DRUG DISPOSITION

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Clinical Pharmacokinetics of Mifepristone

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Summary

Mifepristone is a steroidal antiprogestin and antiglucocorticoid acting at the receptor level. The aromatic dimethylaminophenyl side chain in position 11 of the steroid structure is essential for the antagonistic properties of mifepristone.

The pharmacokinetics of mifepristone are characterised by rapid absorption, a long half-life of 25 to 30 hours and micromolar serum concentrations following ingestion of doses currently in clinical use. The serum transport protein α_1-acid glycoprotein (AAG) regulates the serum kinetics of mifepristone. Binding to AAG limits the tissue availability of mifepristone, explaining the low metabolic clearance rate of 0.55 L/kg/day and the low volume of distribution of mifepristone. Also, similar serum concentrations of mifepristone following ingestion of single doses exceeding 100mg can be explained by saturation of the binding capacity of serum AAG. Following oral intake, mifepristone is extensively metabolised by demethylation and hydroxylation, the initial metabolic steps are catalysed by the cytochrome P450 (CYP) enzyme CYP3A4.

The 3 most proximal metabolites, namely the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward the human progesterone and glucocorticoid receptors; in addition, the

serum concentrations of these 3 metabolites are in a similar range as those of the parent drug. Thus, the combined pool of mifepristone, as well as that of the metabolites, seems responsible for the biological actions of mifepristone.

Combination therapy with mifepristone and low dose prostaglandin is currently in clinical use for termination of early pregnancy in China, France, Sweden and the UK. The combined regimen is well tolerated and highly efficacious with a 95% rate of complete pregnancy terminations. Recent clinical studies on pregnancy termination have focused on dose optimisation of mifepristone and evaluation of the orally active prostaglandin derivative misoprostol. In addition, several other indications for the clinical use of mifepristone, such as induction of labour, contraception, as well as treatment of various hormone dependent disorders, are emerging.

The major obstacles currently inhibiting further evaluation and distribution of mifepristone are political rather than clinical. However, it is hoped that the eventual introduction of new antiprogesterone molecules by several manufacturers will enhance the availability of this important class of new drugs.

Rarely has the introduction, testing and distribution of a single drug provoked as much scientific and political controversy as that associated with the progesterone receptor antagonist mifepristone (RU486). Development of mifepristone was a culmination of several decades of scientific pursuit emerging from the characterisation of the intracellular steroid receptor proteins, the systematic evaluation of steroid structure-receptor binding-relationships as well as understanding the roles of gonadal steroids in the regulation of reproductive physiology. Mifepristone is currently in clinical use for termination of early pregnancy in France, China, the UK and Sweden; application processes are currently underway in the US.

This article reviews the current status of the clinical use of mifepristone with special emphasis on its pharmacokinetics in humans.

1. Pharmacokinetics

1.1 Assay Systems

Various assay methods have been employed in the measurement of serum mifepristone; these include radioimmunoassay (RIA),[1] radioreceptorassays (RRA)[2,3] as well as assays based on high performance liquid chromatography (HPLC).[4-6] However, because of the presence of cross-reacting metabolites, direct RIA and RRA fail to distinguish the parent mifepristone from the considerable pool of metabolites present in the circulation following oral intake of the compound.[5] Serum concentrations of mifepristone are in the micromolar range following ingestion of doses currently in clinical use, thus allowing the use of HPLC for detailed analysis of the pharmacokinetics and metabolism of mifepristone.

1.2 Absorption

Following oral ingestion mifepristone is rapidly absorbed and the time to peak serum concentrations (t_{max}) is approximately 1 to 2 hours.[3,5,6] When analysed by specific RIA or HPLC, the t_{max} has been similar within the dose range 2 to 600mg.[7,8] The peak drug plasma concentrations (C_{max}) rise according to the dose of mifepristone within the dose range of 2 to 25mg.[8] However, at doses of 100 to 800mg, the C_{max} does not differ significantly, this is most likely because of the saturability of the serum binding capacity for mifepristone.[9]

Because of presystemic metabolism, bioavailability of mifepristone has been estimated to be 40% following oral intake of 100mg.[10] Unfortunately, attempts to bypass first pass metabolism by vaginal administration resulted in very low serum concentrations of mifepristone.[11]

1.3 Serum Kinetics

Following the absorption and distribution phase of approximately 4 to 6 hours, the serum concentration of mifepristone remains in the micromolar range for the next 24 to 48 hours.[3,9] Interestingly, following ingestion of single doses of mifepristone 100 to 800mg, the serum concentrations were all approximately 2.5 µmol/L at 24 hours.[9] However, within the dose range of 2 to 25mg, the serum concentrations of mifepristone, as well as the areas under the concentration-time curves (AUC), increase according to the dose.[8] The same phenomenon of similar serum concentrations also occurs during multiple dose administration of 50mg or more of mifepristone.[12] These micromolar serum concentrations of mifepristone also persist during long term (up to 20 months) daily treatment with 200mg.[13]

At serum concentrations below 2.5 µmol/L, 94 to 99% of mifepristone is protein bound in human serum.[2,9] Early studies by Moguilewsky and Philibert[14] 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 the serum concentrations of mifepristone and AAG suggested that AAG has a great affect on the pharmacokinetics of mifepristone in humans.[9,15,16] Studies using centrifugal ultrafiltration dialysis showed that the 2.5 µmol/L plateau serum concentrations of mifepristone represent saturation of AAG binding capacity.[9] In addition, *in vitro* studies suggest that albumin has a high capacity role in the serum transport of mifepristone.[9]

The profound effect of binding to AAG on the pharmacokinetics of mifepristone can be demonstrated by comparing the differences in the distribution of mifepristone between humans and rats. Rat serum does contain AAG; however, it does not bind mifepristone in the same manner as human AAG.[14] In humans the initial volume of distribution and the clearance rate of mifepristone are 10% of bodyweight and 0.55 L/kg/day, whereas in rats the corresponding figures are 135% and 71 L/kg/day, respectively.[10] Thus, in humans the serum AAG seems to limit the tissue availability of mifepristone. However, mifepristone exceeding the binding capacity of AAG may be more susceptible for excretion or possibly for diffusion into peripheral tissues.[12]

1.4 Metabolism in Humans

The elimination phase half-life ($t_{1/2}$) of mifepristone has been reported to vary between 24 and 48 hours when analysed by HPLC.[6,17] However, studies employing either RIA or RBA have reported $t_{1/2}$ values between 54 to 90 hours,[3,18] most likely due to the presence of cross reacting metabolites of mifepristone.

The metabolism of mifepristone is initiated by rapid demethylation and hydroxylation in humans, rats and monkeys.[10] Recently, cytochrome P450 (CYP) 3A4 has been shown to be the primary CYP enzyme responsible for the oxidative metabolism of mifepristone in human liver microsomes.[19] Following oral administration of 100mg or more, constant serum concentrations of mifepristone, but increasing concentrations of the monodemethylated, didemethylated and hydroxylated metabolites are found.[9,20] Within the dose range of 100 to 800mg, the serum concentrations of the monodemethylated metabolite exceed those of the parent drug;[9,20] in addition, following oral administration of doses beyond 400mg, the levels of didemethylated and hydroxylated metabolites exceed those of mifepristone.[9] The demethylated and hydroxylated metabolites are further metabolised and excreted into bile, but in humans only a very small fraction of mifepristone can be detected in urine.[10]

2. Mechanisms of Action at the Receptor Level

Mifepristone binds with ~2.5 times higher affinity to the human progesterone receptor than progesterone itself and with around 4 times higher affinity to the human glucocorticoid receptor than dexamethasone.[7] The subsequent steps in the mechanism of action of mifepristone have been

subject to intensive study. Mifepristone bound progesterone receptors have been shown to undergo receptor dimerisation and they also bind to hormone response elements in DNA, but apparently in an abortive manner unable to execute the final steps of progesterone receptor actions.[21]

The monodemethylated, hydroxylated and didemethylated metabolites of mifepristone retain affinities of 21 to 9% towards the human progesterone receptor (hPR), when compared with mifepristone. The disassociation constant (K_D) of mifepristone for the hPR is 1.3×10^{-9} mol/L. Their binding affinities towards human glucocorticoid receptor (hGR) are 61 to 45%, whereas that of dexamethasone is 23%, of that of mifepristone (1.6×10^{-9} mol/L).[7] These receptor-binding affinities, in combination with the high serum concentrations of the metabolites, suggest that the biological effects of mifepristone are mediated via both the parent compound as well as the pool of metabolites. However, the lower affinities towards hPR may imply a minor importance for the metabolites in the antiprogesterone action of mifepristone.

3. Clinical Uses

3.1 Termination of Early Pregnancy

3.1.1 Mechanism of Action at the Uterine Level

The effects of mifepristone on the secretory primate endometrium (extravasation of the red blood cells, neutrophil infiltration and local necrosis) are evident at 32 hours following administration of the drug.[22] Sloughing of the functional endometrium and that of the chorionic gonadotropin producing trophoblast tissue, results in cessation of the corpus luteum function. Following successful mifepristone-induced termination of pregnancy, the serum concentrations of progesterone and chorionic gonadotropin fall to undetectable levels within 2 and 4 weeks, respectively.[23]

In addition to its role in the secretory transformation and decidualisation of the endometrium, progesterone also maintains the uterus in a quiescent state throughout the pregnancy.[24] Mifepristone augments prostaglandin synthesis in *in vitro* cultures of endometrial and decidual cells.[25] However, mifepristone promotes uterine contractions even during inhibition of prostaglandin synthesis by indomethacin.[26] The increased levels of prostaglandin due to the administration of mifepristone are likely to be mediated via the inhibition of prostaglandin degradation.[27] Additionally, antiprogestins cause a softening of the uterine cervix. Thus, mifepristone has been used successfully to ease the dilatation of the cervix during surgical termination of early pregnancy.[28] Therefore, at the uterine level, the antiprogesterone effects, which result in the termination of early pregnancy, are mediated via several tissue compartments.

3.1.2 Combination of Mifepristone and Prostaglandin

The efficacy of the 'mifepristone only' therapy was evaluated in the first clinical studies. When used alone, the percentage of complete terminations of early pregnancy varied between 50 and 85% regardless of the dose of mifepristone.[23,29] Of the various parameters studied, only low levels of serum hCG significantly predicted clinical efficacy.[23,29] Also the serum concentrations of mifepristone and those of its most proximal metabolites as well as the serum levels of AAG were similar in the patients with complete pregnancy termination and those with continuing pregnancy.[30]

Mifepristone sensitises the myometrium to the contractile effects of prostaglandins.[31] Thus, low doses of prostaglandins, which normally fail to induce uterine contractions, are effective following pretreatment with mifepristone. Addition of low dose prostaglandin to mifepristone treatment increased the rate of complete termination of pregnancy from 60% up to 100%.[32]

Table I summarises some of the latest studies evaluating the clinical use of mifepristone and low dose prostaglandins for termination of early human pregnancy. This combination therapy is also the only accepted regimen for the clinical use of mifepristone. The focus of the latest clinical research has been directed towards optimising the dose of mifepristone as well as the evaluation of the orally active prostaglandin, misoprostol, in the

Table I. Recent studies on the combination of mifepristone and low-dose prostaglandin for early pregnancy termination

Reference	Duration of pregnancy (no. of patients)	Mifepristone and prostaglandin doses[a]	Outcome[b] (%)	Adverse effect
WHO Task Force Multicenter[33]	<56 days (1182)	200-600mg + 1mg gemeprost vaginally	94	Pain requiring medication 26%, vomiting 23%, dizziness 19%
Peyron et al.[34]	<60 days (890)	600mg + 400µg misoprostol po	96	Pain requiring medication 13-16%, vomiting 15-17%, diarrhoea 10-14%
McKinley et al.[35]	<63 days (220)	200-600mg + 600µg misoprostol po	94	Pain requiring medication 46%, opiate 8%, NSAID 38%

a Mifepristone was administered as a single oral dose in all of these studies. The time difference administration of mifepristone and prostglandin was 48 hours.

b Outcome: percentage of complete pregnancy terminations.

Abbreviations: NSAID = nonsteroidal anti-inflammatory drug; po = oral.

combination regimen. Given the long $t_{1/2}$ and the equal serum concentrations of mifepristone following doses exceeding 100mg, a reduction of the mifepristone dose from the recommended 600mg seems plausible. In fact, several recent studies have reported that the mifepristone dose can be effectively reduced from 600 to 200mg with equal clinical efficacy.[33,35] In 1996 Webster et al.[36] calculated a saving of £28.90 per patient when the dose of mifepristone was reduced from 600mg to 200mg for termination of second trimester pregnancy.

The efficacy of the combination regimen of mifepristone and low dose prostaglandin has been surprisingly uniform in the various studies published. In a summary of more than 16 000 patients, Ulmann et al.[37] reported a success rate of 95.3%. In the latest clinical studies, the commonly reported complications have been incomplete termination of pregnancy, requiring further uterine curettage (0.5 to 4% of the patients), continuation of the pregnancy (0.4 to 1%), and excessive uterine bleeding necessitating blood transfusion (0.1 to 1%).

3.1.3 Patterns of Uterine Bleeding

The mifepristone-induced uterine bleeding starts at 2 to 3 days following administration of the drug and lasts for approximately 7 to 14 days. The bleeding patterns appear similar following ingestion of mifepristone alone or in combination with prostaglandin.[29,34,35] In a recent study by the World Health Organization (WHO),[35] 60 to 75% of the patients estimated the quantity of the uterine bleeding to be more than their normal menstruation. Rodger and Baird[38] reported an average quantity of 74ml of menstrual bleeding following mifepristone treatment; however, the variation was large, extending up to 500ml. Following the combination therapy, the fetus and placenta are aborted within the first 4 hours in 70% of the patients following administration of the prostaglandin analogue.[33,35]

3.1.4 Adverse Effects of Mifepristone-Induced Pregnancy Termination

The frequency of the reported adverse effects has varied somewhat in various studies. The commonly encountered adverse effects such as nausea, vomiting, tiredness or breast tenderness are also seen during early pregnancy and spontaneous abortion. In the studies summarised in Table I, the maximal lower abdominal pain occurred soon following administration of the prostaglandin. In the WHO study,[35] 92% of the patients complained of abdominal pain in the 4 hours following administration of the vaginal gemeprost suppository. In the study by McKinley et al.,[35] the use of misoprostol was better tolerated in terms of abdominal pain when compared with gemeprost. The abdominal pain has been effectively treated with mild analgesics such as paracetamol (acetaminophen) or occasionally with opiates.

Blood haemoglobin levels declined mildly but significantly in all the studies summarised in table I. The lowest levels are seen at 1 week following initiation of the treatment, the reported mean de-

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