical performance has been found [1–4]. Preliminary reports suggest that in very early pregnancy a large single dose of RU 486 (i.e. 600 mg) is clinically as effective as multiple dose administration of the compound [7].

Our earlier work on the initial pharmacokinetics of RU 486 following single oral doses ranging from 100 to 800 mg revealed that serum levels of RU 486 were generally not significantly different; partly because of saturation of the serum binding capacity for RU 486, and effective metabolism of the compound [8]. Serum levels of demethylated and hydroxylated metabolites of RU 486 increased along with the increased dose following single oral administration of RU 486 to female volunteers [8]. Hence, to study the pharmacokinetics of RU 486 in women during multiple dose administration of the compound, serum levels of RU 486 following various regimens were examined.

EXPERIMENTAL

RU 486 (17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(propynyl)-estra-4,9-dien-3-one) tablets (5, 10 and 50 mg), [6,7-^{3}H]RU 486 and the corresponding antibody were kindly donated by Roussel-Uclaf Research Center (Romainville, France). Healthy normally menstruating female volunteers, aged 22–40 yr and weighing 46–70 kg, participated in the study.

Multiple dose study (mds)

Groups ingesting 12.5, 25, 50 and 100 mg of RU 486 twice daily (b.i.d.) for 4 days, and 50 mg b.i.d. for 7 days, each consisted of six volunteers. Thus the total doses of RU 486 were 100, 200, 400, 800 and 700 mg, respectively. Volunteers were advised to ingest RU 486 at 9.00–10.00 and at 21.00–22.00 h, beginning on day 12 of the luteal phase (day 0) of the cycle during an hCG-induced pseudopregnancy [for details, see ref. 9]. Blood samples were collected daily at 9.00 h prior to ingestion of RU 486. In the groups ingesting RU 486 for 4 days or 7 days, serum samples were collected daily up to day 5 or day 7, respectively. Figure 1 depicts the protocol of RU 486 administration and sample collection. Some samples were also collected at 9.00 h during the 12 days following the end of RU 486 administration.

*Address for correspondence: Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, Siltavuorenpenger 10 A, SF-00170 Helsinki, Finland.

Presented in part at the *First European Congress of Endocrinology*, Copenhagen, Denmark, 1987.

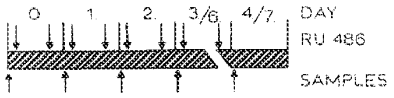

Fig. 1. The protocol of RU 486 administration and collection of serum samples in the multiple dose study.

Single dose study (sds)

The group ingesting a single dose of 200 mg of RU 486 in the mid-luteal phase of the cycle (6–8 days after the LH-surge) consisted of 4 female volunteers. Blood samples were collected at −1/2, 0, 1, 2, 4, 6 and 10 h; thereafter daily up to 7 days and on days 10 and 14.

Serum levels of RU 486 were measured using Chromosorb®-column chromatography prior to quantitation by high performance liquid chromatography (HPLC) [10]. In these HPLC-studies the intra- and interassay coefficients of variation were 6.9 and 11.5%, respectively.

In mds the concentrations of RU 486 measured on days 1–4 and 1–7 following 4 and 7-day treatments, respectively, are referred to as C_{min}. The normalized areas under the serum concentration curves ($AUC_{0\rightarrow 12\,h}$) were calculated over one dosage interval by trapezoidal rule using the C_{min}:s measured on days 3 and 4, and thereafter divided by the corresponding dose. In sds the $AUC_{0\rightarrow\infty}$ was calculated by the trapezoidal rule, and thereafter divided by the dose.

In mds the half-lifes ($t_{1/2}$) were calculated from the concentrations of RU 486 measured following termination of RU 486 administration, and in sds from the concentrations of RU 486 measured after 24 h.

One-way analysis of variance (ANOVA) was used to assess the difference in AUC and $t_{1/2}$ between the groups of different regimen. The AUC:s obtained by various regimens were thereafter compared using the Welch two-tailed t-test. In mds the effect of time and regimen of RU 486 on C_{min}:s measured on days 1–4 were evaluated using two-way ANOVA. The ANOVA:s were performed with the StatWorks—statistical software (Cricket Software, Inc., Philadelphia, PA, U.S.A.).

RESULTS

Figure 2 shows the serum concentrations of RU 486 (mean + SEM) following oral administration of 12.5, 25, 50 and 100 mg of RU 486 b.i.d. for 4 days.

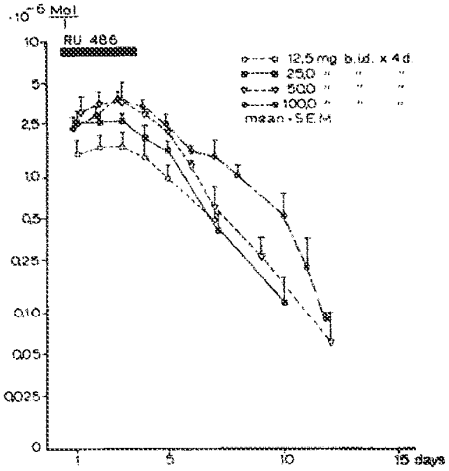

Fig. 2. Serum levels of RU 486 (mean + SEM) following ingestion of 12.5, 25, 50 and 100 mg of RU 486 b.i.d. for 4 days.

In all groups the highest mean C_{min}:s were measured on day 3, and they were 1.7, 2.6, 3.6 and 3.8 μmol/l in the groups receiving 12.5, 25, 50 and 100 mg of RU 486 b.i.d., respectively. For the first 2 days of the RU 486 treatment, the C_{min}:s were at the same level in the groups ingesting 25, 50 or 100 mg of RU 486 b.i.d. Throughout the study, the C_{min} of RU 486 seen after the dose of 12.5 mg b.i.d. were approximately half of those seen after the higher doses of 50 and 100 mg b.i.d. (Table 1).

The individual (open symbols) and the mean + SEM (solid circles) serum concentrations of RU 486 following 7-day administration of 50 mg of RU 486 b.i.d. are depicted in Fig. 3. Serum levels were similar to those seen after the 4-day treatment. The highest mean C_{min} of RU 486 (3.3 μmol/l) was measured on day 3. The mean concentrations were measured to remain above 2.2 μmol/l throughout the 7-day treatment period, and thereafter they began to decline. During the treatment period the individual C_{min}:s of RU 486 were similar in all six volunteers. However, the elimination phase pharmacokinetics showed a wide range of variation. The $t_{1/2}$ of RU 486 in these patients was 40.9 ± 6.2 h (mean ± SEM) (Table 2). In volunteer No. 1, RU 486 was detectable in serum up to 12 days following termination of the RU 486 administration.

In the samples collected following administration

Table 1. Serum concentrations (μmol/l) of RU 486 [mean ± SEM, (n)] following ingestion of 12.5 mg (A), 25 mg (B), 50 mg (C) and 100 mg (D) b.i.d. for 4 days and 50 mg b.i.d. for 7 days (E)

Day	A	B	C	D	E
1.	1.5 ± 0.4 (5)	2.6 ± 0.6 (5)	3.1 ± 0.9 (6)	2.3 ± 0.5 (6)	1.8 ± 0.3 (6)
2.	1.7 ± 0.4 (6)	2.5 ± 0.4 (5)	3.5 ± 0.8 (6)	2.8 ± 0.5 (6)	2.5 ± 0.3 (6)
3.	1.7 ± 0.5 (6)	2.6 ± 0.3 (6)	3.6 ± 1.4 (5)	3.9 ± 0.4 (6)	3.3 ± 0.6 (5)
4.	1.4 ± 0.5 (6)	2.0 ± 0.4 (6)	2.9 ± 0.4 (5)	3.3 ± 0.4 (6)	3.0 ± 0.4 (6)
5.	1.0 ± 0.2 (4)	1.6 ± 0.3 (4)	2.2 ± 0.2 (5)	2.5 ± 0.4 (3)	3.0 ± 0.3 (5)
6.	0.4 ± 0.3 (3)		1.2 ± 0.1 (3)		2.6 ± 0.4 (5)
7.	0.5 ± 0.1 (3)	0.4 ± 0.1 (5)	0.6 ± 0.2 (3)	1.4 ± 0.5 (3)	2.3 ± 0.3 (3)

Table 2. $AUC_{0\to12h}$:s and $t_{1/2}$:s [mean ± SEM, (n)] following ingestion of 12.5, 25, 50 and 100 mg b.i.d. for 4 days and 50 mg b.i.d. for 7 days. Also $AUC_{0\to\infty}$ and $t_{1/2}$ following ingestion of a single dose of 200 mg is included.

Regimen	AUC (μmol/l × h/mg)	$t_{1/2}$ (hours)
12.5 mg b.i.d. × 4d	1.49 ± 0.37 (6)	29.5 ± 3.6 (5)
25.0 mg b.i.d. × 4d	1.09 ± 0.15 (6)	25.5 ± 1.4 (6)
50.0 mg b.i.d. × 4d	0.78 ± 0.21 (5)	31.8 ± 4.0 (6)
100.0 mg b.i.d. × 4d	0.43 ± 0.04 (6)	47.8 ± 7.8 (6)
50.0 mg b.i.d. × 7d	0.72 ± 0.11 (5)	40.9 ± 6.2 (5)
200 mg single dose	0.67 ± 0.21 (4)	29.1 ± 8.3 (4)
ANOVA *f*	3.167	1.922
df	5,26	6,24
P	$P < 0.025$	n.s.

of 50 mg of RU 486 b.i.d. for 7 days, the concentrations of RU 486 were also measured by RIA following the Chromosorb®-column chromatography as described earlier [10]. There was a good correlation between the serum levels of RU 486 measured by HPLC and RIA (Fig. 4). The correlation coefficient was 0.92 ($n = 80$), but at the serum concentrations exceeding 0.64 μmol/l RIA gave higher values than HPLC. The equation for the linear regression line was HPLC = 0.55 RIA + 0.29 μmol/l.

Figure 5 depicts the mean concentrations (+SEM) of RU 486 in four women after single oral intake of 200 mg of RU 486. The peak levels of RU 486 (mean ± SEM = 4.9 ± 1.2 μmol/l) were measured at 1 h after ingestion. After the initial redistribution period within 6 h, a plateau was reached until 24 h. The mean (±SEM) concentration of RU 486 at 1, 2 and 3 days were 1.8 ± 0.4, 1.1 ± 0.3 and 0.6 ± 0.3 μmol/l, respectively. The $t_{1/2}$ of RU 486 in these subjects was 29.1 ± 8.3 h (mean ± SEM, Table 2).

The serum concentrations of RU 486 measured for the first 7 days in the mds are displayed in Table 1. In all groups of different regimen the highest mean C_{min}:s were measured 3 days after beginning of the RU 486 treatment. Two-way ANOVA did not indicate statistically significant effect of time on C_{min}:s measured on days 1–4 in the groups of different regimen (ANOVA $f = 1.660$, df = 3,113, $P = 0.182$).

Table 2 shows the AUC:s and $t_{1/2}$:s of RU 486 in all the groups of different regimen studied. One-way ANOVA revealed statistically significant variation in the AUC:s ($P < 0.025$) calculated for the different groups. In the mds the $AUC_{0\to12h}$:s decreased when the administered dose of RU 486 was increased, the smallest $AUC_{0\to12h}$ was obtained with the regimen of 100 mg b.i.d. for 4 days. The $AUC_{0\to12h}$:s following ingestion of 12.5 mg ($P < 0.05$), 25.0 mg ($P < 0.005$) b.i.d. × 4d, and 50 mg b.i.d. × 7d ($P < 0.05$) were statistically significantly different when compared by the Welch two-tailed *t*-test to the $AUC_{0\to12h}$ following ingestion of 100 mg of RU 486 b.i.d. × 4d.

The mean $t_{1/2}$:s showed a wide range of variation between the groups of different RU 486 regimen, however one-way ANOVA did not indicate statistically significant variation between the $t_{1/2}$:s measured in the different groups.

DISCUSSION

Various oral doses of RU 486 have been used in clinical work. Large doses of ≥400 mg of RU 486 are required for clinical antiglucocorticoid effects [11, 12], whereas the optimal regimen of RU 486 for antiprogesterone action remains obscure [1–4]. Daily doses of 50 mg or more of RU 486 have been used in previous clinical studies in order to terminate early human pregnancy [1–6]. With two different regimens of RU 486, i.e. 25 mg and 50 mg b.i.d. for 7 days, Odlind and Birgerson reported equal success rates of 61% [4]. Using more strict patient selection and three different regimens of RU 486, namely 50 mg b.i.d. for 4 days, 50 mg 3 times daily for 4 days, and 400 mg daily for 2 days, Couzinet *et al.* were able to terminate early pregnancy equally in 82, 88 and 85% of their patients, respectively [3]. Success rates of 60 and 72% reported by Cameron *et al.* and by Shoupe *et al.* following ingestion of 150 mg daily for 4 days and 100 mg daily for 7 days, respectively, are in the same range as the other clinical data published so far [5, 6]. Recent reports suggest that administration of RU 486 at daily doses of 25 and 50 mg might be on the threshold of being effective for induction of uterine bleeding or for termination of early pregnancy, respectively [H. Croxatto, pers. commun., 13].

In previously published clinical articles, the serum levels of RU 486 have been measured by direct RIA [3, 14, 15], which also measures some of the metabolites of RU 486 [14]. The lower precision and accuracy of RIA at high concentrations of RU 486 [10] could explain the higher values obtained by this method (Fig. 4). Due to its higher accuracy at high serum levels of RU 486, the specific HPLC method was chosen for the present study.

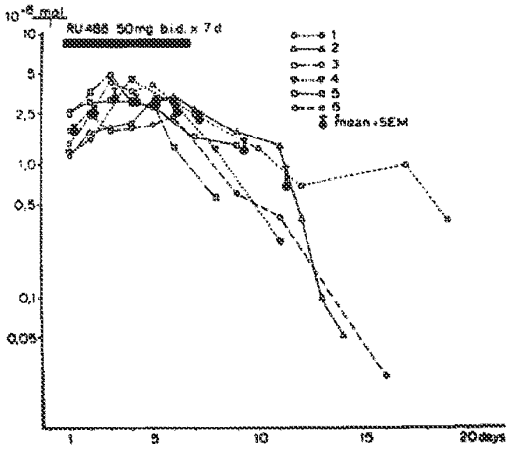

Fig. 3. The individual (open symbols) and mean + SEM (closed circles) serum concentrations of RU 486 following intake of 50 mg b.i.d. for 7 days. the $t_{1/2}$ of RU 486 (mean ± SEM) in these volunteers was 40.9 ± 6.2 h.

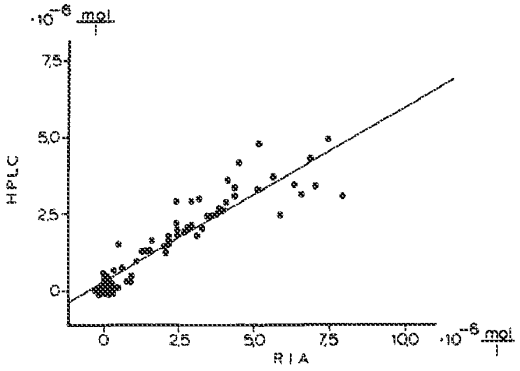

Fig. 4. Comparison of HPLC and RIA after Chromosorb®-column chromatography in the assay of RU 486 in serum. Serum samples were collected following oral intake of 50.0 mg b.i.d. for 7 days. The equation for the linear regression line was HPLC = 0.55 RIA + 0.29 μmol/l, and the correlation coefficient was 0.92 ($n = 80$).

Previous work on the pharmacokinetics of RU 486 has shown that by increasing a single oral dose from 100 to 800 mg, the serum levels of RU 486 cannot be greatly elevated [8]. A similar phenomenon has also been reported to occur during multiple dose administration of the compound [16]. The equal C_{min}:s of RU 486 during the treatment period following intake of daily doses exceeding 50 mg (Table 1) is at least partly explained by saturation of alpha 1-acid glycoprotein, the specific transport protein of RU 486 [8, 17].

The serum concentrations of the monodemethylated, didemethylated and hydroxylated metabolites of RU 486 increased significantly when the single oral dose of RU 486 was increased from 100 to 800 mg; thus equalling or exceeding the serum levels of the parent RU 486 [8]. These metabolites bear lower affinities of 9–21% (RU 486 = 100%) to the human progesterone receptor [18]. Even though the monodemethylated and hydroxylated metabolites behave as weak antiprogesterones in rat [19], the antiprogestagenic nature of the metabolites of RU 486 in humans has not been confirmed. Thus, from

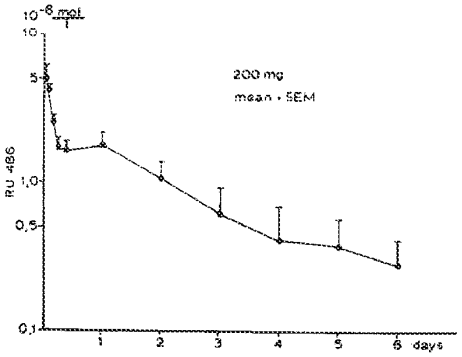

Fig. 5. Serum concentrations of RU 486 in four female volunteers (mean + SEM) following oral intake of a single dose of 200 mg of RU 486.

the pharmacokinetic point of view, the optimal dosage could be the one leading to the highest serum and target tissue levels of RU 486: the strongest competitor for the progesterone receptor and the best characterized antiprogesterone of these steroids.

In agreement with previous pharmacokinetic data [10, 16], 4 and 7-day treatment with daily doses of 100 and 200 mg of RU 486 resulted in nearly identical C_{min}:s of RU 486 during the treatment period (Figs 2 and 3, Table 1). In the mds the $AUC_{0\rightarrow 12\,h}$:s decreased when the administered dose of RU 486 was increased (Table 2). The $AUC_{0\rightarrow 12\,h}$ seen after administration of 100 mg b.i.d. for 4 days was significantly lower than the $AUC_{0\rightarrow 12\,h}$:s obtained with administration of 12.5 mg b.i.d. ($P < 0.05$), 25 mg b.i.d. ($P < 0.005$) for 4 days, and 50 mg b.i.d. ($P < 0.05$) for 7 days. This may further suggest that if multiple dose administration of RU 486 is preferred, daily administration of relatively small (i.e. around 50–100 mg/day) single doses of RU 486 might be advantageous. This might also decrease possible side-effects of RU 486 associated with high oral doses [6, 15].

The elimination phase pharmacokinetics of RU 486 showed a wide range of individual variation (Fig. 3), suggesting large individual variation in the capacity to metabolize and excrete RU 486. The mean $t_{1/2}$:s of RU 486 varied from 25.5 to 47.8 h in the groups of different regimens (Table 2), however the variation was not statistically significant.

A large single dose of RU 486 (i.e. 600 mg) has been reported to be clinically equally effective as multiple dose administration in very early pregnancy [7]. The $AUC_{0\rightarrow\infty}$ following intake of a single dose of 200 mg of RU 486 was in the same range with the $AUC_{0\rightarrow 12\,h}$:s seen in mds (Table 2) indicating that single dose administration of RU 486 may be as efficient as multiple dose administration. Also, due to the long $t_{1/2}$ of RU 486 [Table 2, refs 10, 19], single dose administration might lead to sufficiently high and prolonged serum levels of RU 486 to ensure saturation of the progesterone receptors. In addition, in order to avoid possible misuse of RU 486 [3], single dose administration of the compound would be preferable. On the other hand, the clinical potency of the single dose administration of RU 486 declined from 89% in pregnancies of less than 5 weeks amenorrhoea to 58% when the duration of pregnancy exceeded 6 weeks [7]. Therefore multiple dose administrations of RU 486 might be needed in more advanced pregnancies.

Previously, with daily doses of 50 mg or above, the abortifacient properties of RU 486 have been reported to lack dose-dependency [1–6]. Following multiple daily administration of 100 mg or more of RU 486, the C_{min}:s were similar during the treatment period (Table 1). This phenomenon is partly due to saturation of the specific serum transport capacity for RU 486, and effective metabolism of the compound [8]. Therefore, due to saturation of the serum binding

capacity for RU 486 [Fig. 2, ref. 8], the quantitation of RU 486 in serum following intake of doses exceeding 50 mg may not be very informative. It is concluded that from the pharmacokinetic point of view, administration of RU 486 as relatively small daily dose administered over several days seem to be advantageous.

Acknowledgements—I wish to thank Drs Maija Haukkamaa, Donna Shoupe, Horacio Croxatto, Kari Kivistö, Pekka Lähteenmäki, Tapani Luukkainen and Juhani Toivonen for their help and constructive criticism of this manuscript. Mrs Tuula Kivi and Mrs Marjatta Tevilin are to be thanked for their expert technical help. The financial support provided by the Suomalainen Lääkäriseura Duodecim, the Ford Foundation and the Mello Foundation is gratefully acknowledged. The content does not necessarily reflect the policy of any of the funding sources.

REFERENCES

1. Kovacs L., Sas M., Resch B. A., Ugocsai G., Swahn M. L., Bygdeman M. and Rowe P. J.: Termination of very early pregnancy of RU 486—an antiprogestational compound. *Contraception* **29** (1984) 399–410.
2. Vervest H. A. M. and Haspels A. A.: Preliminary results with the antiprogestational compound RU-486 (mifepristone) for interruption of early pregnancy. *Fert. Steril.* **44** (1985) 627–632.
3. Couzinet B., Le Strat N., Ulmann A., Baulieu E. E. and Schaison G.: Termination of early pregnancy by the progesterone antagonist RU 486 (mifepristone). *N. Engl. J. Med.* **315** (1986) 1565–1569.
4. Birgerson L. and Odlind V.: Early pregnancy termination with antiprogestins: a comparative clinical study of RU 486 given in two dose regimens and Epostane. *Fert. Steril.* **48** (1987) 565–570.
5. Cameron I. T., Michie A. F. and Baird D. T.: Therapeutic abortion in early pregnancy with antiprogestogen RU 486 alone or in combination with prostaglandin analogue (Gemeprost). *Contraception* **34** (1986) 459–468.
6. Shoupe D., Mishell D. R. Jr, Brenner P. F. and Spitz I. M.: Pregnancy termination with a high and medium dosage regimen of RU 486. *Contraception* **33** (1986) 455–461.
7. Elia D.: Uses of RU 486: a clinical update. *IPPF Med. Bull.* **20** (1986) 1–2.
8. Heikinheimo O., Lähteenmäki P. L. A., Koivunen E., Shoupe D., Croxatto H., Luukkainen T. and Lähteenmäki P.: Metabolism and serum binding of RU 486 in women after various single doses. *Human Reprod.* **2** (1987) 379–385.
9. Croxatto H. B., Spitz I. M., Salvatierra A. M. and Bardin W. C.: The demonstration of the antiprogestin effects of RU 486 when administered to the human during hCG-induced pseudopregnancy. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. J. Segal). Plenum Press, New York (1985) pp. 263–269.
10. Heikinheimo O., Tevilin M., Shoupe D., Croxatto H. and Lähteenmäki P.: Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatography. *Contraception* **34** (1986) 613–624.
11. Bertagna X., Bertagna C., Luton J.-P., Husson J.-M. and Girard F.: The new steroid analog RU 486 inhibits glucocorticoid action in man. *J. clin. Endocr. Metab.* **59** (1984) 25–28.
12. Nieman L. K., Chrousos G. P., Kellner C., Spitz I. M., Nisula B. C., Cutler G. B., Merriam G. R., Bardin C. W. and Loriaux D. L.: Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J. clin. Endocr. Metab.* **61** (1985) 536–540.
13. Mishell D. R. Jr, Shoupe D., Brenner B. F., Lacarra M., Horenstein J., Lähteenmäki P. and Spitz I.: Termination of early gestation with the anti-progestin steroid RU 486: medium versus low dose. *Contraception* **35** (1987) 307–321.
14. Salmon J. and Mouren M.: Radioimmunoassay of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. J. Segal). Plenum Press, New York (1985) pp. 99–101.
15. Bertagna X., Bertagna C., Laudat M.-H., Husson J.-M., Girard F. and Luton J.-P.: Pituitary–adrenal response to the antiglucocorticoid action of RU 486 in Cushing's syndrome. *J. clin. Endocr. Metab.* **63** (1986) 639–642.
16. Swahn M. L., Wang G., Aedo A. R., Cekan S. Z. and Bygdeman M.: Plasma levels of antiprogestin RU 486 following oral administration of non-pregnant and early pregnant women. *Contraception* **34** (1986) 469–481.
17. Philibert D., Moguilewsky M., Bonnat C., Busigny M. and Pottier J.: Influence of human alpha 1-acid glycoprotein (AAG) on pharmacokinetics and biological activity of RU 486. *Sixty-Eighth Meeting of the Endocrine Society*, Anaheim, CA, 1986, Abstract 1006.
18. Heikinheimo O., Kontula K., Croxatto H., Spitz I., Luukkainen T. and Lähteenmäki P.: Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *J. steroid Biochem.* **26** (1987) 279–284.
19. Deraedt R., Bonnat C., Busigny M., Chatelet P., Cousty C., Mouren M., Philibert D., Pottier J. and Salmon J.: Pharmacokinetics of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulier and S. J. Segal). Plenum Press, New York (1985) pp. 103–122.