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The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action

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Abstract

The pharmacokinetics of mifepristone is characterized by rapid absorption, a long half-life of 25–30 h, and high micromolar serum concentrations following ingestion of doses of ≥100 mg of the drug. The serum transport protein—α 1-acid glycoprotein (AAG)—regulates the serum kinetics of mifepristone in man. Binding to AAG limits the tissue availability of mifepristone, explaining its low volume of distribution and low metabolic clearance rate of 0.55 L/kg per day. In addition, the similar serum levels of mifepristone following ingestion of single doses exceeding 100 mg can be explained by saturation of the binding capacity of serum AAG. Mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps being catalyzed by the cytochrome P-450 enzyme CYP3A4. The three most proximal metabolites, namely, monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward human progesterone and glucocorticoid receptors. Also, the serum levels of these three metabolites are in ranges similar to those of the parent mifepristone. Thus, the combined pool of mifepristone—plus its metabolites—seems to be responsible for the biological actions of mifepristone. Recent clinical studies on pregnancy termination and emergency contraception have focused on optimization of the dose of mifepristone. In these studies it has become apparent that the doses efficient for pregnancy termination differ from those needed in emergency contraception—mifepristone is effective in emergency contraception at a dose of 10 mg, which results in linear pharmacokinetics. However, the ≥200 mg doses of mifepristone needed for optimal abortifacient effects of mifepristone result in saturation of serum AAG and thus nonlinear pharmacokinetics. In view of the pharmacokinetic data, it may be speculated that dosing of mifepristone for pregnancy termination and for emergency contraception could be reduced to approximately 100 mg and 2–5 mg, respectively. It remains to be seen whether the newly synthesized, more selective antiprogestins will prove more efficacious in the clinical arena.

Keywords: Metabolism; High performance-liquid chromatography; Radioimmunoassay; Emergency contraception; Medical abortion; Dose-response relationships

1. Introduction

Recent clinical studies on the use of mifepristone in medical termination of pregnancy and in emergency contraception have focused on optimization of mifepristone regimens. In termination of first-trimester pregnancy, a 200-mg dose of mifepristone, in combination with vaginally administered prostaglandin, is equally effective as a higher dose (600 mg) of mifepristone [1–3]. In these studies, the percentages of complete abortions have ranged 88–96% [1–3]. The results of preliminary studies have suggested that even a 100-mg dose of mifepristone might be equally effective [4]. However, in a randomized multicenter study arranged by the World Health Organization (WHO), 50 mg of mifepristone combined with vaginally administered prostaglandin was 1.6 times more likely to fail in termination of first trimester pregnancy when compared with a regimen containing 200 mg of mifepristone [5].

In emergency contraception, considerably lower doses of mifepristone are needed. In a randomized study arranged by the WHO, a 10-mg dose of mifepristone was equally effective as 50 mg or 600 mg doses, each preventing 84–86% of pregnancies [6]. In fact, the lowest effective dose of mifepristone in emergency contraception has not been characterized. The more than 10-fold difference in the doses of

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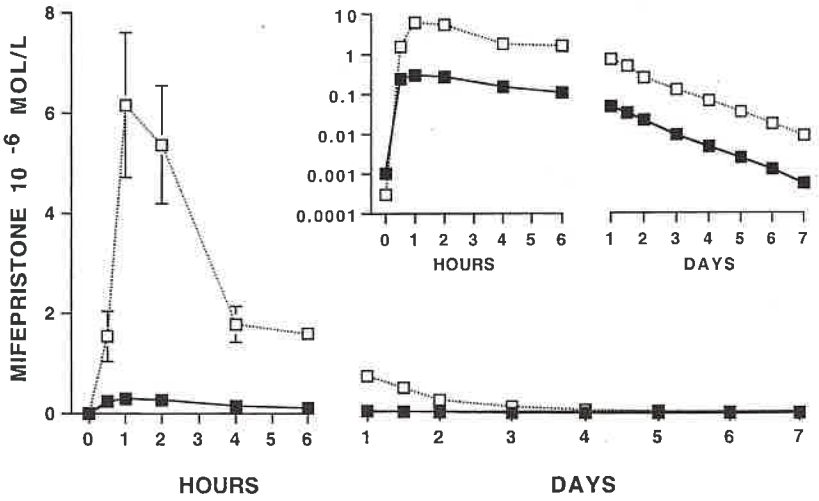

Fig. 1. Serum levels (mean ± SE) of mifepristone following administration of 2 mg (■) and 25 mg (□) to five female volunteers. The data are depicted on both linear (lower) and semilogarithmic (upper) scales. Redrawn from Kekkonen et al. [17].

mifepristone required for optimal clinical effects in emergency contraception and in pregnancy termination suggests that different biological mechanisms mediate these clinical effects of mifepristone.

The antiglucocorticoid effects of mifepristone are in sharp contrast with its antiprogestagenic effects in pregnancy termination or in emergency contraception. Early studies by Bertagna et al. [7] and Gaillard et al. [8] showed that activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to mifepristone is clearly a dose-dependent phenomenon, and significant increases in the circulating concentrations of adrenocorticotropic hormone and cortisol are seen following administration of ≥200 mg of the drug. Moreover, more pronounced activation of the HPA axis is seen as the dose of mifepristone is increased [7,8].

The differences in the clinical effects of mifepristone are also related to its pharmacokinetics—the high efficacy of mifepristone in emergency contraception is seen in the dose range that results in linear kinetics of the drug in serum. However, the doses required for termination of pregnancy or activation of the HPA axis result in saturation level, non linear kinetics of mifepristone. In this article we review the pharmacokinetics of mifepristone in humans, with special emphasis on the relationships between its pharmacokinetics and clinical efficacy.

2. Pharmacokinetics of mifepristone

2.1. Assay systems for mifepristone

Various assay methods such as radioimmunoassay (RIA) [9], radioreceptorassay (RRA) [10,11] and assays based on high-performance liquid chromatography (HPLC) have been used to measure serum mifepristone levels [12–14]. It soon became apparent that mifepristone is extensively metabolized, and due to the cross-reacting metabolites, direct RIA and RRA failed to distinguish the parent mifepristone from its metabolites [15]. However, the micromolar serum levels of mifepristone—seen following ingestion of doses currently used in clinical practice—allowed us to develop methods based on HPLC for detailed analysis of the pharmacokinetics and metabolism of mifepristone [16]. Column chromatography can be used to separate the metabolites from the parent mifepristone, which can then be measured specifically either by RIA or HPLC [13].

2.2. Absorption and distribution of mifepristone

Following oral ingestion, mifepristone is rapidly absorbed and the time to peak serum levels (t_{max}) is approximately 1–2 h [11–13]. Also, when analyzed by specific RIA or HPLC, the t_{max} values have been similar within the dose range of 200–600 mg of mifepristone [16,17]. Peak concentrations (C_{max}) rise according to the dose of mifepristone within the dose range of 2–25 mg [17]. However, at higher doses of 100–800 mg, C_{max} values do not differ significantly, most likely as a result of saturation of the serum binding capacity for mifepristone [16]. The bioavailability has been estimated to be 40% following oral intake of 100 mg of mifepristone [18]. Unfortunately, attempts to bypass the first-pass metabolism by means of vaginal administration resulted in low serum levels of mifepristone [19].

2.3. Serum levels of mifepristone

The pharmacokinetics of mifepristone have been studied following single oral doses ranging 2–800 mg. Following ingestion of 2 and 25 mg doses, the levels of mifepristone, as well as the areas under the concentration curves (AUCs), rise according to the dose (Fig. 1) [17]. However, following

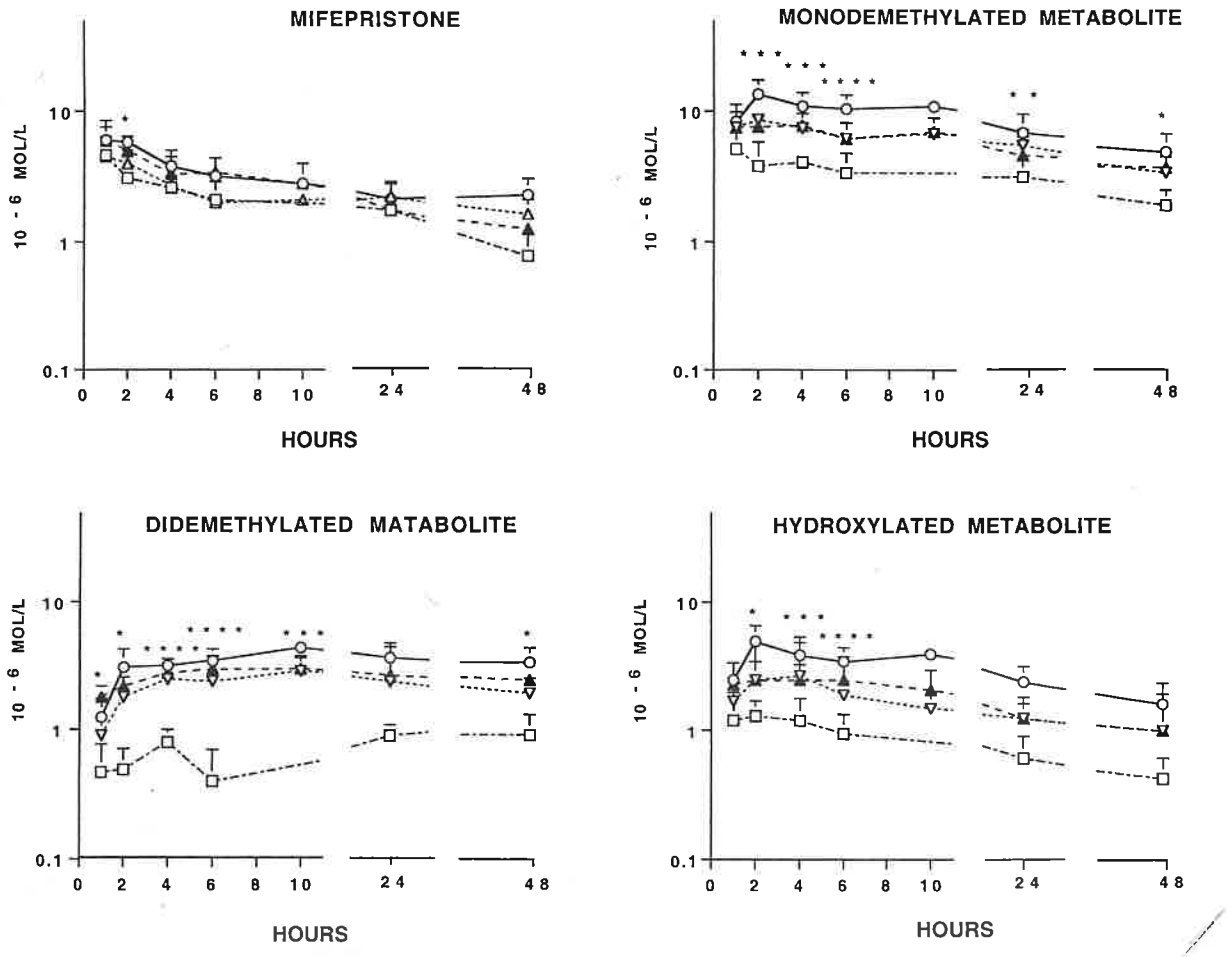

Fig. 2. Serum levels (mean ± SE) of mifepristone and its monodemethylated, hydroxylated and didemethylated metabolites following administration of single doses of 100, 400, 600 and 800 mg to female volunteers. Statistically significant differences in the serum levels between the groups ingesting 100 and 800 mg are indicated by asterisks (*$p < 0.05$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.001$). Redrawn from Heikinheimo et al. [16].

intake of single doses of 100, 400, 600 and 800 mg, the concentrations of mifepristone have all been observed to be at ~2.5 μmol/L at 24 h (Fig. 2) [16] despite the nearly 10-fold difference in the dose ingested.

When administered repeatedly, a similar phenomenon in the plateau levels is seen when the daily dose of mifepristone exceeds 100 mg [20]. Figure 3 shows the individual and mean levels of mifepristone in a group of six women given 50 mg twice a day for 7 days. The individual levels of mifepristone were similar among the subjects, and the individual half-lives of mifepristone varied from 26–48 h. The micromolar serum concentrations of mifepristone also persist during prolonged daily treatment with 200 mg for up to 20 months [21].

2.4. Serum binding characteristics of mifepristone

In human serum, 94–99% of mifepristone is protein bound [10,16]. Early studies by Moguilewsky and Philibert [22] indicated that human serum, unlike rat serum, contains a high-affinity binding protein for mifepristone, which was soon identified as α 1-acid glycoprotein (AAG). The highly significant correlations between serum levels of mifepristone and AAG suggested that AAG has a great impact on the pharmacokinetics of mifepristone in man [16,23]. Studies involving centrifugal ultrafiltration dialysis showed that a serum concentration of mifepristone of 2.5 μmol/L represents saturation of AAG binding capacity (Fig. 4) [16]. In addition, albumin appears to have a high-capacity role in the serum transport of mifepristone [16].

Thus, in humans, serum AAG appears to limit the tissue availability of mifepristone. However, mifepristone exceeding the binding capacity of AAG may be more susceptible to excretion or possibly diffusion into peripheral tissues [24]. In accordance with the low volume of distribution, tissue mifepristone levels have been observed to be in the same range or lower than serum levels following intake of 200 mg of mifepristone prior to hysterectomy [24].

2.5. Metabolism of mifepristone in humans

The elimination phase half-life of mifepristone ($t_{1/2}$) has been reported to vary between 24 and 48 h when analyzed

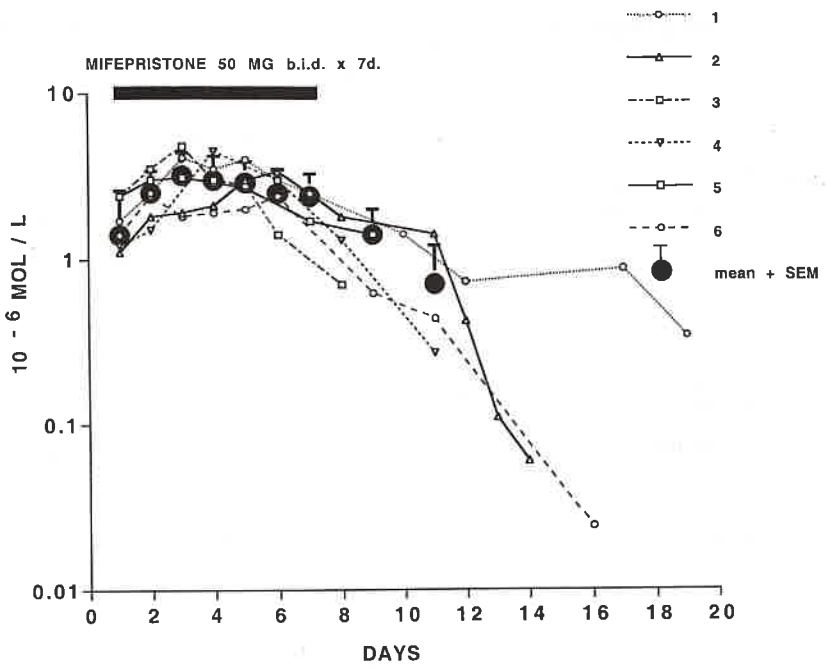

Fig. 3. Individual and mean (±SE) levels of mifepristone during intake of 50 mg twice a day for 7 days in six female volunteers. Redrawn from Heikinheimo [20].

by HPLC [14,20]. However, investigators employing either RIA or RRA have reported $t_{1/2}$ values between 54 and 90 h [11,25], this most likely a result of the presence of cross-reacting metabolites of mifepristone.

The metabolism of mifepristone is initiated by rapid demethylation and hydroxylation in humans, rats and monkeys [18]. The enzyme CYP3A4 has been shown to be the primary cytochrome P-450 enzyme responsible for the oxidative metabolism of mifepristone in human liver microsomes [26]. Following oral intake of 100 mg or more, constant serum levels of mifepristone, but increasing concentrations of the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone are found, with serum levels of the monodemethylated metabolite exceeding those of the parent compound [16,27]. Following administration of mifepristone at doses over 400 mg, the concentrations of the didemethylated and hydroxylated metabolites also exceed those of the parent compound (Fig. 2) [16]. Peak levels of the monodemethylated and hydroxylated metabolites are reached by 2–4 h. The time course of the didemethylated metabolite is somewhat different, with peak levels being measured only after 10 h following ingestion of mifepristone.

The demethylated and hydroxylated metabolites are further metabolized and excreted into bile. In humans, only a very small fraction of mifepristone can be detected in urine [18].

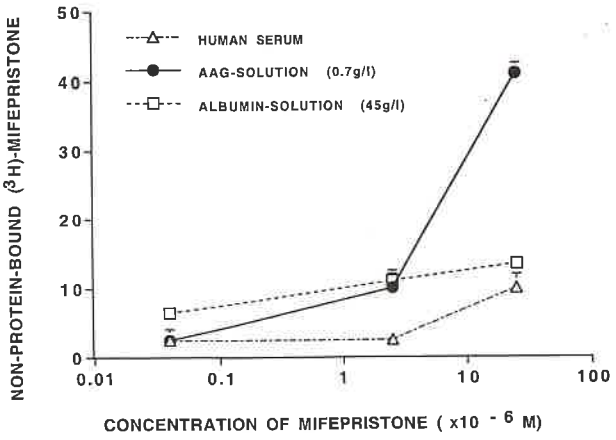

Fig. 4. Percentage of serum non-protein–bound mifepristone (mean ± SE) in human serum, in phosphate-buffered saline (PBS) containing human alpha 1-acid glycoprotein (AAG), and in PBS containing human albumin. Redrawn from Heikinheimo et al. [16].

3. Binding of mifepristone and its metabolites to hPR and hGR

Tables 1 and 2 summarize the relative binding affinities (RBAs) of mifepristone, the monodemethylated, hydroxylated and didemethylated metabolites, as well as those of reference steroids, to the human progesterone receptor (hPR) and glucocorticoid receptor (hGR) [15]. The relatively high receptor-binding affinities of mifepristone's metabolites in combination with the high serum levels of the metabolites suggest that some of the biological effects of mifepristone may be mediated via both the parent compound as well as the pool of metabolites.

The efficacy of mifepristone in pregnancy termination

Table 1
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human uterine progesterone receptor

Compound	RBA %
ORG-2058	374
Mifepristone	100
Progesterone	43
Monodemethylated metabolite	21
Hydroxylated metabolite	15
Didemethylated metabolite	9

cannot be improved by increasing the dose beyond 200 mg [1–3]. Thus, based on the similar serum concentrations of mifepristone, but increasing levels of the metabolites following intake of ≥100 mg of mifepristone (Fig. 2), it may be speculated that the lower affinities of the metabolites towards hPR (Table 1) imply minor importance of these metabolites in the abortifacient action of mifepristone.

In comparison with hPR, the RBAs of the monodemethylated, hydroxylated and didemethylated metabolites toward hGR (Table 2) are more pronounced. The antiglucocorticoid effects of mifepristone increase in a dose-dependent manner following ingestion of doses of ≥200 mg [7,8]. Thus, based on the similar serum levels of parent mifepristone but increasing levels of the metabolites, it may be speculated that the metabolites are important in the antiglucocorticoid actions of mifepristone.

4. Pharmacokinetics vs. clinical effects of mifepristone

Understanding the pharmacokinetics of mifepristone has aided the design of studies aimed at optimizing mifepristone regimens. In several randomized multicenter studies, it has become clear that a 200-mg dose, but not a 50-mg dose, of mifepristone in combination with prostaglandin is effective in pregnancy termination [1–3,5]. In fact, even a 100-mg dose of mifepristone might be acceptably effective [4]. In view of the saturation stage pharmacokinetics of mifepristone following intake of doses of 100 mg and more, the efficacy of the 100 mg dose is not surprising. Thus, for termination of pregnancy, the saturation stage serum kinetics of mifepristone appear important. It may be speculated that the abortifacient properties—decidual bleeding, increased uterine contractility and sensitivity to prostaglandins—require complete saturation of the uterine progesterone receptors.

Table 2
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human placental glucocorticoid receptor

Compound	RBA %
Mifepristone	100
Monodemethylated metabolite	61
Hydroxylated metabolite	48
Didemethylated metabolite	45
Dexamathasone	23
Cortisol	9

When women with complete and incomplete termination of pregnancy following administration of a single dose of 600 mg of mifepristone were compared, the serum levels of mifepristone and those of the three metabolites were indistinguishable [28]. It therefore appears that individual uterine sensitivity to progesterone withdrawal, and not differences in the pharmacokinetics of mifepristone, dictate the eventual clinical outcome of each subject.

In emergency contraception, mifepristone doses in the range of 10–600 mg behave similarly, inhibiting 84–85% of pregnancies [6]. Therefore, the mechanism by which mifepristone acts as an emergency contraceptive is clearly different from its ability to start a cascade resulting in termination of pregnancy. Continuous daily administration of 2 mg of mifepristone or more inhibits ovulation in women [29,30]; this inhibition occurs most likely via central mechanisms [29,30]. As inhibition or delay of ovulation also appears to be a major mechanism of action in emergency contraception [31], 10 mg of mifepristone, and thus linear range serum levels of the drug, are sufficient for the presumed ovulation inhibition. It may be speculated that an even lower dose than 10 mg of mifepristone might be effective in emergency contraception. As the endometrium appears to be very sensitive to the effects of mifepristone [32,33], possible actions on the endometrium might complement the efficacy of mifepristone in emergency contraception.

Mifepristone has several pharmacokinetic features that make it very useful in both termination of pregnancy and in emergency contraception. It is rapidly absorbed and the bioavailability of mifepristone is sufficient for clinical use. The long $t_{1/2}$ of mifepristone allows effective single-dose treatment, and thus controlled distribution for both clinical indications. It may be argued that identification of the minimal effective dose, which may be approximately 100 mg for pregnancy termination and 2–5 mg for emergency contraception, is important. It remains to be seen whether some of the newly synthesized antiprogestins with higher selectivity will be clinically superior to mifepristone.

Acknowledgments

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