0022-3565/87/2412-0401$00.00/0 $02.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS Vol. 241, No. 2

Printed in U.S.A.

Pharmacokinetic Properties of the Antiglucocorticoid and Antiprogesterone Steroid RU 486 in Man[1]

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Accepted for publication January 21, 1987

ABSTRACT

RU 486 (17β-hydroxy-11β-[4-dimethylamino phenyl]-17α-[1-propynyl]estra-4,9-dien-3-one) is a clinically useful glucocorticoid and progesterone antagonist. The authors studied the pharmacokinetic properties of this drug in normal volunteers and patients with Cushing's syndrome using a rat progesterone radioreceptor assay. This assay gave values similar to those obtained with a rat glucocorticoid radioreceptor assay. After a single oral dose of 25 mg/kg ($n = 11$) or 10 mg/kg ($n = 11$) to normal volunteers, plasma concentrations of progesterone receptor-reactive material reached maximal levels of 754 ± 288 (mean ± S.D.) and 517 ± 183 μg/dl. This occurred at 3.1 ± 1.9 and 2.5 ± 1.0 h, respectively. The respective apparent plasma half-lives were 19.2 ± 7.0 and 20.6 ± 7.7 h. Four patients with Cushing's syndrome treated chronically (10–20 mg/kg/day) had relatively constant plasma levels of receptor reactivity ranging from 506 to 1184 μg/dl. Chromatographic characterization of circulating receptor reactivity showed that the active fraction corresponded to RU 486 and its hydrophilic N-mono- and N-didemethylated metabolites. Less than 0.5% of the daily dose was excreted in the urine of two of these patients as receptor reactivity. The drug bound extensively to circulating albumin, which competed with the glucocorticoid receptor of intact human mononuclear leukocytes for [^{3}H]RU 486 in a concentration-dependent manner.

A synthetic glucocorticoid and progesterone antagonist (Philibert *et al.*, 1981; Schreiber *et al.*, 1983; Moguilewsky and Philibert, 1984), RU 486 (17β-hydroxy-11β-[4-dimethylamino phenyl]-17α-[1-propynyl]estra-4,9-dien-3-one), has major clinical uses in the treatment of hypercortisolism (Nieman *et al.*, 1985a) and in the regulation of fertility (Herrman *et al.*, 1982; Kovacs *et al.*, 1984; Schaison *et al.*, 1985; Nieman *et al.*, 1985b). Preliminary limited studies have suggested a long plasma half-life for this drug (Deraedt *et al.*, 1985; Shoupe *et al.*, 1985). These studies were performed in a small number of subjects and used either tracer methods or measurement of drug immunoreactivity.

The purpose of this study was to examine the pharmacokinetic properties of RU 486 using progesterone and glucocorticoid RRAs. The plasma concentrations of receptor-reactive RU 486 and its metabolites were determined in normal subjects after single oral doses of the drug and in four patients with Cushing's syndrome treated chronically with RU 486. The *in vitro* interactions of RU 486 with plasma proteins and the glucocorticoid receptor of intact human leukocytes were also studied.

[1] Presented in part at the American Federation for Clinical Research National Meeting, Washington, D.C., 1986.

[2] Supported in part by the Japanese Society of Clinical Pharmacology and Therapeutics and the Roussel-UCLAF Institute.

Methods

Subjects. Approval for the study was obtained from the U.S. National Bureau for Drugs and Biologics and the Human Investigation Committee for the National Institutes of Health. The nature and aims of the study were explained to all the subjects who gave their consent. The clinical studies were performed at the Clinical Center of the National Institutes of Health.

Seventeen normal men and five normal women, ages 20 to 49 years (mean ± S.D., 30.7 ± 8.6), received RU 486 (table 1). The drug, formulated into 50-mg tablets, was a gift from Roussel-UCLAF (Paris, France). It was administered orally at 8:00 A.M. or 8:00 P.M. after at least 8 h of fasting. Half the volunteers received 25 mg/kg of RU 486, and half received 10 mg/kg. Blood samples were drawn from antecubital vein immediately before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 16 and 24 h after administration. Separated plasma samples were kept frozen at −70°C until assay.

Four patients with Cushing's syndrome treated chronically with RU 486 had plasma concentrations of receptor-reactive RU 486 measured on several occasions. They received RU 486 tablets every 6 h from 8:00 A.M. The age, sex, diagnosis and daily RU 486 doses of these patients are given in table 2. Patient 3 had chronic renal failure with serum creatinine of 6 mg/dl. Twenty-four-hour urinary excretion of RU 486 in patients 2 and 3 and cerebrospinal fluid concentration of the drug in patient 4 were also measured as receptor reactivity. Sampling was performed at least 2 weeks after the onset of treatment with RU 486.

Steroids. [^{3}H]R5020 ([17α-methyl-^{3}H]17,21-dimethyl-19-norpregna-4,9-diene-3, 20-dione; [^{3}H]promegestone; 87.0 Ci/mmol), unla-

TABLE 1

Pharmacokinetic properties of RU 486 after single oral administration in normal volunteers

Case	Dose of RU 486	Administration	Age	Sex	Apparent $T_{1/2}$	Peak Time	C max[a]	C 24 h[b]
	mg/kg		*yr*		*h*	*h*	*μg/dl*	*μg/dl*
1	25	A.M.	26	M	9.5	3	326	75
2	25	P.M.	27	M	22.6	2.5	877	376
3	25	P.M.	34	M	23.6	2	533	483
4	25	P.M.	38	F	33.7	1.5	877	420
5	25	A.M.	23	F	25.8	4	815	370
6	25	P.M.	20	M	13.8	2	846	244
7	25	A.M.	36	M	20.0	4	583	219
8	25	P.M.	45	F	13.5	2	595	188
9	25	A.M.	25	M	13.4	8	589	257
10	25	A.M.	30	M	20.1	4	1441	539
11	25	A.M.	28	M	15.5	1.5	815	219
Mean ± S.D.			30.2 ± 7.4		19.2 ± 7.0	3.1 ± 1.9	754 ± 288	308 ± 140
12	10	A.M.	20	F	10.6	3	420	86
13	10	A.M.	25	M	25.7	2.5	714	271
14	10	A.M.	29	M	25.9	2	162	90
15	10	A.M.	27	M	32.8	2.5	249	146
16	10	P.M.	39	M	12.8	4	602	197
17	10	P.M.	22	M	12.5	0.5	489	135
18	10	P.M.	49	M	31.5	1.5	761	423
19	10	P.M.	43	M	21.2	2.5	536	203
20	10	P.M.	41	F	16.3	4	517	160
21	10	A.M.	27	M	21.6	2	639	214
22	10	A.M.	22	M	15.2	2.5	602	158
Mean ± S.D.			31.3 ± 9.9		20.6 ± 7.7	2.5 ± 1.0	517 ± 183	189 ± 100

[a] Maximum plasma concentration of receptor-reactive RU 486.
[b] Plasma concentration of receptor-reactive RU 486 24 h after administration.

TABLE 2

Concentrations of receptor-reactive RU 486 in biologic fluids from patients with Cushing's syndrome treated chronically with RU 486

Pt., patient; Conc., concentration; CSF, cerebrospinal fluid; CA, carcinoma; ACTH, adrenocorticotropin.

Pt.	Age Sex	Diagnosis	Dose of RU 486	Plasma Conc.	Urinary Excretion	CSF Conc.
	yr		*mg/kg/day*	*μg/dl*	*μg/kg/day*	*μg/dl*
1	25 M	ectopic ACTH	20	506 ± 85[a] (*n* = 22)[b]	—	—
2	36 M	ectopic ACTH	15	910 ± 27 (*n* = 4)	49	—
3	45 F	adrenal CA, renal failure	10	629 ± 152 (*n* = 4)	29	—
4	40 F	ectopic ACTH	10	1184 ± 259 (*n* = 3)	—	42

[a] Mean ± S.D.
[b] Number of samples.

beled R5020, [^{3}H]cortisol ([1,2-^{3}H]cortisol; 40.6 Ci/mmol) and [^{3}H] dexamethasone ([6,7-^{3}H]dexamethasone; 35.0 Ci/mmol) were obtained from New England Nuclear (Bedford, MA). [^{3}H]RU 486 ([6,7-^{3}H]RU 486; 50.6 Ci/mmol), unlabeled RU 486, RU 42 633 (N-monodemethylated RU 486) and RU 42 848 (N-didemethylated RU 486) were gifts from Roussel-UCLAF. All other steroids were purchased from Sigma Chemical Co. (St. Louis, MO).

Rat uterus and thymus cytosol preparation. Ovariectomized and adrenalectomized estrogen-treated female Holtzman rats (140–160 g; Holtzman Co., Madison, WI) were used as a source of uterine progesterone and thymus glucocorticoid receptors. On the 3rd and 4th days after surgery, estradiol (1.5 μg) in sesame oil was administered i.m. Uteri and thymuses were obtained on the 5th day. They were trimmed, rinsed and placed individually in ice-cold homogenization buffer [10 mM Tris-HCl, 1.5 mM EDTA, 0.5 mM dithiothreitol, 3% glycerol (v/v), 20 mM sodium molybdate, pH 7.4]. After homogenization with a motor-driven homogenizer (OMNI-MIXER 17105; E. I. du Pont de Nemours & Co., Newton, CT), cytosol fractions were prepared by ultracentrifugation as previously described (Rifka *et al.*, 1976). These were kept frozen at −70°C. The cytosol fractions were used within 1 month. The protein concentrations of the uterus and thymus cytosol fractions were 4.1 ± 0.1 (mean ± S.D.) and 5.0 ± 0.2 mg/ml, respectively

RRAs. These assays were performed after ethanol extraction of the sample, as mentioned below. Uterus cytosol fraction and [^{3}H]R5020 were used for the progesterone RRA. Thymus cytosol fraction and [^{3}H] dexamethasone were employed for the glucocorticoid RRA.

Four milliliters of ethanol were added to 100 μl of plasma to denature plasma proteins. The recovery of [^{3}H]RU 486 was 102 ± 2% (mean ± S.D.). Three to 10 μl of ethanol solution were then mixed with 20 μl of propylene glycol in a 12 × 75-mm glass tube. Ethanol was evaporated using a Buchler vortex-evaporator, and 100 μl of either [^{3}H]R5020 or [^{3}H]dexamethasone in the homogenization buffer (final concentration in assay tube, 6 nM) with 100 μl of either uterus or thymus cytosol were added to the tube. The mixture was incubated for 18 h at 4°C. The receptor-bound ^{3}H-steroid was separated from the free with 0.5 ml of dextran-coated charcoal solution (0.2% dextran, Pharmacia T 70, and 2% charcoal, Sigma Norit A, in the buffer). The samples were incubated for 15 min and then centrifuged (4°C) for 10 min at 3000 rpm. Half the supernatant was counted in 10 ml of counting fluid (Aquasol; New England Nuclear).

RRAs were performed in duplicate. The sensitivities of the progesterone and glucocorticoid RRAs were 5×10^{-10} and 2.5×10^{-10} M, respectively. The normal plasma samples containing three different known concentrations of RU 486 were measured by these assay pro-

expected values. The intra-assay and interassay coefficients of variation were less than 9 and 17%, respectively. Plasma concentrations of RU 486 were undetectable before administration in normal volunteers and patients with Cushing's syndrome.

Thin-layer chromatography. After extraction with ethanol, plasma samples of a normal volunteer (case 2) and a patient with Cushing's syndrome (patient 1) were chromatographed on thin-layer chromatography (LK6DF plate; Whatman Chemical Separation Inc., Clifton, NJ) in a cyclohexane-ethylacetate (1:1) system at 22°C. Scraped 1.1-cm fractions were extracted with ethanol and assessed for progesterone and glucocorticoid receptor reactivity. Recovery was checked by addition of 10,000 cpm of tracer. The same system was used for examination or purification of tracer RU 486, unlabeled RU 486 standard and ethanol-extracted RU 486 tablets. The R_f values of RU 486 from each of these three preparations were identical.

Equilibrium dialysis. The plasma protein-binding properties of RU 486 and cortisol were evaluated by an equilibrium dialysis at 37°C as described by Kley *et al.* (1977) using normal human plasma (obtained from the National Institutes of Health Blood Bank) and 4.5 g/dl of human albumin (Sigma) solution PBS, containing 0.9% sodium chloride, pH 7.4. The final concentration of ^{3}H-steroid was 0.2 nM.

Intact cell-binding study. The effect of albumin on the binding of [^{3}H]RU 486 and [^{3}H]dexamethasone to intact human mononuclear leukocytes was examined using a previously described system (Murakami *et al.*, 1979). The human buffy coat was obtained from the National Institutes of Health Blood Bank. Mononuclear leukocytes were separated using lymphocyte separation medium (Bionetics, Bethesda, MD). After washing with PBS, cells were suspended in RPMI-1640 media with or without human albumin and adjusted to 1.0×10^7 per milliliter. They were then incubated with 0.1 to 20 nM [^{3}H]RU 486 or [^{3}H]dexamethasone under 5% CO_2 and 95% O_2 for 18 h at 22°C in a shaking incubator. Nonspecific binding was determined by the addition of a 500-fold molar excess of respective unlabeled steroid. After three washings with ice-cold PBS, the pellets were resuspended in PBS and the radioactivity counted. The cell viability determined by trypan blue dye was more than 95% in various conditions of media. The equilibrium dissociation constant of RU 486 for the human mononuclear leukocyte glucocorticoid receptor was determined by this method (with no added albumin) to be 0.32 nM, as compared with that of dexamethasone, which was 1.1 nM.

Analyses of data. Least-squares linear regression analysis for the elimination curves of plasma RU 486 levels (logarithm) from the peak to the 24-h sample was used for determination of the apparent plasma half-life of the drug.

Student's paired *t* test was used for comparison of RRAs.

Results

RRAs. The displacement of [^{3}H]R5020 by various steroids in the progesterone RRA is shown in figure 1. The concentrations that inhibited 50% of [^{3}H]R5020 binding to the uterus progesterone receptor were (in molar) RU 486, 2.9×10^{-9}; R5020, 7.5×10^{-9}; progesterone, 1.1×10^{-7}; and estradiol, 8.5×10^{-7}. Cortisol had negligible cross-reactivity in this system.

The displacement curves of [^{3}H]dexamethasone by various steroids were also obtained. The concentrations that inhibited 50% of [^{3}H]dexamethasone binding to the thymus glucocorticoid receptor were (in molar) RU 486, 2.0×10^{-9}; dexamethasone, 1.2×10^{-8}; and cortisol, 1.0×10^{-7}.

The concentrations of RU 486 in 20 plasma samples including two from a patient with Cushing's syndrome (patient 1) were measured by both the progesterone and glucocorticoid RRAs (fig. 2). No significant difference between these RRAs was found ($P > .2$).

Pharmacokinetic study. The plasma concentrations progesterone receptor-reactive RU 486 after a single oral dose of the drug in normal subjects are shown in figure 3 and table 1. The mean apparent half-life values in normal subjects who received 25 and 10 mg/kg of RU 486 were 19.2 ± 7.0 (± S.D.) and 20.6 ± 7.7 h, respectively. The maximum plasma concentrations of RU 486 after oral administration of 25 and 10 mg/kg of the drug were 754 ± 288 (mean ± S.D.) and 517 ± 183 μg/dl, respectively. In both groups, plasma RU 486 levels reached the maximum about 3 h after ingestion. RU 486 was still measurable 24 h after ingestion. No differences in these measurements were observed between men and women or between morning and evening administration.

The plasma concentrations of receptor-reactive RU 486 in four patients with Cushing's syndrome are shown in table 2. Patient 1 had RU 486 measured every 30 min over 12 h (8:00 A.M.–8:00 P.M.). The mean plasma concentration was 506 μg/dl, with a coefficient of variation of 16.8%. The 24-h urinary excretion of RU 486 receptor reactivity was measured in patients 2 and 3. Less than 0.5% of the daily dose was excreted in the urine. In patient 4, cerebrospinal fluid concentration of RU 486 receptor reactivity was approximately 4% of the total plasma receptor-reactive RU 486 concentration.

Metabolites of RU 486 in plasma. Receptor reactivities and [^{3}H]RU 486 recoveries in the chromatographed fractions of plasma samples are shown in figure 4. Although we recovered the highest amount of [^{3}H]RU 486 in fraction 5, receptor reactivity was also found in fractions 4 and 2 (fig. 4). The R_f values of RU 486, RU 42 633 and RU 42 848 were 0.33, 0.26 and 0.14, which corresponded to chromatographic fractions 5, 4 and 2, respectively. There was no difference between the progesterone and glucocorticoid RRAs of these fractions. The chromatographed pretreatment plasma samples from a normal subject and a patient with Cushing's syndrome had receptor reactivities less than the blank.

Plasma-bound fraction of RU 486. The bound fraction of [^{3}H]RU 486 in plasma as determined by equilibrium dialysis was 94.3 ± 1.8% (mean ± S.D.). High concentrations of unlabeled RU 486 (up to 3000 μg/dl of plasma), cortisol (700 μg/dl) or progesterone (400 μg/dl) had no effect on percent bound [^{3}H]RU 486. The bound fraction of [^{3}H]RU 486 to human albumin solution (4.5 g/dl) was 91.8 ± 0.7%.

The mean of bound [^{3}H]cortisol in plasma was 94.0%. This was reduced to 64.5% by addition of large amounts of unlabeled cortisol (700 μg/dl).

Effect of albumin on RU 486 binding to mononuclear leukocytes. Figure 5 shows the effect of albumin on the binding of 20 nM [^{3}H]RU 486 or [^{3}H]dexamethasone to human mononuclear leukocytes. Total and specific binding of [^{3}H]RU 486 decreased significantly with increasing albumin concentrations. Compared with control (0% albumin), only 8.1% of RU 486 bound specifically to cells when the media contained 4.5% albumin. In contrast, the specific binding of [^{3}H]dexamethasone to intact cells was minimally affected by the albumin concentration. The same results were observed using the lower concentrations of ^{3}H-steroids.

Discussion

The mean apparent plasma half-life of progesterone receptor-reactive RU 486 in our normal volunteers was about 20 h. Because the terminal log-linear phase was not reached at 24 h

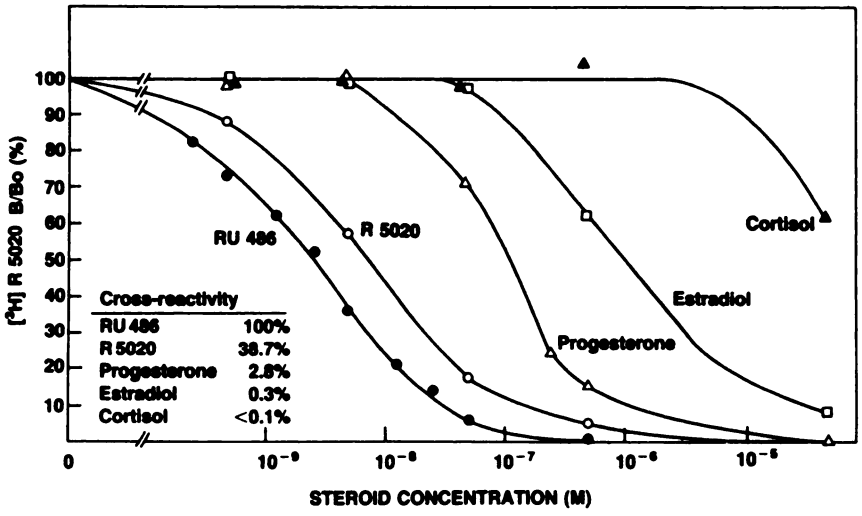

Fig. 1. Competition (displacement) curves of various steroids for the rat uterus progesterone receptor. Results are expressed as percentage of control binding in the absence of competitors. Values shown were determined in duplicate.

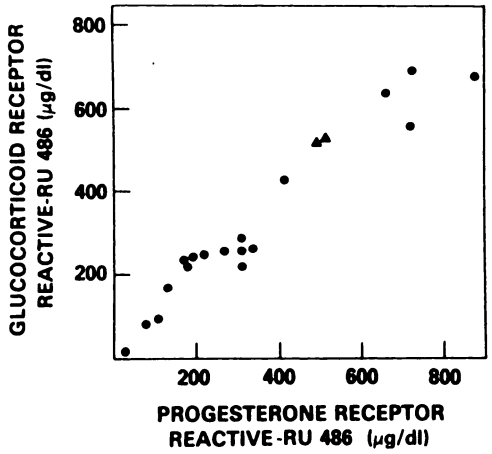

Fig. 2. Correlation between plasma concentrations of RU 486 measured by progesterone and glucocorticoid RRAs. Circles and triangles indicate plasma samples from normal volunteers and a patient with Cushing's syndrome, respectively. No significant difference between RRAs was found ($P > .2$).

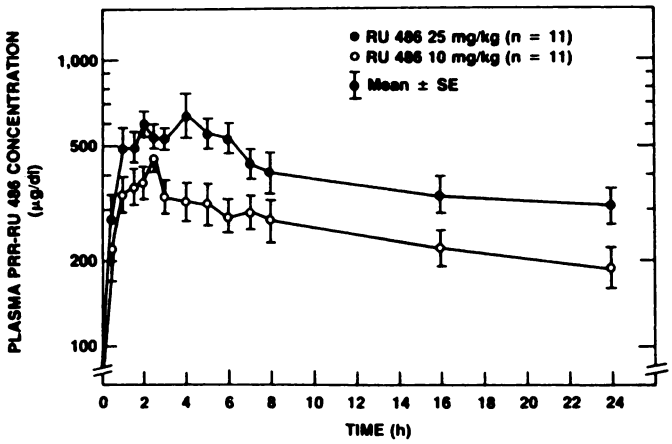

Fig. 3. Plasma concentrations of progesterone receptor-reactive (PRR-) RU 486 after oral administration of 25 or 10 mg/kg of the drug to normal volunteers.

erably longer. Despite this potential caveat, this value is similar to that reported by Deraedt *et al.* (1985) and implied by Shoupe *et al.* (1985). The apparent plasma half-life of RU 486 is long utes (progesterone) (Little *et al.*, 1966) to 3 to 5 h (dexamethasone) (Kawai *et al.*, 1985). The closest approximation of the metabolic clearance rate of RU 486 that we can make is in the patients with Cushing's syndrome. If we assume that the absorption of RU 486 from the gastrointestinal tract was 100%, the metabolic clearance rate computed by the constant infusion model (Tait *et al.*, 1961) would range between 0.84 and 4.0 (mean, 2.0) liters/kg/day. Because the amount of receptor-reactive RU 486 excreted in the urine of our patients was less than 0.5% of the total daily dose, we suggest that the kidneys play an insignificant role in the clearance of this drug and its receptor-reactive metabolites.

The long apparent plasma half-life of RU 486 may explain the long biologic effect seen in other studies using single oral doses of RU 486 in man. Plasma cortisol, β-lipotropin (Gaillard *et al.*, 1984; Bertagna *et al.*, 1984) and adrenocorticotropin (Gaillard *et al.*, 1984) levels clearly increased, but only starting 5 to 6 h after administration of the drug and only at hours (morning) of presumably elevated endogenous corticotropin-releasing hormone secretion. In addition, the concentrations of these hormones in plasma and 24-h urinary 17-ketogenic steroid excretion remained higher than control in the 2 days after a 6-mg/kg dose of RU 486 (Gaillard *et al.*, 1984). In nonhuman primates, RU 486 antagonist activity was observed as early as 0.5 h after i.m. injection of the drug in the early morning (Healy *et al.*, 1985). The different time and mode of administration of RU 486 may account for the observed differences in its onset of action in man and monkey.

One of the reasons for the long apparent plasma half-life of RU 486 may be the extensive binding of this drug (and possibly its metabolites) to plasma proteins. We have previously shown that RU 486 does not bind to corticosteroid-binding globulin or testosterone-estradiol-binding globulin (Nieman *et al.*, 1985a). Philibert *et al.* (1986) have suggested that α-1-acid glycoprotein may account for some of the plasma RU 486 binding. Because specific binding of [^{3}H]RU 486 to intact human mononuclear leukocytes was severely inhibited by the presence of physiologic concentration (4.5%) of human albumin (whereas that of [^{3}H]dexamethasone was much less affected), we believe that the binding of RU 486 to plasma albumin is pharmacologically important. The concentration of receptor-reactive RU 486 in the cerebrospinal fluid of the patient with Cushing's syndrome was approximately 4% of her concurrent

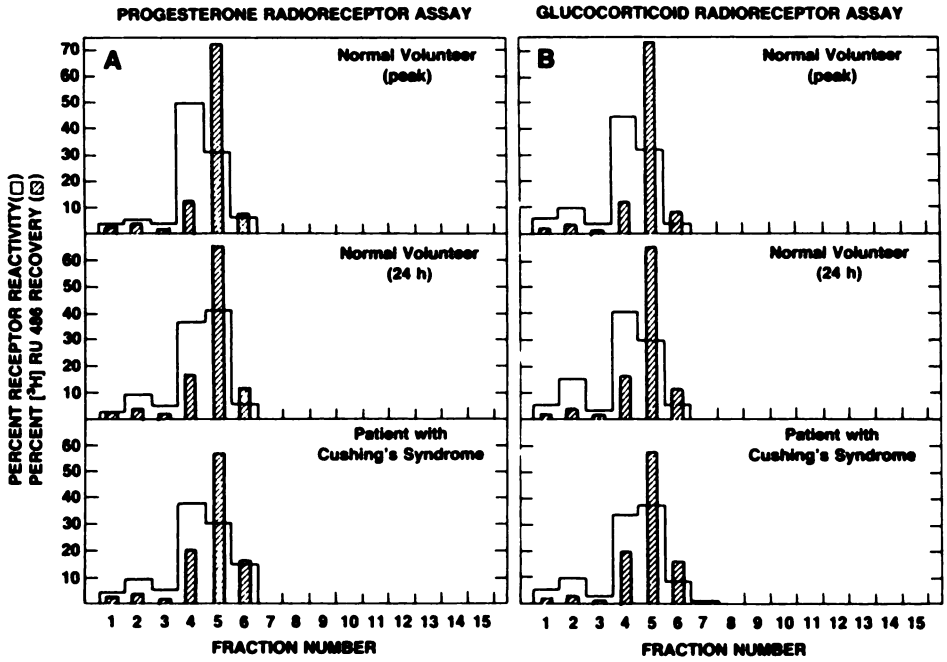

Fig. 4. Receptor reactivities (open column) in the chromatographed fractions of plasma samples from a normal volunteer (at peak level and 24 h after administration of the drug) and a patient with Cushing's syndrome who received RU 486 orally. Shaded column represents the percent recovery of [³H]RU 486 in each fraction. Fractions are numbered from the origin of the thin-layer chromatography. N-monodemethylated RU 486 (RU 42 633) and N-didemethylated RU 486 (RU 42 848) correspond to fractions 4 and 2, respectively.

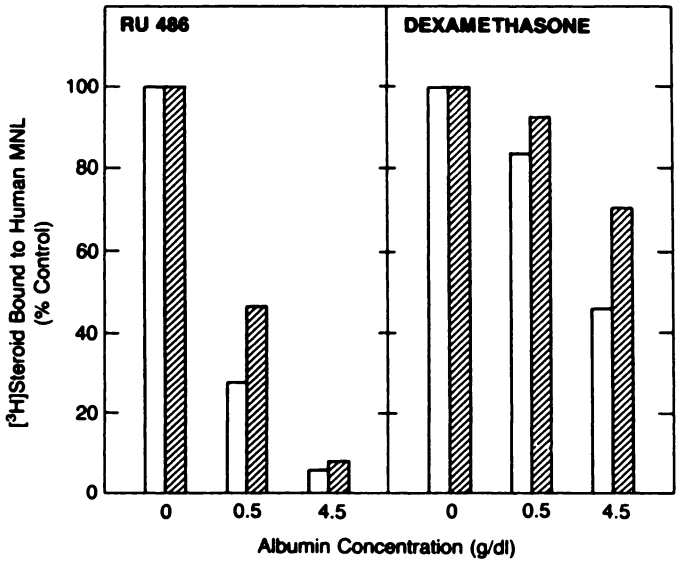

Fig. 5. The effect of albumin on the total (open column) and specific (shaded column) binding of 20 nM [³H]RU 486 or [³H]dexamethasone to intact human mononuclear leukocytes (MNL). Results are expressed as percentage of those in media without human albumin. Values shown were determined in duplicate.

the free fraction of this drug crosses plasma membranes and is biologically active.

The effective plasma concentrations of RU 486 in the patients with Cushing's syndrome were more than 20 times greater than the mean plasma cortisol concentrations of these patients. This was unexpected from the affinity of RU 486 to the human mononuclear leukocytes glucocorticoid receptor, which is approximately 3 times greater than that of dexamethasone [or, by deduction, approximately 18 times greater than that of cortisol (Murakami *et al.*, 1979)]. The tight binding of the drug to plasma albumin may explain this discrepancy.

The chromatographic fractions of the plasma receptor-reactive material(s) corresponded to RU 486 and its N-mono- and N-didemethylated metabolites. Deraedt *et al.* (1985) have the progesterone and glucocorticoid receptor and some bioactivity. We suggest that circulating RU 486 receptor reactivity in man is due primarily to RU 486 and secondarily to its hydrophilic products that lack one or two methyl groups in the 11β-phenyl chain.

Acknowledgments

The authors would like to thank Roussel-UCLAF for generously providing RU 486 for this study. We are also grateful to Mr. Gerald W. Peden and Ms. Terry M. Wood for their superb technical assistance.

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