Clinical Article

Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women

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RU 486 and three of its metabolites (RU 42633 - monodemethyl, RU 42848 - didemethyl, and RU 42698 - hydroxymetabolite) were determined by HPLC in plasma from nine non-pregnant and 36 pregnant women. Each non-pregnant subject took an oral dose of RU 486 (25, 100, 400 and 600 mg consecutively) once per menstrual cycle. Six of the nine women also received a dose of 200 mg. The 36 pregnant women were randomized into four groups which were given a single dose of 25, 100, 400 or 600 mg RU 486. Blood samples were taken up to 120 h after dosing. Peak concentrations of RU 486 occurred on most occasions within 2 h. Plasma concentrations at 1 h and at 24 h increased in proportion to log dose. There was a wide variability (up to ten-fold) in the pharmacokinetic parameters within each dose group. Plasma concentra- tions of RU 42633 were similar to those of RU 486 but concentrations of RU 42848 and RU 42698 were much lower. As with RU 486, the plasma concentrations of the metabolites were maintained at high levels for

Submitted for publication January 11, 1993
Accepted for publication June 18, 1993
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up to 48-72 h after dosing. The findings were consistent with a rapid metabolism of RU 486 to RU 42633; removal of the second methyl group leading to RU 42698 occurred much more slowly and to a much less extent than removal of the first. There appeared to be no significant differences between the non-pregnant and pregnant women in either the plasma concentrations or pharmacokinetic parameters of RU 486 and its metabolites.

Keywords: Mifepristone (RU 486), RU 486 metabolites, human pharmacokinetics

Introduction

RU 486 [mifepristone; 17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one] is a potent antiprogestational steroid (1) which has been shown to be effective in terminating early pregnancy, especially in combination with a prostaglandin (2-5). Three metabolites of RU 486 have been identified (Fig. 1). The compound undergoes demethylation to give the mono- (RU 42633) and di- (RU 42848) demethylated derivatives as well as hydroxylation of the propynyl group (RU 42698). RU 486 and its metabolites can be readily assayed in blood by HPLC (6),

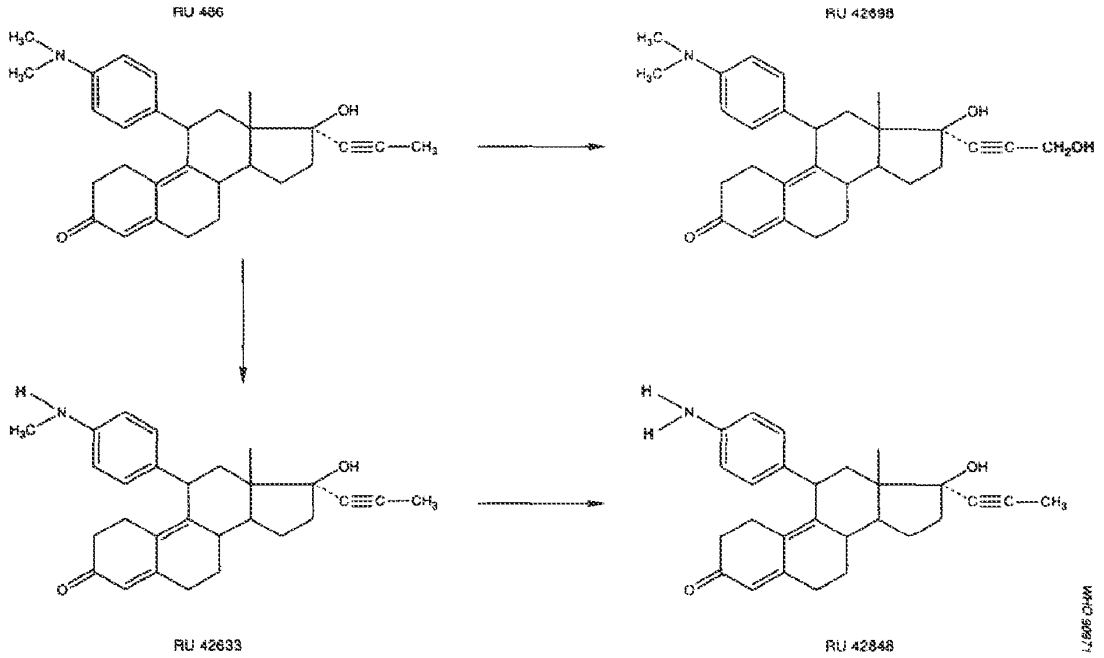

FIGURE 1. RU 486 and its three metabolites assayed in the present study.

and information is available regarding the blood concentrations of the three metabolites in non-pregnant women (7-9). The results of these studies suggest that the pharmacokinetics of RU 486 vary depending on the dose given, probably because the compound binds to a high affinity-limited capacity binding protein in serum (8). The absence of a proportional increase in the plasma concentrations of RU 486 following ingestion of larger doses may explain the lack of a dose-response relationship when the drug is used alone for the termination of early pregnancy (10).

In order to further examine the pharmacokinetics of RU 486, the blood levels of the parent compound and its three main metabolites were measured by HPLC after administration of various doses to the same group of non-pregnant women, and the derived pharmacokinetic parameters compared to those found in pregnant women taking similar doses of the antiprogestin.

Subjects and Methods

Permission for the study had been granted by the Ethics Committees of the Shanghai Institute for Planned Parenthood Research and of the World Health Organization, and informed consent was obtained from the volunteers after the purpose of the study and the procedures involved had been explained.

Nine non-pregnant and 36 pregnant women were recruited. All subjects were healthy with no history of liver, renal, cardiovascular or endocrine disease and none had taken any steroid-containing drugs for at least three months. The non-pregnant subjects had had normal menstrual cycles (25-35 days) for at least three months prior to admission to the study. The pregnant subjects also had had regular menstrual cycles (25-35 days) for at least three months prior to conception and, at the time of study, had been amenorrhoeic for up to 49 days with an ultrasonographically confirmed, normal intrauterine pregnancy.

Each non-pregnant subject received a dose of RU 486 once per menstrual cycle, three days before the expected time of menses. The doses, administered consecutively, were 25, 100, 400 and 600 mg. In six of the nine women, a dose of 200 mg was also given. The pregnant subjects were randomized into four groups which were given a single dose of 25, 100, 400 or 600 mg RU 486. The pregnancies were terminated by vacuum aspiration after collection of the last blood sample.

In both pregnant and non-pregnant women, blood samples were taken from an antecubital vein immediately before and 20 min, 40 min, 1, 2, 4, 8, 12, 48, 72, 96 and 120 h after administration of RU 486. Heparin was used as anticoagulant and the plasma obtained after centrifugation was stored at -20°C until analysed.

RU 486 and its three metabolites were determined in the plasma sam-

ples by HPLC as described previously (6) with minor modifications. An ODS reversed phase column (200mm x 3.5mm ID) was used with a mobile phase of methanol: methylcyanide: water (42: 28: 30 by vol) at a flow rate of 1 ml/min. Recoveries of RU 486 and its three metabolites RU 42633, RU 42698 and RU 42848 were 92%, 93%, 94% and 64%, respectively, the sensitivity of detection for the four steroids in plasma was 10 ng/ml, and the intra- and interassay coefficients of variation were $< 10\%$. Adequate separation of the four steroids was achieved as illustrated in Fig. 2.

Plasma RU 486 concentration-time curves were analysed by the iterative method. With doses of 200 mg or less, the curves were in agreement with a two-compartment open model, whereas with higher doses, zero-order kinetics applied for a period of about 48 h after completion of the absorption and distribution phases. Accordingly, the values were computed according to a non-compartment model (11,12). Clearance (Cl) was calculated from dose/AUC (area under the plasma concentration-time curves obtained by the trapezoid rule). Volume of distribution (Vd) was calculated from Cl/kel.

Statistical analysis was done by t-test and differences were considered significant if $P < 0.05$. Because of the size of the dose groups (nine women),

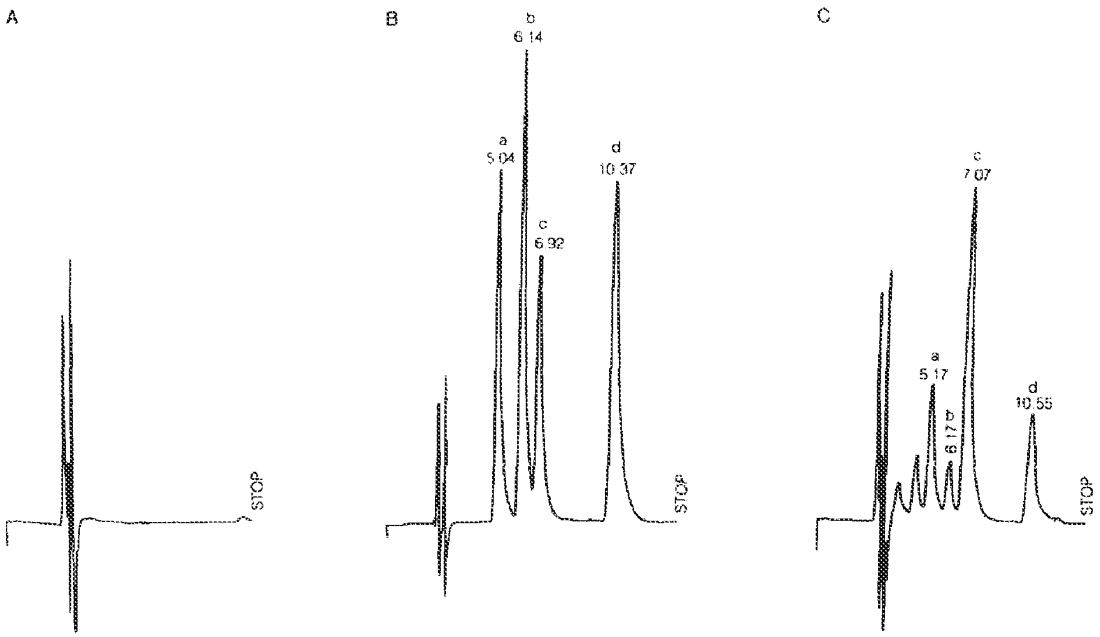

FIGURE 2. HPLC of RU 486 and its metabolites (a: RU 42848; b: RU 42698; c: RU 42633; d: RU 486); A: blank plasma; B: blank plasma with standards added; C: plasma obtained eight hours after a single dose of 100 mg RU 486.

the study could be expected to demonstrate differences between groups of about 1 SD (95% level two-tailed test; 90% power). Based on our previous work (6), this discriminatory power would be sufficient to demon- strate differences in pharmacokinetic parameters of biological relevance.

Results

Characteristics of subjects

There were no significant differences in physical characteristics between the groups studied (Table 1).

Plasma levels of RU 486 and its metabolites

Mean plasma concentrations of RU 486 and its three metabolites at various times after oral administration of single doses of RU 486 to the nonpregnant women are shown in Fig. 3A. Absorption of RU 486 was rapid, as illustrated by the presence of detectable amounts of the steroid in all 20 min samples of all subjects except one who received a 25 mg dose. The rapidity of absorption was also shown by the finding that peak plasma concentrations were achieved at 1 h or less for 21 of the 42 administrations of RU 486, between 1 and 2 h for 15 administrations and after 2 h in only six. There was a very marked between-subject variation in the plasma concentrations after the same dose of RU 486, and examples of the size of this variation are given for some sample times in Table 2. Detectable levels of RU 486 were found in the 96 h samples of all women receiving 200 mg or more, in seven of the nine samples after 100 mg, but in none of the samples after the 25 mg dose.

The ratio of the lh:24h concentrations for the five doses of RU 486 decreased with increase in dose (25 mg, 5.8; 100 mg, 3.5; 200 mg, 2.9; 400 mg, 2.6; 600 mg, 2.4) suggesting that the rate of metabolism decreased with increase in dose. This is also suggested by the data in Fig. 3A where

TABLE 1. Physical characteristics of subjects (X ± SE)

	Non-pregnant	Pregnant			
Dose (mg)	25–600	25	100	400	600
Age (yrs)	28.9 ± 5.1	29.1 ± 3.9	26.1 ± 5.5	28.7 ± 4.6	30.2 ± 4.8
Height (cm)	159.6 ± 4.7	161.7 ± 1.5	162.4 ± 3.8	161.4 ± 3.8	161.0 ± 2.7
Weight (kg)	55.4 ± 7.0	54.6 ± 4.4	52.3 ± 4.2	51.7 ± 5.3	53.5 ± 4.4
Body mass index	21.7 ± 2.1	20.7 ± 1.7	19.8 ± 1.7	19.8 ± 1.5	20.6 ± 1.8

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