ELSEVIER

European Journal of Obstetrics & Gynecology and Reproductive Biology 101 (2002) 113–120

EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY

www.elsevier.com/locate/ejogrb

Mifepristone: bioavailability, pharmacokinetics and use-effectiveness

N.N. Sarkar

Department of Reproductive Biology, All India Institute of Medical Sciences, Ansarinagar, New Delhi 110029, India

Abstract

The potentiality of mifepristone as an abortifacient and contraceptive drug along with its pharmacokinetic parameters is reviewed. Mifepristone or RU486 acts as antagonist to progestational and glucocorticoid functions. It is an orally active compound with nearly 70% absorption rate but its bioavailability is reduced to around 40% because of the first-pass effect. Peak plasma concentrations of 1.9 ± 0.8, 3.8 ± 0.9 and 5.3 ± 1.3 μmol/l are reached within 1–2 h after oral administration of 50, 200 and 600 mg mifepristone in women, respectively, and are maintained at relatively high level up to 48 or 72 h depending on the ingested dose. The plasma kinetics of mifepristone followed two-compartment open model with a mean α-half-life of 1.4 h, volume of distribution 1.47 l/kg and β-half-life of 20–30 h in most of the subjects studied. Clearance from the body was mainly through feces (83%). Biologically active mono-demethylated, di-demethylated and hydroxylated metabolites were found in plasma soon after oral administration of mifepristone. RU486 and its mono-demethylated metabolite bind to progesterone receptors with high affinity. Mifepristone-bound receptor dimers suppress transcription activation and thus, bring about anti-progestational activity that makes mifepristone a potential abortifacient and contraceptive agent. Clinical trials for termination of early pregnancy with 50–600 mg mifepristone plus a prostaglandin analogue achieved a success rate of 82–97%. However, abdominal pain, cramping, nausea, vomiting, bleeding and delay in onset of the next menstrual cycle were the side effects. Administration of 25 mg mifepristone twice 12 h apart, as a post-coital contraceptive showed 100% contraceptive efficacy. A low dose of mifepristone which does not inhibit ovulation reduced fertility significantly by affecting endometrial milieu. These findings suggest that reduced dose(s) of mifepristone, 200 mg or less, may be used as a post-coital contraceptive and in combination with vaginal misoprostol for termination of early pregnancy with high efficacy and minimal or no side effects.

Keywords: RU486; Abortifacient; Contraceptive; Anti-progestin; Progesterone; Receptor; Steroid

1. Introduction

Mifepristone is a derivative of norethindrone, a synthetic 19-nor-steroid, and is also known as RU486. Mifepristone strongly binds to progesterone as well as glucocorticoid receptors and thus, acts as an antagonist to progestational and glucocorticoid functions. Chemically it is 17β -hydroxy-11β-(4 dimethyl aminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one [1,2].

Mifepristone is an effective abortifacient and its efficacy increases when used in combination with prostaglandin [3]. It has also been used or tested in post-coital or emergency contraception, treatment for endometriosis, uterine myomata, progesterone receptor positive tumors in the breast and brain (meningioma), Cushing's disease due to ectopic ACTH secretion and adrenal carcinoma, reduction of intraocular pressure in glaucoma and steroid induced myopathy [4].

This compound thus appears to have tremendous potentialities to be a useful drug for multi-disciplinary health problems. The present article however, is a comprehensive review of the pharmacokinetic parameters and use-effectiveness of mifepristone and an evaluation of its potentialities to be an effective abortifacient and contraceptive drug.

2. Dose and route of administration

Mifepristone has usually been administered orally in single or multiple doses so far ranging from 12.5 to 800 mg per day in various studies [5–10]. This compound is rapidly absorbed from the gut but undergoes first-pass effect in the liver.

3. Absorption, metabolism and tissue uptake

Mifepristone is an orally active compound with an approximately 70% absorption rate from the gut. However, it undergoes first-pass effect in the liver and gets partially metabolized and eventually its bioavailability is reduced to 40% in human beings and rats and 15% in monkeys [11,12]. Experimental assessment of enterohepatic cycling of this compound after an oral dose in normal subjects has

0301-2115/02/$ – see front matter
PII: S0301-2115(01)00522-X

suggested that mifepristone may be partly pooled in the enterohepatic cycle [13]. Three metabolites of mifepristone have been identified. This compound undergoes demethylation to produce mono-demethylated (RU42633) and di-demethylated (RU42848) derivatives as well as hydroxylation of the propynyl group to yield hydroxylated metabolite (RU42698). The study showed that metabolism of RU486 to RU42633 and RU24698 was rapid but removal of the second methyl group leading to formation of RU42848 occurred much more slowly and to much lesser extent than removal of the first [5]. Like mifepristone, these metabolites are immunologically and biologically active and retain anti-progestational and anti-glucocorticoid properties [5,14]. Elimination of mifepristone and its metabolites from the body is mainly through feces (83%) and urine (8.8%) within 6–7 days after administration of a single oral dose [12].

The study in women showed that concentrations of mifepristone were 344 ± 195 and 1040 ± 444 pmol/g in myometrial and abdominal adipose tissues, respectively, at 12–15 h after oral administration of 200 mg RU486, while its concentration in serum was 921 ± 603 nmol/l. In these women, the non-protein bound fraction of RU486 varied from 1.4 to 3.1% (mean 2.3%). There was a lot of individual variation in concentration of RU486 in serum and adipose tissues. In these subjects, concentration of combined mono- and di-demethylated metabolites were approximately 1.4, 3.1 and 5.2 times higher in adipose tissues, myometrium and serum, respectively, than those of the parent compound mifepristone [13]. However, concentration of mifepristone in cerebrospinal fluid was relatively low, about 4% of plasma concentration, perhaps in consequence of relatively low amount of protein in cerebrospinal fluid [12]. The above results indicate that the pattern of uptake of mifepristone and its metabolites by adipose and myometrial tissues is similar after oral administration of mifepristone.

4. Plasma concentration

4.1. Low dose (1–50 mg)

Daily oral administration of mifepristone for one menstrual cycle yielded steady plasma RU486 levels that ranged from 65 nmol/l with 1 mg per day to 1000 nmol/l with 10 mg per day [15]. However, peak plasma concentrations of 0.36 ± 0.1, 1.2 ± 0.1 and 6.7 ± 3.4 μmol/l were reached within 0.5–2 h after oral administration of 2, 8 and 25 mg mifepristone, respectively [16]. After oral doses, twice a day for 4 days in normal subjects, plasma concentration of mifepristone was found up to day 5, to be steady-state ranging from 1–1.5, 1.6–2.6 and 2.2–3.1 μmol/l with 12.5, 25 and 50 mg per dose, respectively [8]. It was also demonstrated that daily oral administration of 25 mg mifepristone for 14 days produced a steady-state plasma concentration of approximately 1 μmol/l [17]. In another study, steady plasma level of RU486 and its metabolites was found to be 2.9 μmol/l after daily ingestion of 50 mg RU486 for 4 days [6]. No cumulative increase in serum concentration was found with prolonged daily administration of low doses of mifepristone [6,8,16]. Thus, the findings suggest the possibility of the low-dose mifepristone to be a potential drug for various clinical applications.

The time required to reach the peak plasma concentration after single oral dose of 50 mg or less ranges from 0.5 to 2 h [5,6,18]. The maximum plasma concentration of mifepristone was found to be 1.9 ± 0.8 and 1.7 ± 0.4 μmol in non-pregnant and pregnant women, respectively, after oral dose of 50 mg RU486. This difference was not statistically significant [5]. The peak plasma concentration of two active metabolites along with the parent compound was also reached approximately to 3.5–4.0 μmol/l in both pregnant and non-pregnant women after oral administration of 25 or 50 mg mifepristone [6]. With 50 mg oral dose, peak plasma level of RU486 was 2.2 ± 1.0 μmol/l in both Chinese and non-Chinese women, indicating there was no ethnic variation regarding bioavailability of mifepristone [18]. However, high individual variations in plasma concentration virtually rendered similar dose response effect with 25 or 50 mg dose of mifepristone. Overall, these findings have shown no significant difference in the plasma concentrations or pharmacokinetic parameters of mifepristone and its metabolites between non-pregnant and pregnant women [5].

4.2. Medium dose (100–200 mg)

Following repeated oral administration of 100 and 200 mg RU486 daily for 4 days, maximum plasma levels reached to 4.5 and 5.4 μmol/l, respectively, in both pregnant and non-pregnant women. The increase in plasma levels was not directly proportional to the increase in the dose [6]. In a similar dose schedule with 100 mg, the steady plasma level of mifepristone ranged from 2.3 ± 0.5 to 2.5 ± 0.4 μmol/l [8]. The discrepancies in the values were probably due to use of different assay system for measurement.

After a single oral dose, the peak plasma concentrations were 3.8 ± 1.4 and 3.8 ± 0.9 μmol/l for 100 and 200 mg RU486, respectively, within 1–2 h after ingestion, in non-pregnant women; whereas, the value for 100 mg dose was relatively low (3.0 ± 0.9 μmol/l) in pregnant women [5]. The peak plasma binding equivalent of RU486 measured by radioreceptor assay was 9.3 μmol/l after 200 mg oral dose in pregnant women [10]. This value was comparable to the findings of another study in which peak plasma concentration of mifepristone was 4.6 μmol/l within 1 h after oral administration of 100 mg single dose in normal subjects [14]. These values have shown that differences in plasma concentration of mifepristone after 100 and 200 mg dose is not significant.

The above findings have shown that dose-response effects of 25, 50 and 200 mg mifepristone are widely studied and are found to be equally effective as 600 mg recommended

dose. However, a standard reduced dose of mifepristone for a particular clinical application is yet to be determined.

4.3. High dose (400–600 mg)

The peak plasma concentrations of mifepristone were 4.8 ± 1.3 and 5.3 ± 1.3 μmol/l in non-pregnant women and 4.0 ± 0.8 and 4.4 ± 0.8 μmol/l in pregnant women after oral administration of 400 and 600 mg RU486, respectively [5]. Following oral dose of 100–800 mg mifepristone in women, peak plasma concentration reached 4.6–5.8 μmol/l within 1 h and after distribution phase, this was not significantly affected by the dose but remained in the same range throughout 48 h [9]. In another study, peak plasma equivalent of RU486 were 10.65 and 12.30 μmol/l in pregnant women after intake of 400 and 600 mg dose, respectively [10]. This showed plasma levels did not increase proportionately with the high doses given. However, significant differences were found in peak plasma values ($P < 0.05$) between 200 and 400 mg doses [10,19].

After a single oral dose, plasma concentration of RU486 at 1 and 24 h increased in proportion to log dose. The ratio of the 1:24 h concentration for the doses of RU486 decreased with increase in doses (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 discrepancy arose because the time for elimination (Tel) increased three- to four-fold with dose. This change resulted from changes in volume of distribution (V_d) and clearance (Cl) which determine Tel. The increase of V_d with dose suggests that mifepristone binds weakly to plasma glycoprotein and that this binding is of limited capacity. Clearance appeared to reach limiting value at doses above 200 mg and this was probably the major factor in determining the elevated plasma levels of mifepristone over a long duration [5,17]. The pharmacokinetic parameters also suggest retention of mifepristone in tissues from which the drug is slowly released [5,13,18]. Elimination from the body is mainly through feces and urine [12].

The plasma concentration of mono-demethylated metabolite (RU42633) reached peak levels that were similar to those of parent compound, RU486 but the peak was attained more slowly. The peak plasma levels of di-demethylated and hydroxylated metabolites were only about 25% of those of RU486 and mono-demethylated metabolite and occurred much later [5]. Mifepristone and its metabolites maintained high plasma levels up to 48 h for low dose and 72 h for medium or high dose of RU486 [5,14,18,20]. No significant difference was found in plasma concentrations of mifepristone and its metabolites between pregnant and non-pregnant women [5,6].

The finding that increasing dose of mifepristone from 200 to 600 mg produces little increase in its plasma concentrations for up to 72 h suggests that clinically, the lower dose is as effective as the higher dose and little, if anything, may probably be gained by giving multiple doses of mifepristone instead of a single dose [5].

5. AUC, half-life and clearance rate

After rapid absorption, there was also rapid distribution of mifepristone with the mean α-half life 1.4 h, fitting the equation for a two-compartment open model [18]. The mean apparent volume of distribution was also reported to be 1.47 ± 0.25 l/kg [7]. Significant difference was found between area under curve (AUC) for 200 and 600 mg doses ($P < 0.01$) or 400 and 600 mg doses ($P < 0.05$) in pregnant women [10,19]. Values for AUC were consistently higher in the non pregnant than in the pregnant women for similar doses, whereas, the reverse was the case for clearance values. However, the differences were not statistically significant. Difference between mean AUC values for 25 and 600 mg doses was about 10-fold [5]. Elimination of mifepristone was rather slow. The elimination or β-half-life ranged from 20 to 30 h in most of the subjects [6,8,9,16,18,21]. However, it was approximately 45–55 or 80–90 h in some subjects [7,10,16,17]. The metabolic clearance rate was also low ranging from 1.04 to 3.0 l/h [7,18]. The serum transport protein, α_1-acid glycoprotein (orosomucoid) regulates the serum kinetics of mifepristone. The steroid does not bind to sex-hormone-binding globulin or cortisol-binding globulin [2]. The binding to α_1-acid glycoprotein limits the tissue availability of mifepristone explaining the low metabolic clearance rate and low volume of distribution. Thus, similar serum concentrations following ingestion of single doses exceeding 100 mg could also be explained by saturation of binding capacity of serum α_1-acid glycoprotein [21].

6. Mechanism of action

Progesterone receptor (PR) contains well defined functional domains: the N-terminal transcription domain, the central DNA binding domain, the hinge region and the C-terminal hormone binding domain. The DNA binding domain of PR contains invariant cysteine repeats that form two ''zinc finger'' structure with four cysteines in each finger for binding to DNA [22]. The nature of the crystal structure of progesterone-bound ligand-binding domain of the human PR explains the receptors selective affinity for progesterone and establishes a common mode of recognition of 3-oxy steroids by the cognate receptors. Although the overall fold of PR is similar to that found in related receptors, the PR has a quite different mode of dimerization. A hormone-induced stabilization of the C-terminal secondary structure of the ligand-binding domain of PR accounts for stereo-chemical properties of this distinctive dimer, and explains the receptor's characteristic pattern of ligand-dependent protease resistance and its loss of regression and also indicates how anti-progestin, RU486 works as contraceptive [23].

The binding of both progesterone and mifepristone produces conformational changes in the form of PR that permits it to bind to DNA [24]. The activation of PR by progesterone

or mifepristone is accommodated by a loss of associated heat shock proteins and dimerization. Human PR has two isoforms (A and B) that form in solution homo and/or heterodimers as intermediate step in the transcription activation process. The activated receptor dimers (A:A, B:B or A:B) bind to progesterone response elements in the promoter region of progesterone genes. The extent of binding is proportional to the extent of dimerization [25,26]. In the case of progesterone, this binding increases the transcription of these genes, producing progesterone effects. In contrast, a receptor dimer complex that has been activated by mifepristone also binds to progesterone response elements, but an inhibitory function in the C-terminal region of hormone binding domain renders this DNA-bound receptor transcription inactive. This is the basis of the progesterone antagonistic action of mifepristone underlying its abortifacient and contraceptive actions [4]. The study also suggests that RU486 bound A-receptor homodimers are functionally silent, whereas, RU486-bound B-receptor homodimers can activate transcription but RU486 bound A:B heterodimers act to dominantly suppress transcriptional activation and it is this activity that is typically seen in progesterone responsive cells [12].

7. Binding affinity

The relative binding affinity of mifepristone for human uterine PR in vitro was higher (100%) than that of progesterone (43%), mono-demethylated (21%), hydroxylated (15%) and di-demethylated (9%) metabolites. Thus, the pool of certain metabolites of RU486 may contribute to a significant extent to the anti-progesterone (23–30%) and even greater extent to the anti-glucocorticoid (47–61%) effects of RU486 [14].

In fact, all receptors that bind mifepristone have a glycine at the corresponding position in hormone binding domain. Substitution of this glycine by cysteine in human PR abrogated binding of mifepristone but not that of an agonist. It is suggested that the hormone binding domain of human PR may at least or in part correspond to the so-called ''11β-pocket'' of the receptor and glycine_{722} is at a critical position in the 11β-pocket. The glycine at 722 position is a critical amino acid without side chain, for binding of bulky aliphatic and aromatic 11β-substitutes, because the maturation of glycine_{722} to cysteine results in 40,000-fold lower affinity for mifepristone [27].

8. Clinical applications

8.1. Abortifacient potentiality

Use of 600 mg mifepristone for termination of pregnancy up to 7 weeks of gestation was approved by the French authority [28]. In a multicentre clinical study, women ($n = 1018$) with gestation up to 9 weeks were given 600 mg oral mifepristone followed 48 h later by 1 mg vaginal gemeprost for termination of pregnancy. There was 94.8% complete abortion and 5.2% required surgical evacuation. No significant relationship was found between outcome and age of gestation or the day mifepristone was given. Seven women were given blood transfusion. Narcotic analgesia was administered after gemeprost treatment to 38.1% nullipara and 10.7% of multipara. The findings suggested that mifepristone and prostaglandin combination was an effective and acceptable alternative (not replacement) to surgical method for termination of early pregnancy [29]. However, a need to explore the efficacy of reduced doses was felt by investigators to be an important issue.

In a similar study with 1182 women, pregnant for 1–4 weeks, the rate of complete abortion was 93.8, 94.1 and 94.3% with a single dose of 200, 400 and 600 mg mifepristone followed 48 h later by vaginal pessary of 1 mg gemeprost, respectively, with overall 3.7% incomplete and 0.3% missed abortion. About 50% of those who had incomplete abortion underwent emergency uterine curettage usually for hemostatic purpose, besides blood transfusion to three women. The number of reported complaints such as bleeding patterns, changes in blood pressure and hemoglobin concentration were similar with the three treatment doses. Thus, for termination of early pregnancy, a single dose of 200 mg mifepristone was reported to be as effective as the recommended dose of 600 mg when used in combination with a vaginal pessary of 1 mg gemeprost [30]. This clinical finding also correlates well with plasma mifepristone levels up to 72 h after a single oral dose.

In a WHO sponsored study, treatment with 25 mg mifepristone five times at 12 h intervals to women ($n = 192$) pregnant for $\leq$49 days, or 600 mg as a single dose ($n = 193$) followed by 1 mg gemeprost 60 h after start of mifepristone showed complete abortion rate of 92.7%. Frequency of complaints such as bleeding patterns and changes in hemoglobin, β-hCG, estradiol and progesterone levels were similar in both groups. However, levels of cortisol at 12 and 36 h and prolactin at 12 h after administration of mifepristone were significantly higher in 600 mg dose group [31]. The findings suggest that a lower dose of mifepristone may suffice for termination of early pregnancy.

In another multicentre trial in China, treatment with initial dose of 50 mg RU486 followed by 25 mg every 12 h up to a total dose of 150 mg plus a single oral dose of 600 μg misoprostol in the morning of the third day was given to women of group I ($n = 301$) pregnant for $\leq$49 days. The group II women ($n = 155$) received the same dose of mifepristone plus 1 mg vaginal suppository of PGO5 inserted on the third day and group III ($n = 149$) was given a single dose of 200 mg RU486 plus 600 μg misoprostol as in group I. No significant difference was found in the rate of complete, incomplete abortion and treatment failure among group I (94.4, 3 and 1.7%), group II (97.3, 2 and 0.7%) and group III (94.6, 2.7 and 2%), respectively. Lower abdominal

pain was the main complaint reported by 82% of women after PGO5 administration. Incidence of diarrhea in PGO5 group II (38.7%) was significantly higher than that in group I (21.6%) and group III (20.1%) ($P < 0.001$) and so was vomiting [32]. The clinical findings confirm abortifacient potentiality of repeated doses of 25 or 50 mg or single dose of 200 mg mifepristone as well as conform with kinetic and metabolic outcome of low and medium dose of mifepristone. Even a single oral dose of 50 mg mifepristone plus 0.5 mg gemeprost yielded 82% complete abortion [33].

The medical abortion with mifepristone plus prostaglandin analogue had more side effects such as cramping, nausea, vomiting, and particularly bleeding, than surgical abortion but very few serious side effects [34,35]. The average blood loss due to medical abortion with RU486 plus prostaglandin was found to be 136.8 ml but this did not adversely affect the hemoglobin level in volunteers. They described it as a heavy period [36].

In the comparative study of blood loss or side effects, between surgical and medical abortion with 600 mg RU486 plus 400 μg misoprostol, an oral regimen in women ($n = 1373$) pregnant for ≤56 days in China, Cuba and India, the medical group perceived their bleeding to be heavier than did the surgical group. However, their perception did not prevent them from having higher satisfaction levels [37]. The medical group experienced more side effects than the surgical group. Disparity between these two groups was more pronounced for bleeding and pain but reports of well-being and satisfaction were similar in both groups [38]. In the similar study in the US women ($n = 269$), pregnant for ≤63 days, the median time delay for therapeutic curettage was significantly longer in the medical group, 35 versus 8 days. They also experienced significantly longer bleeding. No significant change in hemoglobin occurred in either group. However, the medical group reported significantly greater pain and nausea or vomiting [39].

In the US multicentre trial ($n = 2015$), pregnancies were terminated in 92, 83 and 77% women, pregnant for ≤49, 50–56 and 57–63 days, respectively, with 600 mg mifepristone and 400 μg misoprostol ($p < 0.001$). This occurred within 4 h in 49% women and within 24 h in 75% women after administration of misoprostol. The failure rate increased with increasing duration of pregnancy, 1% in ≤49 days group to 9% in 57–63 group ($P < 0.001$). Abdominal pain, nausea, vomiting, diarrhea and vaginal bleeding also increased with advancing gestational age [40]. However, no difference in efficacy or side effects was found during the treatment with 600 mg mifepristone and 1 mg gemeprost, whether latter was administered 24 or 48 h after mifepristone intake, suggesting that the treatment period could be reduced from conventional 48 to 24 h [41].

Women received 200 mg mifepristone orally followed 36–48 h later by 800 μg misoprostol vaginally for termination of pregnancy up to 63 days ($n = 2000$). The rates of complete, incomplete and missed abortion were 97.5, 1.4 and 0.4%, respectively. This regimen appeared effective in term of high complete abortion rate and low continuing pregnancy rate (0.6%) and was also less costly as the dose of mifepristone was lower and misoprostol was less expensive, easy for transport and storage [42]. With the same treatment regimen, 80% of women ($n = 933$), pregnant for 8 weeks bled within 4 h and 98% within 24 h of using misoprostol. The success rate was 97%. Side effects were acceptable to 85% and 94% women found procedure acceptable. The findings suggested that low-dose mifepristone plus vaginal misoprostol was highly effective as an abortifacient [43].

In the WHO sponsored trial, 1589 women, pregnant for ≤35 days received a single dose of 200 or 600 mg mifepristone followed 48 h by 400 μg oral misoprostol. The complete abortion rates were 89.3 and 88.1% for lower and higher doses, respectively. This finding suggests that the same outcome can be achieved by reducing the dose of mifepristone from 600 to 200 mg [44].

In a multicentre trial, 200 mg mifepristone followed by 800 μg vaginal misoprostol was received by 827 women, pregnant for ≤56 days, and 308 women, pregnant for 57–63 days, for termination of pregnancy. Complete medical abortion occurred in 97% of women in the former group and 96% in the latter group. However, side effects were less in the former group [45].

The results of mifepristone–misoprostol clinical trials have shown that the dose of mifepristone can be reduced from 600 to 200 mg when followed by vaginal misoprostol without loss of efficacy. In fact, vaginal misoprostol extends efficacy to 56 days' LMP and associated with less nausea and vomiting [46,47]. The studies have also shown that efficacy decreases with increasing gestational age ($P < 0.001$), and difference by regimens are not statistically significant, except at gestational age ≥57 days [48].

The vaginal misoprostol, 800 μg is found to be more effective than oral misoprostol, 400 μg for uterine evacuation of early pregnancy failure [49]. The regular uterine contraction developed slowly in all women treated vaginally, irrespective of the dose of misoprostol. However, this was not the case after oral treatment. Only 20 and 50% of women treated orally with 200 and 400 μg of misoprostol, respectively, developed such an effect [50].

A significant difference in the pharmacokinetics of misoprostol administered by vaginal and oral routes was observed. The mean AUC of misoprostol was much higher when administered through the vaginal than oral route. This discrepancy may explain the difference observed in clinical efficacy [51]. The long lasting and continuously increasing uterine contractility after vaginal administration may be explained, only in part by the direct effect and the longer period of elevated plasma level of misoprostol [50].

No significant difference was observed in serum levels of mifepristone or its metabolites and concentration of serum binding protein, α_1-acid glycoprotein, between responders and non-responders. This suggested that failure to abort in response to mifepristone therapy was not associated with altered pharmacokinetics or metabolism of mifepristone

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.