ORIGINAL RESEARCH ARTICLE

ELSEVIER

Pharmacokinetics of Mifepristone After Low Oral Doses

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Relatively low doses of the antiprogestin mifepristone (RU 486) have recently proven to be efficient for a variety of possible clinical uses of the drug. However, the pharmacokinetics after low single oral doses have not been characterized. We evaluated the pharmacokinetics of mifepristone following single ingestion of 2 and 25 mg in five women as well as repeated ingestion of 8 mg in two women. Maximal serum concentrations were reached rapidly (within 0.5–2 h) with all doses used. Serum mifepristone concentrations were proportional to the oral doses taken. The mean (±SD) areas under the concentration curves (AUCs) (0–24 h) were 1134 (±144), 4846 (±64), and 17,015 (±4,421) h × ng/mL following 2, 8, and 25 mg doses, respectively. No cumulative increases in serum concentrations were detected with prolonged daily administration of 8 mg of mifepristone. The study subjects appeared to vary in their ability to metabolize mifepristone, as two different half-lives ($t_{1/2}$) emerged after both 2 and 25 mg single doses (24.2 ± 0.6 [SD] h for three subjects; and 44.4 ± 1.8 [SD] h for two subjects). We conclude that within the dose range of 2–25 mg/day, the pharmacokinetics of mifepristone are linear, unlike those seen following ingestion of higher daily doses. Keeping in mind previously published data on the biological effects of low dose mifepristone administration, these data infer that certain effects of the drug, such as inhibition of ovulation, might be achieved at serum concentrations of approximately 100 ng/mL. CONTRACEPTION 1996;54: 229–234

KEY WORDS: antiprogestin RU 486, single dose, multiple doses, radioimmunoassay, individual variability

Introduction

Pregnancy termination using mifepristone in combination with a prostaglandin is the only accepted purpose for the clinical use of mifepristone. When used for pregnancy termination, single doses of mifepristone have ranged from 200–600 mg.[1,2] Hence the pharmacokinetics of mifepristone have mainly been examined in connection with these relatively large doses.

Different target organs appear to have different sensitivities to mifepristone. High single doses, 400 mg or more, are needed to induce an increase in ACTH secretion. Similarly, 400 mg of mifepristone is needed to overcome the suppressive effect of 1 mg dexamethasone (DXM) on ACTH and cortisol secretion[3] and 600 mg of the drug is needed to overcome the clinical symptoms of hypercortisolemia.[4] Inhibition of ovulation has been achieved with daily repeated doses of 2–25 mg of RU 486,[5–8] but not in all studies has a dose of 2 mg been sufficient.[9] However, when given just prior to ovulation, as little as 1 mg of the drug is inhibitory.[10,11] Thus, the threshold to disturb the hypothalamic-pituitary-ovarian-axis (HPO-axis) in humans appears to be about 2 mg.[6,7,10,11] Similarly, regression of uterine leiomyomata has been shown to occur in a dose-dependent manner, daily administration of 25 or 50 mg being significantly more effective than 5 mg.[12] Endometrial changes which might result in disturbances of implantation of fertilized ova have been achieved at both moderate (50 mg/day)[13] and low (1 mg/day)[14] repetitive doses of the drug. Mifepristone is perhaps the most promising candidate for effective emergency contraception.[15,16] However, the optimal dose for this indication remains to be determined.

In view of the various clinical possibilities of low-dose mifepristone therapy, especially its potential contraceptive uses, the purpose of this study was to examine the pharmacokinetics of relatively low doses of mifepristone in women. Our hypothesis was that the doses used in this study (2, 8, and 25 mg) would produce linear, dose-dependent serum mifepristone concentrations.

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Materials and Methods

Subjects

The study was performed at the outpatient clinic of Lohja District Hospital, City of Lohja, Finland. The study protocol and human experimentation were approved by the ethics committee of the hospital. Five healthy women (subjects 1–5), aged between 29 and 37 years, volunteered for the two stages of the single-dose study (2 and 25 mg). Informed consent was obtained prior to initiation of the study. The subjects did not use hormonal contraception or any other hormonal therapy for the three months preceding the study or during it. The two subjects (subjects 6 and 7) undergoing daily administration of 8 mg for 30 days were part of a previous study in which we evaluated ovulation inhibition after low-dose mifepristone administration.[8] We now report the pharmacokinetics of mifepristone, evaluated from the same samples.

Medication

Mifepristone (RU 486;17β-hydroxy-11β-[4-dimethylamino-phenyl]-17α-[1-propynyl]-estra-4,9-dien-3-one) was obtained as 200 mg tablets from Roussel-Uclaf (Romainville, France) and as 50 mg tablets from the Population Council (New York City, NY) (also manufactured by Roussel-Uclaf). The 200 mg tablets were divided into 2 mg capsules at the Pharmacy of the University of Helsinki, Helsinki, Finland. Subjects 1–5 received a single oral capsule (2 mg) of mifepristone in the morning of one of cycle days 1–7. In the next menstrual cycle, they received half of a 50-mg tablet (25 mg) by the same route. Subjects 6 and 7 received four capsules of 2 mg of mifepristone (8 mg) daily for 30 days, starting in the morning of day 1 of the study. Thereafter, the capsules were ingested in the evenings.[8]

Sample Collection and Hormone Assays

Venous blood samples were collected from subjects 1–5 before mifepristone administration (0-sample) and at 1/2, 1, 2, 4, 6, 24, and 36 h, then daily until 7 days after ingestion. From subjects 6 and 7, the samples were obtained in the same way for the first 24 h. Samples were then collected daily for the first week of mifepristone treatment, and thereafter three times a week until the next menstrual period, which occurred 19 days following termination of the treatment in both subjects.[8] Serum was separated by centrifugation and the samples were stored at –20°C until assayed.

The concentrations of serum mifepristone were determined by a specific radioimmunoassay (RIA) following Chromosorb-column chromatography.[17] The practical detection limit of the RIA was 0.61 ng/mL. The mean intra- and interassay coefficients of variation (CV) of the RIA were 9.3% and 12.7%, respectively.

To convert metric values (ng/mL) into molar values (nmol/l), the serum concentrations of mifepristone are multiplied by 2.30.

Pharmacokinetic Parameters

Areas under the concentration curves of serum mifepristone during the first 24 h after drug ingestion

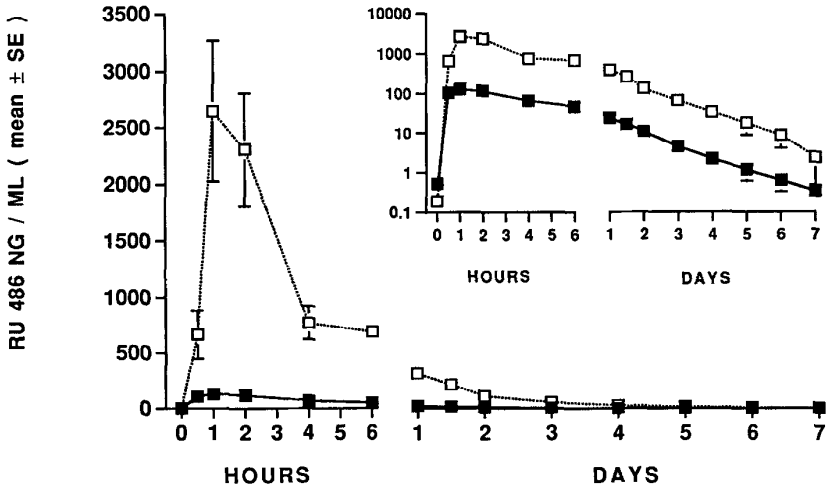

Figure 1. Mean serum concentrations of mifepristone (ng/mL) in study subjects 1–5 over the first 6 h and the first 7 days after single oral doses of 2 mg (solid squares) and 25 mg (open squares) of the drug. The data are depicted on both linear (lower) and semilogarithmic (upper) scales.

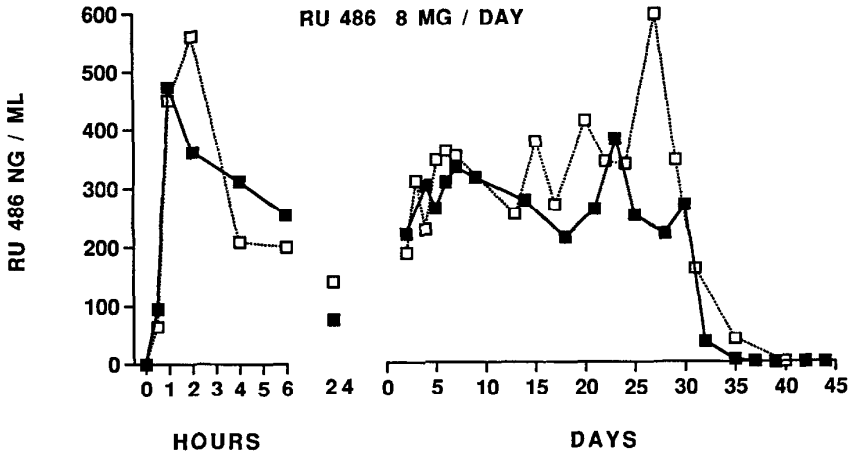

Figure 2. Serum mifepristone concentrations (ng/mL) in subjects 6 (solid squares) and 7 (open squares). The subjects ingested 8 mg mifepristone orally once a day for 30 days.

(AUC_{0-24h}) were determined for each subject using the trapezoidal rule.[18] Estimation of elimination half-life ($t_{1/2}$) of serum mifepristone was determined using the method of residuals.[19] The highest concentration detected in each subject after different doses was defined as the maximal serum concentration (C_{max}). Times from drug ingestion until C_{max} (t_{max}) were registered.

Results

Serum mifepristone concentrations (ng/mL; means ± SD) in subjects 1–5 after single doses of 2 mg and 25 mg are shown in Figure 1; both linear and semilogarithmic scales are shown. Figure 2 shows the concentrations of mifepristone in subjects 6 and 7 during daily oral repetitive administration of 8 mg. In Table 1 the pharmacokinetic parameters of study subjects 1–5 are shown after 2 and 25 mg single oral doses. Table 2 shows the mean (±SD) $t_{1/2}$, C_{max}, t_{max}, and AUC_{0-24h} values for all doses ingested.

Peak concentrations of mifepristone (C_{max}) ranged between 104 and 227 ng/mL after a 2-mg single dose of mifepristone, between 474 and 561 ng/mL after the first 8 mg dose, and between 1285 and 4851 ng/mL after a 25-mg single dose. Peak concentrations of mifepristone were rapidly reached following all doses.

The semilogarithmic scale (Figure 1) clearly shows that although the serum concentrations differed by roughly an order of magnitude, the rate of metabolism was similar following the two single doses of 2 and 25 mg. The C_{max} observed following ingestion of 25 mg of mifepristone was 18.6-fold higher than that after 2 mg (Table 2). However, there was only a 12.5-fold difference in the two doses. The decreases in serum mifepristone concentrations from C_{max} were more prominent after 25 mg than after 8 and 2 mg single oral doses of mifepristone. The mean C_{max} values compared with the mean mifepristone concentrations after 4 h of ingestion (C_{max}:C4h) were 3.75 (25 mg), 1.99 (8 mg), and 2.34 (2 mg).

The mean $t_{1/2}$ values were 32.7 h (2 mg) and 32.0 h (25 mg). However, two different $t_{1/2}$ values were found (Table 1). Subjects 3 and 4 showed longer half-lives after both 2 mg and 25 mg doses, ranging between 41.7 and 45.5 h. Subjects 1, 2, and 5 had half-lives between 23.8 and 25.0 h. Linear correlation between the $t_{1/2}$ values following the 2 mg and 25 mg doses was highly significant ($r = 0.99$; $p = 0.001$). This indicates that each subject metabolized mifepristone at an individual rate irrespective of the dose ingested.

After beginning the treatments, daily administration of 8 mg of mifepristone resulted in serum steady-state concentrations in two days. These concentrations ranged between 188 and 596 ng/mL, the mean (±SD) being 308 (±82) ng/mL. No cumulatively in-

Table 1. Pharmacokinetic parameters in subjects 1–5 for both single oral doses of mifepristone (RU 486): 2 and 25 mg

	$t_{1/2}$		C_{max}		t_{max}	
Subject	2 mg	25 mg	2 mg	25 mg	2 mg	25 mg
1	25.0	23.8	104	1285	2	1
2	23.8	25.0	183	2361	0.5	1
3	45.5	41.7	227	4851	0.5	1
4	45.5	45.0	121	1967	2	2
5	23.8	23.8	142	3958	2	2

$t_{1/2}$ = half-life (h); C_{max} = maximal serum concentration (ng/mL); t_{max} = time from drug ingestion to maximal serum concentration (h). To convert metric values (ng/mL) into molar values (nmol/l), the serum concentration of mifepristone is multiplied by 2.30. The correlation coefficient between the $t_{1/2}$ values following the 2 and 25 mg doses in the study subjects was statistically significant; $r = 0.99$ ($p = 0.001$).

Table 2. The mean (±SD) half-lives ($t_{1/2}$; h), maximal serum concentrations (C_{max}; ng/mL), and times from drug ingestion to C_{max} (t_{max}; h)

	2 mg	8 mg	25 mg
$t_{1/2}$	32.7 (±11.7)	n.a.	32.0 (±10.7)
C_{max}	155 (±49)	518 (±62)	2884 (±1474)
t_{max}	1.4 (±0.8)	1.5 (±0.7)	1.4 (±0.5)
AUC_{0-24h}	1134.4 (±143.9)	4846.0 (±63.7)	17015.2 (±4421.0)

The mean (±SD) areas under the curve (AUC; h × ng/mL) were calculated from serum mifepristone concentrations in each subject between 0–24 h after ingestion; subjects 1–5 ingested 2 and 25 mg (n = 5), subjects 6 and 7 ingested 8 mg (n = 2).

creasing concentrations were seen during multiple doses of the drug (Figure 2).

The clinical results from subjects 6 and 7 are reported elsewhere.[8]

Discussion

The pharmacokinetics of mifepristone (RU 486) in humans are characterized by extensive metabolism, a long half-life of approximately 25 h, and non-linearity following ingestion of 50 mg or more of the drug.[17,20–23] The non-linear pharmacokinetics have been explained in part by saturation of the specific serum transport protein for mifepristone, serum alpha-1-acid glycoprotein (AAG)(orosomucoid).[24] AAG has been shown to become saturated at a serum concentration of approximately 2500 nmol (1100 ng/mL) of mifepristone/L.[20,25] Thus, after single dose administration of 100 mg or more, serum concentrations of mifepristone do not rise in accordance to the dose.[17,20]

In the present study, more than a tenfold difference was seen in serum concentrations following ingestion of 2 mg and 25 mg of mifepristone. This is consistent with previous data regarding the saturation of AAG by mifepristone.[20,25] Serum concentrations of mifepristone (AUC_{0-24h}) were proportional to the oral doses of 2, 8, and 25 mg.

In the single-dose results of this study, the $t_{1/2}$ of mifepristone was similar in individual subjects following both 2 mg and 25 mg doses. Thus, each individual appeared to metabolize mifepristone similarly following both doses. The correlation coefficient between the two $t_{1/2}$ values was highly significant. The study subjects appeared to vary in their ability to metabolize mifepristone. Individual differences in mifepristone metabolism have also been demonstrated in dogs.[26] Studies with the hepatic cytochrome P-450 superfamily have revealed that P-450 IIIA is involved, inter alia, in mifepristone and estrogen metabolism, and P-450 IIC, i.a., in progesterone metabolism. Genetic polymorphism as it relates to the cytochrome P-450 system, is suggested to be a primary factor in interindividual differences in drug metabolism with a great variety of drugs.[27,28] The results of the present study do not, however, allow us to compare details of the metabolic pathways of mifepristone between subjects.

Daily administration of 25 mg of mifepristone has been demonstrated to bring about steady-state concentrations of approximately 400 ng/mL,[29] and with 50 mg doses, approximately 1100 ng/mL.[25] Recently, using a different assay system for mifepristone, Croxatto and co-workers reported steady-state levels of approximately 35 ng/mL after 1 mg daily doses, 175 ng/mL after 5 mg, and 350 ng/mL after 10 mg daily prolonged administration of mifepristone.[7] The results of the present study support the results of these earlier studies; continuous daily administration of mifepristone does not result in cumulative increases in serum drug concentrations. Steady-state levels with the dose of 8 mg were approximately 310 ng/ml, which is also in line when compared with the results of these other studies.

Serum mifepristone concentrations reached their maxima rapidly, in approximately 1.2–1.4 h after all the doses studied. This is in agreement with the results of studies in which, for the most part, higher doses of the drug were used.[17,20,21,23,25,30,31] In earlier studies with single oral doses, C_{max} values were not linearly dose-dependent. In the redistribution phase, the concentrations reached a plateau at a level of about 1100 ng/mL. These plateau concentrations did not rise in a dose-dependent manner after administration of more than 100 mg in single doses.[17,20,21,23] In the present study, linearly increasing mean C_{max} values were measured following 2, 8, and 25 mg of mifepristone. Furthermore, although the C_{max} with the 25 mg dose rose above 1100 ng/mL, no clear plateau was seen with any of the doses used. This is in agreement with the concept that AAG will not be fully saturated after a single dose of 25 mg of mifepristone.

In conclusion, peak serum concentrations of mifepristone are rapidly achieved in 1.2–1.4 h. Serum concentrations of mifepristone were proportional to the oral doses of 2, 8, and 25 mg. This in consistent with previous data regarding the saturation of AAG by

mifepristone.[20,25] There appears to be interindividual differences in the elimination of mifepristone, even with low single oral doses.

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References

1. World Health Organization. Pregnancy termination with mifepristone (RU 486) and gemeprost: a multicentre comparison between repeated doses and a single dose of mifepristone. Fertil Steril 1991;56:32–40.
2. World Health Organization. Termination of pregnancy with reduced doses of mifepristone. BMJ 1993;307: 532–7.
3. Bertagna X, Bertagna C, Luton J-P, Husson J-M, Girard F. The new steroid analog RU 486 inhibits glucocorticoid action in man. J Clin Endocrinol Metab 1984;59: 25–8.
4. Garrel DR, Moussali R, Oliveira AD, Lesiège D, Larivière F. RU 486 prevents the acute effects of cortisol on glucose and leucin metabolism. J Clin Endocrinol Metab 1995;80:379–85.
5. Luukkainen T, Heikinheimo O, Haukkamaa M, Lähteenmäki P. Inhibition of folliculogenesis and ovulation by the antiprogesterone RU 486. Fertil Steril 1988; 49:961–3.
6. Ledger WL, Sweeting VM, Hillier H, Baird DT. Inhibition of ovulation by low-dose mifepristone (RU 486). Human Reprod 1992;7:945–50.
7. Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. Human Reprod 1993;8:201–7.
8. Kekkonen R, Lähteenmäki P. Cyclic progestin administration brings about luteinization during continuous antiprogestin treatment. Contraception 1996;53:193–5.
9. Cameron ST, Thong KJ, Baird DT. Effect of daily low dose mifepristone on the ovarian cycle and on dynamics of follicle growth. Clin Endocrinol 1995;43:407–14.
10. Batista MC, Cartledge TP, Zellmer AW, Nieman LK, Merriam GR, Loriaux DL. Evidence for a critical role of progesterone in the regulation of the midcycle gonadotropin surge and ovulation. J Clin Endocrinol Metab 1992;74:565–70.
11. Batista MC, Cartledge TP, Zellmer AW, Nieman LK, Loriaux DL, Merriam GR. The antiprogestin RU486 delays the midcycle gonadotropin surge and ovulation in gonadotropin-releasing hormone-induced cycles. Fertil Steril 1994;62:28–34.
12. Murphy AA, Morales AJ, Kettel LM, Yen SSC. Regression of uterine leiomyomata to the antiprogesterone RU 486: dose-response effect. Fertil Steril 1995;64:187–90.
13. Murphy AA, Kettel LM, Morales AJ, Roberts V, Parmley T, Yen SSC. Endometrial effects of long-term low-dose administration of RU 486. Fertil Steril 1995;63: 761–6.
14. Batista MC, Cartledge TP, Zellmer AW et al. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: A potential new contraceptive strategy. Am J Obstet Gynecol 1992;167:60–5.
15. Glasier A, Thong KJ, Dewar M, Mackie M, Baird DT. Postcoital contraception with mifepristone. Lancet 1991;337:1414–5.
16. Glasier A, Thong KJ, Dewar M, Mackie M, Baird DT. Mifepristone (RU 486) compared with high-dose estrogen and progestogen for emergency postcoital contraception. N Engl J Med 1992;327:1041–4.
17. Heikinheimo O, Tevilin M, Shoupe D, Croxatto H, Lähteenmäki P. Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatography. Contraception 1986;34:613–24.
18. Rowland M, Tozer TN. Clinical pharmacokinetics. Concepts and applications. 2nd ed. Philadelphia and London:Lea and Febiger, 1989:459–63.
19. Rowland M, Tozer TN. Clinical pharmacokinetics. Concepts and applications. 2nd ed. Philadelphia and London:Lea and Febiger, 1989:469–72
20. Heikinheimo O, Lähteenmäki PLA, Koivunen E et al. Metabolism and serum binding of RU 486 in women after various single doses. Human Reprod 1987;2:379–85.
21. Heikinheimo 0, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P. Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. J Steroid Biochem 1987;26:279–84.
22. Wang JD, Shi WL, Zhang GQ, Bai XM. Tissue and serum levels of steroid hormones and RU 486 after administration of mifepristone. Contraception 1994;49: 245–53.
23. Shi YE, Ye ZH, He CH et al. Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women. Contraception 1993;48:133–49.
24. Philibert D, Moguilevski M, Bonnat C, Busigny M, Pottier J. Influence of human alpha-1-acid glycoprotein (AAG) on pharmacokinetics and biological activity of RU 486. In: Abstracts of the 68th Meeting of the Endocrine Society, Anaheim, CA; Abstract 1006, Bethesda, MD:The Endocrine Society 1986:282.
25. Heikinheimo O. Pharmacokinetics of the antiprogesterone RU 486 in women during multiple dose administration. J Steroid Biochem 1989;32:21–5.
26. Spitz IM, Heikinheimo O, Wade CE. The divergent effect of RU 486 on adrenal function in the dog is related to differences in its pharmacokinetics. Acta Endocrinol 1993;128:459–65.
27. Jacqs-Aigrain E, Panserat S, Sica L, Krishnamoorthy R.

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