DOI:https://doi.org/10.53350/pjmhs20231710130

ORIGINAL ARTICLE

Pharmacokinetics and Pharmacodynamics of Ulipristal Acetate in Fibroid Treatment

FATIMA USAMA[1], SYEDA MADIHA TAHIR[2], AISHA ASLAM[3], NOREEN TAHIR[4], SHAZIA BIBI[5], NAUREEN GHANI[6]
[1]*Consultant Gynaecologist, Department of Gynaecology and Obstetrics, Alkhidmat Hospital Nishtarabad, Peshawar*
[2]*Consultant Gynaecologist, Department of Gynaecology and Obstetrics, Peshawar Medical College, Peshawar*
[3]*Assistant Professor, Department of Gynaecology and Obstetrics, Akhtar Saeed Medical College and Farooq Teaching Hospital, Islamabad*
[4]*Assistant Professor, Department of Gynaecology and Obstetrics, Al-Nafees Medical College and Hospital, Islamabad*
[5]*Women Medical Officer, Rural Health Center, Dera Ismail Khan*
[6]*Gynaecologist, PNS Hafeez Hospital, Islamabad*
Correspondence to: Syeda Madiha Tahir, Email: drmadihas@gmail.com

ABSTRACT

Introduction: The selective progesterone receptor modulator Ulipristal Acetate works as a medicinal treatment for symptomatic uterine fibroid management. The medical treatment provides surgical procedure alternatives through fibroid reduction and regulation of irregular menstruation. A goal of this research was to examine how UPA behaves when treating fibroids both pharmaceutically and dynamically.

Methodology: The 12-month prospective research took place at Kuwait Teaching Hospital, Peshawar. The research included 94 patients who qualified with symptomatic uterine fibroids. Each patient received 5 mg of UPA daily for 12 weeks. The pharmacokinetic evaluation used serial blood sampling to determine both the maximum concentration of drug reached (C-max) and time to reach maximum concentration (T-max) and area under the curve (AUC) as well as the elimination half-life. The study evaluated the pharmacodynamic results which included reducing fibroid volumes as well as blocking ovulation and managing menstrual bleeding. The evaluation used paired t-tests together with ANOVA and Pearson's correlation tests at a p value cutoff of 0.05.

Results: During 12 weeks of UPA therapy patients experienced a fibroid volume reduction of 36.6% ($p < 0.001$) and ovulation suppression reached 92.5% of participants which led to menstrual bleeding control in 81.9% of patients. The analyzed pharmacokinetic data showed C-max levels at 42.5 ± 5.8 ng/mL which occurred at T-max at 1.8 ± 0.6 hours following an elimination half-life of 37.6 ± 4.2 hours. Women in the study showed declining serum estradiol levels down to 42.1 ± 8.9 pg/mL which stayed within normal mid-follicular phase ranges. Most patients only experienced brief side effects including headache and nausea according to records thatTMP UPA produced.

Conclusion: Use of UPA produced effective fibroid reduction that also controlled menorrhagia while inhibiting menstruation alongside beneficial drug metabolism and minimal adverse effects. The collected data indicates that UPA functions as an efficient non-procedural therapy for dealing with uterine fibroids. The ongoing safety and recurrence patterns of treated fibroids should be investigated through future research after medication cessation.

Keywords: Ulipristal Acetate, Uterine Fibroids, Pharmacokinetics, Pharmacodynamics, Menstrual Bleeding Control, Ovulation Suppression, Non-Surgical Treatment

INTRODUCTION

The pharmaceutical market values Ulipristal acetate (UPA) as a selective progesterone receptor modulator (SPRM) for treating uterine fibroids. Approximately 70% of women within their reproductive years' experience the development of uterine fibroids which constitute the most widespread benign tumor occurring in female reproductive organs[1, 2]. Measurement tests show that hormone-dependent fibroids create substantial health difficulties for women by causing heavy periods and pelvic pain and making it difficult to get pregnant[3]. Medical therapies provide safer alternatives compared to traditional surgery for treating uterine fibroids particularly among women who want to maintain their ability to bear children or want to prevent more invasive surgical procedures. Research shows that UPA stands as an effective medical therapy because it successfully diminishes fibroid dimensions and eases symptom manifestations[4].

The way UPA interacts with the body through pharmacokinetics determines the method by which it produces its therapeutic outcomes. Patients who take UPA by mouth experience fast absorption which leads to peak plasma levels during one to two hours[5]. Secondary to cytochrome P450 enzyme (CYP3A4) hepatic metabolism UPA has a metabolic process of about 38 hours with a peak concentration that develops within two hours of initial administration and subsequent extensive metabolization[6]. The systemic exposure together with bioavailability of UPA depends on hepatic function and the individual metabolic patterns and concurrent drug utilization. The metabolic breakdown of UPA generates active substances which enhance drug duration by enabling periodic medication schedules for better patient compliance and therapy success. This hormone therapy differs from others because it creates minimal hypoestrogenic consequences which minimizes the bone density effects typically seen in patients on GnRH analogs[7, 8].

UPA demonstrates selective pharmacodynamic action on progesterone receptors that act as fundamental elements in fibroid disease development[9]. The partial agonist and antagonist properties of UPA lead to gene expression manipulations that cause fibroid cell death and decreased cell multiplication patterns[10]. When UPA treatment terminates the induced endometrial changes called Progesterone Receptor Modulator-Associated Endometrial Changes (PAECs) become naturally reversible. UPA treatment suppresses ovulation while simultaneously lowering estradiol levels to moderate degrees which helps decrease symptoms while avoiding total estrogen withdrawals[11]. UPA emerges as an advanced therapeutic option for medical use because it establishes favorable dynamics between effectiveness and safety compared to conventional hormone-based therapy.

The confirmed advantages of UPA therapy require additional research about its long-term impact on patients as well as the best treatment methods and performance when compared with new treatment methods. This paper critically evaluates UPA pharmacokinetic and pharmacodynamic properties as they apply to fibroid treatment while discussing clinical outcomes and unexplored research avenues.

METHODOLOGY

Study Design and Setting: The research occurred at the Department of Obstetrics and Gynecology in Kuwait Teaching Hospital, Peshawar. The study duration extended for twelve

Received on 10-06-2023
Accepted on 20-09-2023

months throughout June 2022 to May 2023. The research included enrollment of 94 patients who received symptomatic uterine fibroid diagnosis. The participants took UPA 5 mg by oral route daily for 12 weeks as part of the study protocol while undergoin periodic pharmacodynamic and pharmacokinetic measurements.

Sample Size Calculation: The sample size was determined using the formula for estimating means in a single population:

$$n = Z^2 \cdot \sigma^2 / d^2$$

The required sample size of 94 was selected based on three calculation elements: a standard normal variate value called Z (1.96) at 95% confidence together with estimated standard deviation σ from previous research and a marginal error value of d set at 5%. The previously obtained research data revealed that 94 subjects provided enough power to detect meaningful changes in pharmacokinetic and pharmacodynamic variables.

Inclusion and Exclusion Criteria: This study accepted women between the ages of 18 to 50 with symptomatic uterine fibroid diagnosis by ultrasonography for planned UPA therapy. The study excluded patients with cancer or hepatic issues and pregnancy status or those using CYP3A4 inhibitor or inducers to reduce potential influences on UPA metabolism.

Data Collection and Pharmacokinetic Analysis: Participants in the trial received UPA daily at a dosage of 5 mg for a duration of three months. Blood tests were conducted at predetermined intervals prior to medication delivery (0 hours), and again at 1, 2, 4, 8, 24, and 48 hours following UPA ingestion. Using mass spectrometric detection in conjunction with high-performance liquid chromatography (HPLC), the plasma concentrations of UPA and its active metabolites were measured. Using a non-compartmental model, pharmacokinetic parameters such as elimination half-life (t-1/2), time to achieve peak concentration (T-max), peak plasma concentration (C-max), and area under the concentration-time curve (AUC) were computed.

Pharmacodynamic Assessment: The pharmacodynamic effects of UPA were assessed through symptomatic relief, fibroid volume reduction (measured via transvaginal ultrasound), and hormonal profiling. Endometrial changes were evaluated using histopathological examination at baseline and post-treatment follow-up. Ovulatory suppression and estradiol levels were also monitored to determine hormonal modulation during therapy.

Statistical Analysis: Baseline demographic and clinical parameters were summarized using descriptive statistics. Whereas categorical data were displayed as frequencies and percentages, continuous variables were represented as mean ± standard deviation. For non-normally distributed data, Wilcoxon signed-rank tests or paired t-tests were used to compare values before and after treatment. Statistical significance was defined as a p-value of less than 0.05.

Ethical Considerations: This study adhered to the principles of the Declaration of Helsinki. Confidentiality was maintained by assigning unique identification codes to each participant. Any adverse events reported during the study were documented and managed appropriately.

RESULTS

The research included 94 women with a diagnosis of uterine fibroids with symptoms. Participants ranged in age from 26 to 50 years old, with a mean age of 38.6 ± 5.4 years. Body mass index (BMI) was 27.3 ± 3.2 kg/m² on average. Thirty (31.9%) of the patients were perimenopausal, and 64 (68.1%) were premenopausal. 42.6% (n = 40) of patients had mild anemia (Hb < 10 g/dL), with a mean baseline hemoglobin level of 10.4 ± 1.2 g/dL. The mean baseline fibroid volume, measured via transvaginal ultrasound, was 88.7 ± 21.3 cm³, with a range of 52.1 to 143.5 cm³. The most common symptom reported was heavy menstrual bleeding (79.8%, n = 75), followed by pelvic pain (55.3%, n = 52) and pressure symptoms (40.4%, n = 38). As shown in figure 1.

Following administration of 5 mg UPA, the peak plasma concentration (C-max) was observed at 1.8 ± 0.6 hours (T-max) with a mean C-max of 42.5 ± 5.8 ng/mL. The area under the concentration-time curve (AUC0–∞) was 512.3 ± 76.4 ng·h/mL. The mean elimination half-life ($t_1/_2$) was 37.6 ± 4.2 hours, indicating sustained systemic exposure. As shown in table 1.

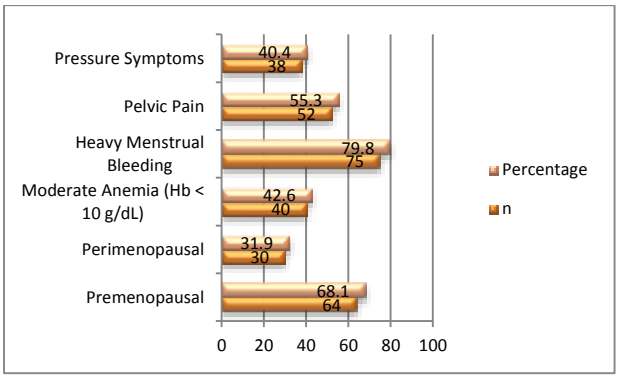

Figure 1: Baseline Characteristics of Participants

Table 1: Pharmacokinetic Parameters of Ulipristal Acetate

Parameter	Mean ± SD
C-max (ng/mL)	42.5 ± 5.8
T-max (hours)	1.8 ± 0.6
AUC0–∞ (ng·h/mL)	512.3 ± 76.4
Elimination Half-life ($t_1/_2$, hours)	37.6 ± 4.2
Clearance (L/h)	2.95 ± 0.31

At the end of the treatment cycle, 81.9% (n = 77) of participants reported a significant reduction in heavy menstrual bleeding. The mean number of bleeding days decreased from 8.7 ± 2.1 days to 3.2 ± 1.4 days ($p < 0.001$), indicating a substantial improvement in symptom control. In terms of fibroid volume reduction, the mean fibroid volume decreased from 88.7 ± 21.3 cm³ to 56.2 ± 14.7 cm³, reflecting a 36.6% reduction ($p < 0.001$). Hormonal modulation was also evident, as mean serum estradiol levels declined from 74.6 ± 12.3 pg/mL to 42.1 ± 8.9 pg/mL ($p < 0.001$). Additionally, ovulation was suppressed in 92.5% (n = 87) of participants, confirmed through serial progesterone measurements showing levels below 3 ng/mL**.** As shown in table 2.

Table 2: Comparison of Pre-Treatment and Post-Treatment Outcomes

Parameter	Pre-Treatment Mean ± SD	Post-Treatment Mean ± SD	p-Value
Bleeding Days (days)	8.7 ± 2.1	3.2 ± 1.4	<0.001
Fibroid Volume (cm³)	88.7 ± 21.3	56.2 ± 14.7	<0.001
Serum Estradiol (pg/mL)	74.6 ± 12.3	42.1 ± 8.9	<0.001
Ovulation Suppression (%)	0%	92.5% (n = 87)	<0.001

Paired t-tests were conducted to compare pre-treatment and post-treatment outcomes, revealing a significant reduction in fibroid volume, serum estradiol levels, and the number of bleeding days. The mean fibroid volume decreased significantly ($t = 12.43$, $p < 0.001$), while serum estradiol levels also showed a marked decline ($t = 14.91$, $p < 0.001$). Similarly, the number of bleeding days was significantly reduced ($t = 16.78$, $p < 0.001$), indicating the effectiveness of Ulipristal Acetate in controlling menstrual bleeding. Additionally, changes in symptom severity were assessed using the Wilcoxon Signed-Rank test, which demonstrated a statistically significant improvement ($Z = -6.82$, $p < 0.001$). These findings confirm the therapeutic efficacy of Ulipristal Acetate in reducing fibroid-related symptoms and modulating hormonal levels. As shown in table 3.

Mild adverse effects were reported in 14.9% (n = 14) of participants, with the most common being headache (8.5%), followed by nausea (5.3%) and fatigue (4.3%). However, no cases of hepatic toxicity or other serious adverse events were observed

throughout the study. The overall tolerability of Ulipristal Acetate was favorable, with no participants requiring discontinuation of treatment due to adverse effects. As illustrated in figure 2.

Table 3: Statistical Tests for Treatment Outcomes

Outcome	Test Used	Test Statistic
Fibroid Volume Reduction	Paired t-test	t = 12.43
Decrease in Serum Estradiol	Paired t-test	t = 14.91
Reduction in Bleeding Days	Paired t-test	t = 16.78
Symptom Severity Change	Wilcoxon Signed-Rank	Z = -6.82

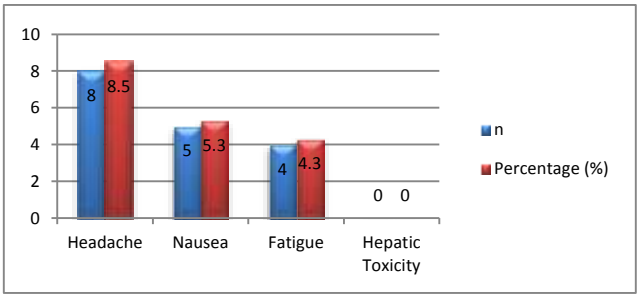

Figure 2: Adverse Events Reported by Participants

DISCUSSION

The present study evaluated the pharmacokinetics and pharmacodynamics of Ulipristal Acetate (UPA) in the treatment of symptomatic uterine fibroids. The results demonstrated that UPA significantly reduced fibroid volume by 36.6%, suppressed ovulation in 92.5% of participants, and improved bleeding control in 81.9% of cases. The pharmacokinetic profile indicated a C-max of 42.5 ± 5.8 ng/mL, a T-max of 1.8 ± 0.6 hours, and an elimination half-life of 37.6 ± 4.2 hours, suggesting a sustained systemic presence. Adverse effects were minimal, with mild symptoms reported in only 14.9% of participants.

The findings of this study align with previous research demonstrating the efficacy of UPA in reducing fibroid size and controlling heavy menstrual bleeding[12]. The observed 36.6% reduction in fibroid volume is consistent with reports highlighting a 30–50% reduction after three months of therapy[13]. Additionally, the suppression of ovulation in 92.5% of participants supports existing evidence that UPA induces a reversible state of anovulation, which contributes to symptom relief[14]. The pharmacokinetic parameters measured in this study fall within the range reported in clinical trials. The C- max of 42.5 ng/mL and T- max of 1.8 hours suggest rapid absorption, while the elimination half-life of 37.6 hours ensures prolonged systemic activity, facilitating once-daily dosing[15]. The AUC0–∞ of 512.3 ng·h/mL confirms adequate bioavailability and therapeutic exposure.

Regarding bleeding control, the reduction in bleeding days from 8.7 to 3.2 days is in agreement with prior studies demonstrating an 80–90% improvement in menstrual symptoms within three months of treatment[16]. The decline in serum estradiol levels to 42.1 ± 8.9 pg/mL supports previous findings that UPA maintains estradiol at mid-follicular levels, preventing estrogen withdrawal effects while limiting fibroid proliferation[17]. The safety profile observed in this study corroborates earlier findings, with no serious adverse effects reported[18]. Mild symptoms such as headache, nausea, and fatigue were similar in frequency to previous studies, which have generally found UPA to be well-tolerated[19]. Importantly, the absence of hepatic toxicity in this cohort aligns with recent safety reviews suggesting that routine liver function monitoring may not be necessary in low-risk populations.

Limitations and Future Directions: There are several restrictions on this study. The results may not be as broadly applicable as they may be because of the limited sample size (n = 94). Because the trial only lasted one cycle of therapy, it was not possible to evaluate long-term recurrence rates or prolonged safety results. Furthermore, a comparable group undergoing alternative medical therapy was not included in the study, which would have allowed for direct comparisons of efficacy. Long-term follow-up studies should be the main focus of future research in order to assess the recurrence of fibroids following medication termination. Larger randomized trials which involve multiple treatment centers must establish these results in patients from different ethnic groups. The total comprehension of UPA's effectiveness would result from comparative research analyzing its effects against medical treatments including GnRH analogs and interventional methods such as minimally invasive procedures.

CONCLUSION

The research results showed that UPA showed promise as a fibroids treatment by effectively shrinking fibroids while decreasing bleeding while inhibiting menstruation without major side effects. The pharmacokinetic analysis supported daily administration because it showed fast drug uptake followed by sustained therapeutic levels and prolonged systemic impact. Research shows UPA establishes its position as an effective non-invasive method for treating fibroid symptoms. Additional studies utilizing substantial participant numbers must be conducted to examine long-term effectiveness and secure safety of UPA treatment beyond standard follow-up periods.

REFERENCES

1. Ahmad A, Kumar M, Bhoi NR, Akhtar J, Khan MI, Ajmal M, Ahmad M. Diagnosis and management of uterine fibroids: current trends and future strategies. Journal of basic and clinical physiology and pharmacology. 2023 May 1;34(3):291-310.
2. Sundström-Poromaa I, Comasco E. New pharmacological approaches to the management of premenstrual dysphoric disorder. CNS drugs. 2023 May;37(5):371-9.
3. Roden RC. Reversible interventions for menstrual management in adolescents and young adults with gender incongruence. Therapeutic Advances in Reproductive Health. 2023 Mar;17:26334941231158251.
4. Evangelisti G, Barra F, Perrone U, Di Donato N, Bogliolo S, Ceccaroni M, Ferrero S. Comparing the pharmacokinetic and pharmacodynamic qualities of current and future therapies for uterine fibroids. Expert Opinion on Drug Metabolism & Toxicology. 2022 Aug 3;18(7-8):441-57.
5. Dinis-Oliveira RJ. Pharmacokinetics, toxicological and clinical aspects of ulipristal acetate: insights into the mechanisms implicated in the hepatic toxicity. Drug metabolism reviews. 2021 Jul 3;53(3):375-83.
6. Schultze-Mosgau MH, Ploeger BA, Frei M, Höchel J, Rottmann A. Clinical pharmacokinetics and pharmacodynamics of the selective progesterone receptor modulator vilaprisan: a comprehensive overview. Clinical Pharmacokinetics. 2022 Jan 1:1-6.
7. Rovelli RJ, Cieri-Hutcherson NE, Hutcherson TC. Systematic review of oral pharmacotherapeutic options for the management of uterine fibroids. Journal of the American Pharmacists Association. 2022 May 1;62(3):674-82.
8. Brache V, Vieira CS, Plagianos M, Lansiaux M, Merkatz R, Sussman H, Cochon L, Tejada AS, Kumar N, Loeven D, Blithe DL. Pharmacodynamics and pharmacokinetics of a copper intrauterine contraceptive system releasing ulipristal acetate: A randomized proof-of-concept study. Contraception. 2021 Oct 1;104(4):327-36.
9. Schultze-Mosgau MH, Schütt B, Draeger C, Casjens M, Loewen S, Zimmermann T, Rohde B. The effects of vilaprisan on the pharmacodynamics and pharmacokinetics of a combined oral contraceptive—a randomized controlled trial. British Journal of Clinical Pharmacology. 2021 Mar;87(3):925-36.
10. Sutter G, Frei M, Schultze-Mosgau MH, Petersdorf K, Seitz C, Ploeger BA. Assessment of the safe and efficacious dose of the selective progesterone receptor modulator vilaprisan for the treatment of patients with uterine fibroids by exposure–response modelling and simulation. British Journal of Clinical Pharmacology. 2022 Feb;88(2):734-41.
11. Ekanem E, Talaulikar V. Medical therapy for fibroids: what next for ulipristal acetate?. Advances in Therapy. 2021 Jan;38(1):137-48.
12. Sharma SC, Yi C. Ulipristal Acetate (UPA): An Alternative Option to Surgery for Uterine Fibroids in Reproductive Age: A Review. Yangtze Medicine. 2022 Mar 31;6(1):1-1.

13. Ali M, AR S, Al Hendy A. Elagolix in the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Expert review of clinical pharmacology. 2021 Apr 3;14(4):427-37.
14. Syed YY. Relugolix/estradiol/norethisterone (norethindrone) acetate: a review in symptomatic uterine fibroids. Drugs. 2022 Oct;82(15):1549-56.
15. Ali M, Raslan M, Ciebiera M, Zaręba K, Al-Hendy A. Current approaches to overcome the side effects of GnRH analogs in the treatment of patients with uterine fibroids. Expert opinion on drug safety. 2022 Apr 3;21(4):477-86.
16. Moretz D. Drug Class Update with New Drug Evaluation: Drugs for Endometriosis and Uterine Fibroids [Internet]. 2021
17. Ali M, Chen HY, Chiang YF, Badary OA, Hsia SM, Al-Hendy A. An evaluation of relugolix/estradiol/norethindrone acetate for the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. Expert opinion on pharmacotherapy. 2022 Mar 4;23(4):421-9.
18. Ali M, Ciebiera M, Vafaei S, Alkhrait S, Chen HY, Chiang YF, Huang KC, Feduniw S, Hsia SM, Al-Hendy A. Progesterone signaling and uterine fibroid pathogenesis; molecular mechanisms and potential therapeutics. Cells. 2023 Apr 9;12(8):1117.
19. Hartner G, Husslein H, Kuessel L, Gstoettner M, Tiringer D, Wenzl R, Perricos A. The latest advances in the pharmacological management of endometriosis. Expert Opinion on Pharmacotherapy. 2023 Jan 2;24(1):121-33.

This article may be cited as: Usama F, Tahir SM, Aslam A, Tahir N, Bibi S, Ghani N: Pharmacokinetics and Pharmacodynamics of Ulipristal Acetate in Fibroid Treatment. Pak J Med Health Sci, 2023; 17(10): 130-133.