Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Pharmacokinetics of hard micronized progesterone capsules via vaginal or oral route compared with soft micronized capsules in healthy postmenopausal women: a randomized open-label clinical study

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Video abstract

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Purpose: This study aimed to evaluate the pharmacokinetics of hard micronized progesterone capsules (Yimaxin) via the vaginal or oral route compared with soft micronized progesterone capsules (Utrogestan) in a Chinese population.

Methods: A prospective single-center randomized open-label trial was conducted in 16 healthy postmenopausal women. They were randomized into two groups to receive four phases of treatment: vaginal Yimaxin, vaginal Utrogestan, oral Yimaxin, or oral Utrogestan, with different sequences.

Results: By the vaginal route, steady-state maximum concentration (C_{max}) of Yimaxin and Utrogestan was 29.13±8.09 and 12.30±1.60 mg/L, time to C_{max} 9.72±10.50 and 11.03±9.62 hours, central compartment volume of distribution 4.26±1.86 and 10.40±2.32 L, clearance rate 0.18±0.05 and 0.38±0.10 L/h, and AUC 261.42±74.36 and 116.83±19.72 h·ng/mL, respectively. By the oral route, C_{max} of Yimaxin and Utrogestan was 62.97±40.59 and 169.53±130.24 mg/L, time to C_{max} was 2.88±1.35 and 2.06±1.55 hours, central compartment volume of distribution 132.16±52.13 and 85.08±55.07 L, clearance rate 3.43±1.07 and 2.50±1.04 L/h, and AUC 274.86 ±160.28 and 472.00±250.54 h·ng/mL, respectively. By the vaginal route, C_{max}, minimum concentration, AUC_{0-72}, and AUC of Yimaxin were higher than Utrogestan, while by the oral route the C_{max}, AUC_{0-72}, and AUC of Utrogestan were higher than Yimaxin.

Conclusion: Pharmacokinetic parameters were different between Yimaxin and Utrogestan on vaginal and oral administration. By the oral route, the metabolism and absorption of Utrogestan was superior to Yimaxin, while by the vaginal route Yimaxin was superior.

Keywords: micronized progesterone hard capsule, micronized progesterone soft capsule, pharmacokinetics, vaginal administration, oral administration

Introduction

Progesterone is a hormone secreted by ovarian corpus lutea. After the endometrium has been affected by sufficient estrogen, progesterone converts proliferative endometrium into secretory endometrium, which is conducive to embryo implantation and persistent pregnancy. Progesterone plays a very important role in endometrial receptivity, immunosuppression, and development of decidual tissue.[1,2]

In women with adequate luteal function, a serum progesterone concentration of 20±5 ng/mL[3] at the luteal phase can enable progesterone to act well, and serum progesterone concentration of 25±5 ng/mL[4,5] at 4 weeks of pregnancy can maintain

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the need for pregnancy. When endogenous progesterone production is insufficient, in order to ensure pregnancy, it is necessary to add exogenous progesterone to maintain normal endometrial development.

There are many routes of administration of exogenous progesterone, and the common ones are oral, intramuscular, and vaginal. Progesterone for vaginal use has shown to be effective in supporting the corpus luteum, and is more easily accepted by patients due to convenience, no injection-site pain and lack of dizziness or other side effects. Since the 1980s, soft micronized progesterone capsules (Utrogestan; Besins Healthcare, Paris, France) have been used widely in Europe, and can be administered orally and vaginally.[6]

In 2004, a new product — hard micronized progesterone capsule (Yimaxin; Zhejiang Xianju Pharmaceutical, Taizhou, China) was introduced. Progesterone is synthesized with diosgenin extracted from the plant *Dioscorea zingiberensis* (*Dioscorea nipponica*). Its chemical structure is completely identical to physiological progesterone in the human body, and is a natural progesterone. Yimaxin is prepared by solid dispersion and superfine grinding. In theoretical analysis, Yimaxin particles are at the nanometer level. Progesterone is present in solid dispersion in a molecular state, which is designed to enhance the progesterone dissolution rate. Sales of Yimaxin reached 9.5 million boxes in 2018, and the drug was used by approximately 4.75 million people. Calculated by number of boxes, it accounted for about 21% of the Chinese progesterone market.

Utrogestan was introduced in China in 1992. Though Yimaxin has been used in China for 14 years, there is lack of the pharmacokinetic (PK) parameters for the Chinese population. This study for the first time enrolled healthy postmenopausal Chinese women to explore the PK paprameters and tolerability of different routes of administration of Yimaxin and Utrogestan in a Chinese population.

Methods

This was a prospective, single-center, randomized, open-label study that was approved by the Ethics Committee of Peking Union Medical College Hospital (HS-1451) and registered with the Chinese Clinical Trial Register website (www.chictr.org.cn; ChiCTR1800019081). Written consent was obtained from each patient.

Study subjects

A total of 16 Chinese healthy menopausal women aged 45–60 years were enrolled from December 2017 to June 2018. Inclusion criteria were natural or idiopathic menopause for > 1 year before enrollment or bilateral ovariectomy (uterus remaining) at least 1 year before enrollment, follicle-stimulating hormone level showing postmenopausal status, basal progesterone <1 ng/ml, passing safety screening, body-mass index 20–25 kg/m^2, no smoking or drinking history or drug addiction, good communication with investigators, willing to participate, and signing the informed consent.

Exclusion criteria were initial physical assessment indicating participant having abnormalities that may affect the study, any abnormal laboratory-test results prior to the study, having participated in other clinical trials in the past 3 months, receiving any steroid hormone drug in the past 3 months, allergic reactions or serious adverse reactions to the test drugs, often or currently using enzyme inducers or inhibitors and other drugs that might affect drug metabolism, such as sex hormones, phenytoin, barbital, primidone, carbamazepine, rifampicin, or griseofulvin, history of thromboembolism, thrombophlebitis, or serious cardiovascular disease, history of any tumors, blood-system disorders, or severe or frequent headache, and previously or currently suffering from mental illness, depression, or epilepsy.

After the subjects had signed the informed-consent form, their general information was collected and physical examination and laboratory testing performed, including evaluation of vital signs and systemic organ systems, electrocardiography, chest X-ray, breast ultrasound, basic sex-hormone examination, gynecological examination, transvaginal uterine adnexa ultrasound, blood and urine routine testing, and blood biochemical testing. Subjects were included according to the inclusion and exclusion criteria and evenly randomized into two groups (designated groups A and B).

Study procedure

The study had four phases (Figure 1). In the first phase, daily estradiol valerate 2 mg orally was given on days 1–20. On days 11–20, group A received Yimaxin (vaginal route, 50 mg/capsule, Figure 2), 200 mg twice daily while group B received Utrogestan (vaginal route, 100 mg/capsule, Figure 2) 200 mg twice daily. Fasting blood was collected to measure E_2 and P, and vaginal ultrasound was performed to measure endometrial thickness on days 1 and 11. On day 11, blood samples were also collected before administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the first administration to analyze PK parameters.

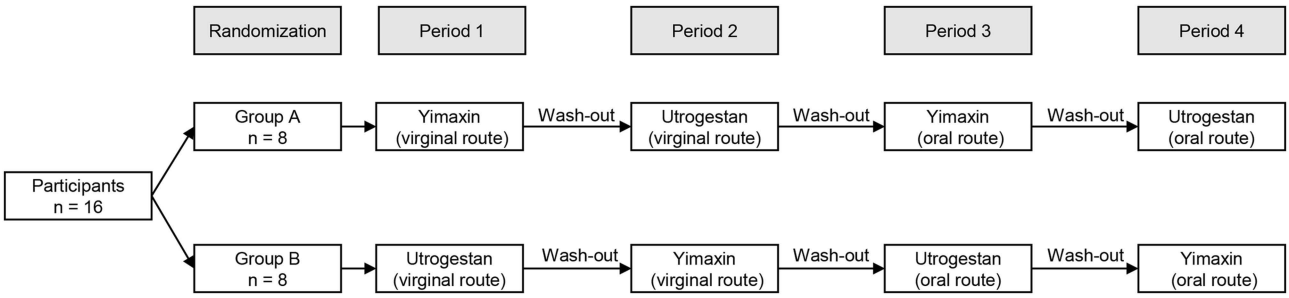

Figure 1 Flow chart of the study.

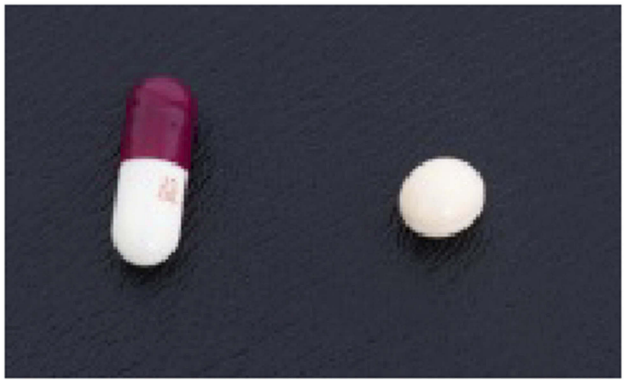

Figure 2 Yimaxin (left, 50 mg) and Utrogestan (right, 100 mg) capsules. Both can be used orally or vaginally.

The second administration was after all blood samples had been collected. On days 12–19, blood samples were collected each day before the first administration to analyze PK parameters. On day 20, blood samples were collected before administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs after the first administration to analyze the pharmacokinetics. The second administration was after all blood samples had been collected. On day 21, drugs (estrogen and progesterone) were discontinued, fasting blood samplescollected, and specimens of endometrium collected and examined independently by two experienced pathologists. Fasting blood was collected every morning for PK analysis for 3 days after drug withdrawal. Washout lasted for 15 days after the last administration. Adverse events and concomitant medications were recorded. After washout, subjects entered the second period, in which group A received Utrogestan (vaginal route) 200 mg twice daily, while group B received Yimaxin (vaginal route) 200 mg twice daily. The study procedure was same as previously mentioned.

In the third period, group A received Yimaxin (oral route) and group B received Utrogestan (oral route) while in the fourth round, group A received Utrogestan (oral route) and group B received Yimaxin (oral route). The study procedure was same as previously mentioned. Physical examination and laboratory testing were performed again after the study.

Blood-sample collection and processing

Blood was drawn via an indwelling needle placed on the forearm of the subject and the initial 0.2–0.3 mL blood was discarded before collection. About 3 mL venous blood sample was collected each time. Heparin was used to seal the sampling tubes. Blood samples were centrifuged (2,000 *g* at 4 °C for 10 minutes) within 60 minutes after collection and the serum concentration of progesterone determined immediately with an electrochemical method. Serum samples were placed at −20 °C for 2 hours for prefreezing and then stored at −70°C. PK parameters were calculated: maximum concentration (C_{max}), time to C_{max} (T_{max}), $AUC_{0\text{-}72}$ half-life ($t_{1/2}$), time to steady state (T_{steady}), minimum concentration (C_{min}), residual area, volume of distribution (V/F), clearance rate (Cl/F), mean residence time (MRT), and AUC after reaching steady state (AUC). A case-report form was used for data collection, and data were deposited in a database after being reviewed and verified.

Statistical methods

Statistical analysis of PK parameters was performed with a noncompartmental model in the WinNonlin standard edition version 5.7 software. One-way ANOVA was used to evaluate statistical differences in geometric mean ratios of ln-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between two groups with 95% CIs, as well as mean values of $t_{1/2}$ and CL/F between groups. The Hodges–Lehmann method was employed to compare median T_{max} values between groups with 95% CIs.

Results

Sixteen subjects successfully completed the study. Their demographic characteristics are shown in Table 1. Blood pressure, heart rate and body temperature showed no significant changes from baseline data after the study. Mean plasma

Table 1 Demographic characteristics of participants

	Mean ± SD	Range	Min	Max	Median
Age (years)	53.4±3.7	48–59	48	59	53
Menopausal period (years)	4.7±2.5	1–10	1	10	5
Height (cm)	160.47±4.49	150–172	172	150	160
Weight (kg)	58.59±4.84	48–68	68	48	59
Body-mass index (kg/m^2)	36.49±2.55	31.65–41.21	41.21	31.65	36.71

concentration–time curves of Yimaxin and Utrogestan administration via vaginal and oral routes are shown in Figures 3 and 4, respectively. PK parameters of Yimaxin and Utrogestan via vaginal and oral routes obtained by noncompartmental analysis are shown in Tables 2 and 3, respectively. PK parameters of exposure from oral vs vaginal routes for Yimaxin are compared in Table 4, and the corresponding mean plasma concentration–time curve is shown in Figure 5. Those for Utrogestan are shown in Table 5 and Figure 6.

Discussion

The main ingredient of Yimaxin is progesterone (50 mg/capsule). After oral administration, it is metabolized by the liver, about 12% is metabolized to pregnanediol, and the metabolites are combined with glucuronic acid to be excreted with urine. It has four metabolites, which are γ-GABA receptor agonists and have sedative and hypnotic effects. Bioavailability is approximately 10% of the progesterone via intramuscular injection.[7–9] Utrogestan is progesterone 100 mg/capsule. It is a soft micronized progesterone capsule that can be administered orally or vaginally. Both routes have good endometrial transformation.[10] The progesterone capsule was initially developed for oral administration, but given its low progesterone bioavailability due to hepatic clearance, it has gained acceptance as a vaginal application. Studies have claimed that due to the first-pass effect through the liver, oral progesterone was the least effective form, contrary to intramuscular, which was reported to be the most efficient.[11] Many studies have confirmed that vaginal administration of micronized progesterone tablets and progesterone vaginal gel have similar effects on persistent pregnancy rate, but progesterone gel is more convenient to use.[12–16] There have not been any studies undertaking comparative study of the PK parameters of Yimaxin. Since the efficacy of vaginal administration of micronized progesterone has been well recognized, we selected the long-used Utrogestan, with good safety and stable efficacy, as a reference drug to investigate the PK parameters of Yimaxin, a hard micronized progesterone capsule.

In this study, selection of postmenopausal women eliminated the effects of hormones secreted by functional ovaries. Because blood-drug concentration is low after a single dose, the general single-dose protocol is not suitable for clinical use, but twice a day is usually selected in clinical practice, which is adopted for PK study. This showed that Yimaxin and

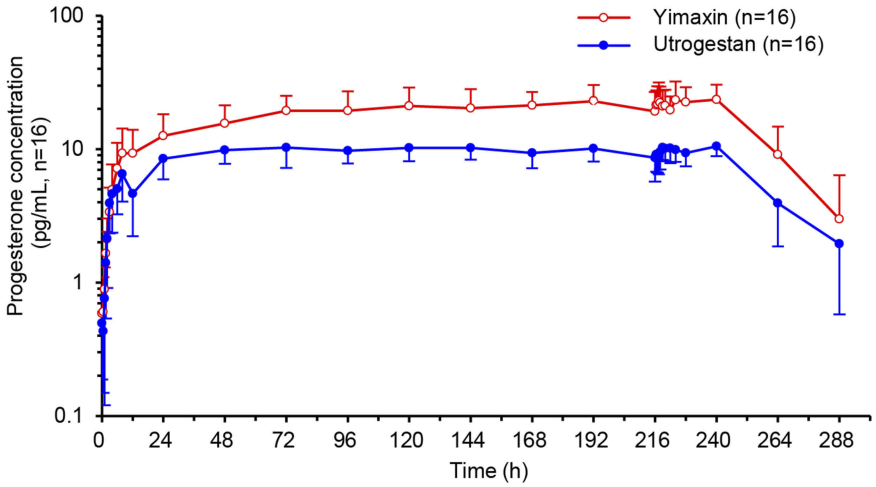

Figure 3 Serum progesterone concentration after vaginal administration of Yimaxin and Utrogestan (n=16).

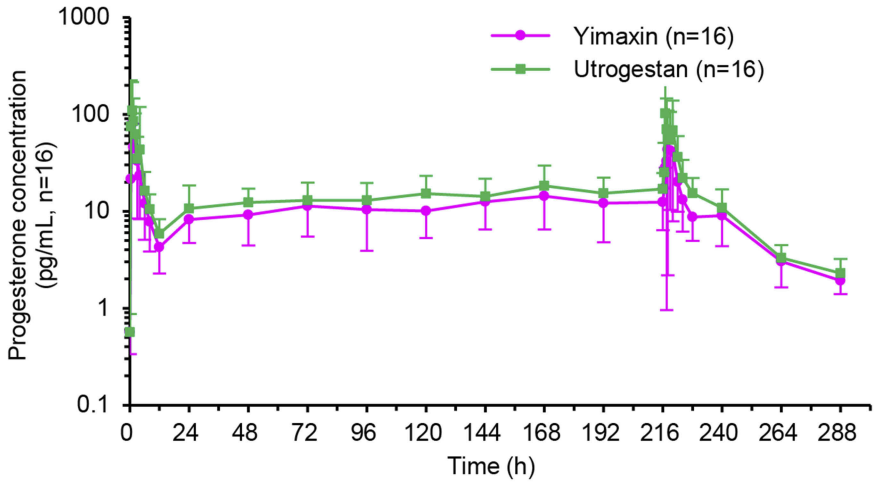

Figure 4 Serum progesterone concentration after oral administration of Yimaxin and Utrogestan (n=16).

Table 2 Pharmacokinetic parameters of Yimaxin and Utrogestan after vaginal administration

Parameters	Utrogestan (n=16)	Yimaxin (n=16)	Point estimate (95% CI)	*P*-value
	Median (range)/mean (SD)	Median (range)/mean (SD)		
T_{lag} (hours)	0	0		
T_{max} (hours)	6 (0–24)	5 (0–24)	0.5 (−2 to 6)[b]	0.477
C_{max} (ng/mL)	12.3 (1.6)	29.13 (8.09)	0.43 (0.37–0.51)[a]	<0.001
T_{steady} (hours)	48 (24–48)	60 (24–120)	−24 (−24 to 0)[b]	0.01
C_{min} (ng/mL)	9.65 (7.8–12.51)	18.55 (15.09–39.08)	−9.08 (−11.19 to −7.11)[b]	<0.001
AUC_{0-72} (h·ng/mL)	479.4 (77.54)	1073.73 (199.77)	0.45 (0.39–0.51)[a]	<0.001
$t_{1/2}$ (hours)	20.66 (10.22)	20.21 (18.97)	0.46 (−10.69 to 11.6)[c]	0.933
Residual area %	7.33 (2.18–40.64)	2.97 (1.19–59.13)	2.86 (0.99–6.71)[b]	0.017
V/F (L)	9.81 (7.79–15.91)	4.04 (1.91–8.52)	5.88 (4.77–7.53)[b]	<0.001
Cl/F (L/h)	0.38 (0.1)	0.18 (0.05)	0.21 (0.15– 0.27)[c]	<0.001
MRT (hours)	24.86 (3.77)	24.48 (5.07)	0.38 (−2.86 to 3.62)[c]	0.812
AUC (h·ng/mL)	116.83 (19.72)	261.42 (74.36)	0.46 (0.39–0.54)[a]	<0.001

Notes: [a]Geometric mean ratio on one-way ANOVA; [b]Hodges–Lehmann method; [c]one-way ANOVA.
Abbreviations: C_{max}, maximum concentration ; C_{min}, minimum concentration ; Cl/F, clearance rate; MRT, mean residence time; $t_{½}$, half-life; T_{lag}, time difference; T_{max}, time to C_{max}; T_{steady}, time to steady state; V/F, volume of distribution.

Utrogestan can be absorbed rapidly, regardless of route of administration, as the uptake differnce between the two drugs via two the two routes was zero. There was no significant difference in T_{max} between the two drugs via the same route. There were no significant difference in T_{max} and T_{steady} among different drug–route combinations. Absorption of the two drugs were different in different routes of administration. After vaginal administration, Yimaxin had higher C_{max}, lower V/F, larger AUC, and lower Cl/F than Utrogestan. In contrast, after oral administration, Utrogestan had a significantly higher C_{max}, lower Vc/F, larger AUC, and lower Cl/F than Yimaxin. It is suggested that by the oral route, Utrogestan had higher plasma concentration, while by the vaginal route, Yimaxin had higher plasma concentration. There was no statistically significant difference in MRT between the two drugs via vaginal administration, but via oral administration the MRT of Yimaxin was longer than that of Utrogestan, suggesting Yimaxin stayed longer in the body than Utrogestan.

For exposure from oral vs vaginal Yimaxin, oral administration had higher C_{max}, residual area, V/F, and Cl/F than those vaginal administration, but vaginal administration had higher C_{min}, AUC_{0-72}, MRT than oral administration. This suggested that the vaginal route had better absorption and more effective use than oral route. Meanwhile, comparison of exposure from oral vs vaginal Utrogestan revealed that oral administration had higher C_{max}, C_{min}, AUC_{0-72}, Vc/F, Cl/F, and AUC than vaginal administration, but vaginal administration had higher T_{max}

Table 3 Pharmacokinetic parameters of Yimaxin and Utrogestan after oral administration

Parameters	Utrogestan (n=16)	Yimaxin (n=16)	Point estimate (95% CI)	*P*-value
	Median (range)/mean (SD)	Median (range)/mean (SD)		
T_{lag} (hours)	0	0		
T_{max} (hours)	1.5 (0.5–6)	3 (1–6)	−1 (−2 to 0)[b]	0.066
C_{max} (ng/mL)	169.53 (130.24)	62.97 (40.59)	2.44 (1.49–4)[a]	<0.001
T_{steady} (hours)	48 (24–120)	48 (24–120)	0 (−24 to 24)[b]	0.711
C_{min} (ng/mL)	15.41 (6.65)	11.69 (4.97)	1.3 (0.98–1.73)[a]	0.07
AUC_{0-72} (h·ng/mL)	866.49 (398.08)	585.04 (269.91)	1.46 (1.08–1.97)[a]	0.016
$t_{1/2}$ (hours)	22.78 (6.3)	26.12 (4.78)	−3.34 (−7.39 to 0.71)[c]	0.102
Residual area (%)	7.07 (3.99–18.63)	12.43 (4.52–17.48)	−3.3 (−7.2 to 0.2)[b]	0.061
V/F (L)	85.08 (55.07)	132.16 (52.13)	0.61 (0.42–0.88)[a]	0.01
Cl/F (L/h)	2.5 (1.04)	3.43 (1.07)	−0.93 (−1.7 to −0.17)[c]	0.018
MRT (hours)	16.31 (3)	19.21 (2.79)	−2.9 (−4.99 to −0.81)[c]	0.008
AUC (h·ng/mL)	472 (250.54)	274.86 (160.28)	1.69 (1.17–2.43)[a]	0.006

Notes: [a]Geometric mean ratio on one-way ANOVA; [b]Hodges–Lehmann method; [c]one-way ANOVA.
Abbreviations: C_m, maximum concentration; C_{min}, minimum concentration ; Cl/F, clearance rate; MRT, mean residence time; $t_{1/2}$, half-life; T_{lag}, time difference; T_{max}, time to Cmax; T_{steady}, time to steady state; V/F, volume of distribution.

Table 4 Pharmacokinetic parameters of Yimaxin after oral and vaginal administration

Parameters	Yimaxin		Point estimate (95% CI)	*P*-value
	Oral (n=16)	Vaginal (n=16)		
	Median (range)/mean (SD)	Median (range)/mean (SD)		
T_{lag} (hours)	0	0		
T_{max} (hours)	3 (1–6)	5 (0–24)	−1.17 (−18, 1.5)[b]	0.582
C_{max} (ng/mL)	62.97 (40.59)	29.13 (8.09)	1.89 (1.34, 2.66)[a]	<0.001
T_{steady} (hours)	48 (24–120)	60 (24–120)[a]	0 (−24, 24)[b]	0.531
C_{min} (ng/mL)	10.32 (5.82–26.37)	18.55 (15.09–39.08)	−8.15 (−10.89, −5.59)[b]	<0.001
AUC_{0-72} (h·ng/mL)	585.04 (269.91)	1073.73 (199.77)	0.51 (0.41, 0.64)[a]	<0.001
$t_{1/2}$ (hours)	26.12 (4.78)	20.21 (18.97)	5.91 (−4.41, 16.24)[c]	0.243
Residual area (%)	12.43 (4.52–17.48)	2.97 (1.19–59.13)	8.18 (4.48, 10.99)[b]	<0.001
V/F (L)	132.16 (52.13)	4.26 (1.86)	30.63 (22.23, 42.2)[a]	<0.001
Cl/F (L/h)	3.43 (1.07)	0.18 (0.05)	3.26 (2.69, 3.83)[c]	<0.001
MRT (hours)	19.66 (14.24–23.32)	23.25 (18.91–36.44)	−4.7 (−7.55, −1.71)[b]	0.001
AUC (h·ng/mL)	274.86 (160.28)	261.42 (74.36)	0.97 (0.73, 1.29)[a]	0.827

Notes: [a]Geometric mean ratio on one-way ANOVA; [b]Hodges–Lehmann method; [c]one-way ANOVA.
Abbreviations: C_{max}, maximum concentration ; C_{min}, minimum concentration ; Cl/F, clearance rate; MRT, mean residence time; $t_{1/2}$, half-life; T_{lag}, time difference; T_{max}, time to C_{max}; T_{steady}, time to steady state; V/F, volume of distribution.

and MRT than oral administration. For Yimaxin and Utrogestan, $t_{1/2}$ remained the same, regardless of route. For both drugs, MRT for the vaginal route was longer than the oral route. After achieving a constant concentration of medicines, AUC in dosing intervals of vaginal administration of Yimaxin was higher than Utrogestan. However, via the oral route, Utrogestan AUC was higher than Yimaxin. For Yimaxin, there was no difference in AUC in dosing intervals after achieving constant concentration, regardless of administration route, but for Utrogestan, AUC for the oral route was higher than the vaginal route.

Differences in PK parameters between Yimaxin and Utrogestan administered vaginally or orally may be related to their different pharmaceutical processes. The fact that the active progesterone concentration in blood of vaginally administered Yimaxin is higher than orally administered Utrogestan is related to the first-pass effect through the liver for the orally administered drug. For Yimaxin, progesterone is dispersed in a molecular state through the solid

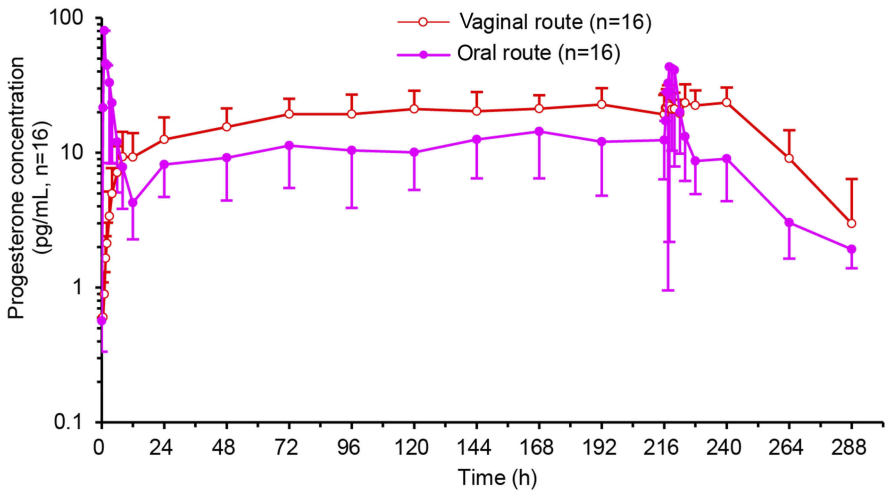

Figure 5 Serum progesterone concentration after oral and vaginal administration of Yimaxin (n=16).

Table 5 Pharmacokinetic parameters of Utrogestan after oral and vaginal administration

Parameters	Utrogestan		Point estimate (95% CI)	*P*-value
	Oral (n=16)	Vaginal(n=16)		
	Median (range)/mean (SD)	Median (range)/mean (SD)		
T_{lag} (hours)	0	0		
T_{max} (hours)	1.5 (0.5–6)	6 (0–24)	−5 (−18, −2)[b]	0.002
C_{max} (ng/mL)	169.53 (130.24)	12.3 (1.6)	10.64 (7.07, 15.99)[a]	<0.001
T_{steady} (hours)	48 (24–120)	48 (24–48)	24 (0, 24)[b]	0.062
C_{min} (ng/mL)	14.3 (7.25–31.26)	9.65 (7.8–12.51)	4.78 (1.25, 7.82)[b]	0.007
AUC_{0-72} (h·ng/mL)	866.49 (398.08)	479.4 (77.54)	1.67 (1.3, 2.14)[a]	<0.001
$t_{1/2}$ (hours)	22.78 (6.3)	20.66 (10.22)	2.12 (−4.06, 8.3)[c]	0.487
Residual area (%)	7.07 (3.99–18.63)	7.33 (2.18–40.64)	0.16 (−3.97, 3.76)[b]	0.897
V/F (L)	74.09 (24.71–260.55)	9.81 (7.79–15.91)	62.24 (45.18, 77.39)[c]	<0.001
Cl/F (L/h)	2.5 (1.04)	0.38 (0.1)	2.11 (1.56, 2.67)[c]	<0.001
MRT (hours)	16.31 (3)	24.86 (3.77)	−8.55 (−11.02, −6.09)[c]	<0.001
AUC (h·ng/mL)	472 (250.54)	116.83 (19.72)	3.58 (2.67, 4.8)[a]	<0.001

Notes: [a]Geometric mean ratio on one-way ANOVA; [b]Hodges–Lehmann method; [c]one-way ANOVA.
Abbreviations: C_{max}, maximum concentration ; C_{min}, minimum concentration ; Cl/F, clearance rate; MRT, mean residence time; $t_{1/2}$, half-life; T_{lag}, time difference; T_{max}, time to C_{max}; T_{steady}, time to steady state; V/F, volume of distribution.

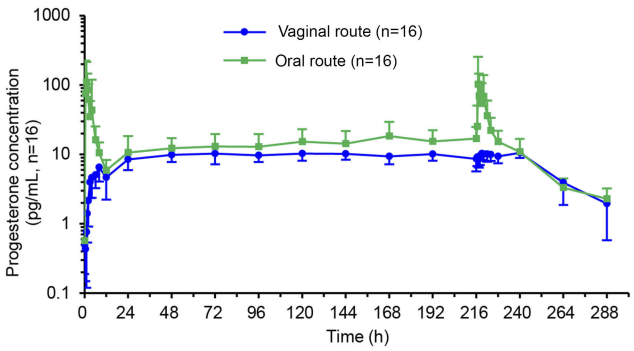

Figure 6 Serum progesterone concentration after oral and vaginal administration of Utrogestan (n=16).

suspension of glyceride stearate. When administered vaginally, the progesterone molecules in Yimaxin can dissolve and be absorbed quickly, while for orally administered Utrogestan, the first-pass effect would be applied directly to the dissolved progesterone and thus reduce adsorption.

Orally administered Yimaxin is rapidly metabolized during first liver pass and then disappears from the general circulation. On the other hand, vaginal-route Yimaxin reaches higher progesterone concentrations in endometrial tissue than oral-route Yimaxin.[12] Progesterone blood concentration of vaginal-route Utrogestan is lower than oral-route Utrogestan, probably because of the fact that for Utrogestan, progesterone

is surrounded by oil agents. After gastroinstestinal hormone metabolism, progesterone molecules form chylous particles that then enter lymph circulation and thus bypass the first-pass effect of liver. On the other hand, there is no gastrointestinal hormone metabolism in the vagina, and the progesterone is dispersed and absorbed directly by the vaginal mucus, thus reducing the adsorption of progesterone.

Conclusion

This is the first pharmacokinetic comparison between hard progesterone hard capsule and soft (oil-based) capsules. It is also the first PK comparison of the different delivery routes of the two drugs. By the oral route, the metabolism and absorption of Utrogestan is superior to Yimaxin, while by the vaginal route Yimaxin is superior. This study provides PK data that can guide clinical medication.

Data-sharing statement

We would like to share all individual de-identified participant data related to this study in a spreadsheet format. The data will be accessible upon request and will be available for at least 5 years after publication.

Disclosure

The authors report no conflicts of interest in this work.

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