

Penetration of Oral Fluconazole into Gynecological Tissues

HIROSHIGE MIKAMO,* KYOKO KAWAZOE, YASUMASA SATO, KOJI IZUMI, TOSHIYA ITO,
KUNIHICO ITO, AND TERUHIKO TAMAYA

Department of Obstetrics and Gynecology, School of Medicine, Gifu University, Gifu, Japan

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Penetration of fluconazole into female genital tissues was examined. Fluconazole was administered orally at a dose of 150 mg to patients undergoing total abdominal hysterectomy 1 to 151 h prior to surgery. During surgery, blood, uterus, ovary, and oviduct were sampled. Fluconazole concentrations in each tissue were determined by high-performance liquid chromatography. The peak concentrations in serum reached approximately 6.1 µg/ml 1.0 h after a drip infusion was begun. At each time after the infusion, the concentrations in portio vaginalis, cervix uteri, myometrium, endometrium, ovary, and oviduct were higher than those in the serum: the peaks in the tissues ranged from 6.4 to 9.5 µg/g around 1.0 h after the drip infusion was begun. Thus, the levels of penetration of fluconazole into gynecological tissues appeared to be similar to or slightly above those in serum samples. Fluconazole can rapidly penetrate from plasma into the female genital organs, supporting high efficacy of fluconazole against fungal infections in the field of gynecology.

Vaginal candidiasis is an infection caused by *Candida albicans* or related fungi. The fungi isolated from the vaginas of patients with candidiasis include *C. albicans* (80 to 90% of patients), *Candida glabrata*, and *Candida tropicalis*.

The usual transvaginal treatment of candidiasis can be messy and displeasing and can include local irritation, burning, and frequency of micturition. Consequently, compliance with this form of treatment is poor, as women often stop the treatment as soon as their symptoms disappear but before eradication of the fungi. The rectum is a carrier of the fungi, and relapses are common.

Fluconazole is one of the antifungal agents which are effective against not only systemic fungal infection but vaginal candidiasis; however, there have been no published data on penetration of oral fluconazole into gynecological tissues. The concentrations of fluconazole in serum and gynecological tissues (uterus, ovaries, and oviducts) were determined to reveal the drug's effective distribution.

MATERIALS AND METHODS

Drug. Fluconazole [α -(2,4-difluorophenyl)- α -(1H-1,2,4-triazol-1-ylmethyl)-1H-1,2,4-triazole-1-ethanol] (150 milligrams) was used in this study.

Subjects. Fifty-seven patients (mean age \pm standard deviation, 54.7 \pm 7.5 years; mean weight \pm standard deviation, 54.8 \pm 6.4 kg) were chosen for the study. Patients underwent total abdominal hysterectomy for the treatment of myoma uteri and other conditions at the Department of Obstetrics and Gynecology, School of Medicine, Gifu University; Gifu Municipal Hospital; Gihoku General Hospital; and Gifu Prefectural Gifu Hospital from June 1996 to March 1997. They agreed to participate in this study. These patients showed no abnormalities in liver function, having normal levels of transaminase in serum, or in renal function, having normal levels of urea nitrogen and creatinine in serum.

Experimental methods. (i) Drug administration. Before the operation, 150 mg of fluconazole was orally administered to each patient.

(ii) Sampling method. After ligation of the uterine artery on one side in the hysterectomy, blood from the uterine artery on the other side and cubital venous blood were taken. Also, approximately 1 g each of tissue from the portio vaginalis, cervix uteri, myometrium, ovary, and oviduct was taken from the normal portions of the samples immediately after hysterectomy. After centrifugal separation (1,000 \times g, 15 min) of blood samples, the supernatant was immediately frozen and stored at -80°C . Each tissue sample was homogenized, immediately frozen, and stored at -80°C .

(iii) Measurement of drug concentration. The concentrations of fluconazole were measured by a modification of the validated high-performance liquid chro-

matography method of John et al. (13). Each tissue sample was homogenized with a solution containing 2 ml of 5 M NaOH and 3 ml of ethyl acetate. In accordance with a cross-matrix compatibility study, serum was used as a control matrix to prepare a standard curve for tissue samples. Samples prepared from a rat control liver were assayed against the standard curve for serum. Levels of accuracy for rat liver were less than 13%. The percent recovery was 80% for serum.

Chromatographic analysis was performed on an octyldecyl silane-M column (25 cm [length] by 4.6 mm [inner diameter], 5- μm particles) by isocratic elution, with a mobile phase of 0.5% ammonium acetate (pH 3.8)-acetonitrile (3:1 [vol/vol]) and UV detection of 260 nm.

Standard curves showed a good linear relationship between peak-height ratios and fluconazole concentration, with γ^2 consistently being >0.999 . The lower limits of quantitation were 0.4 µg/ml in serum (with 0.5-ml samples) and 0.2 µg/sample in tissues (with 0.03- to 0.86-g samples). The between-day (6 days) precision values (as percents coefficient of variation) were less than 3.2%.

(iv) Method of analysis. Results were analyzed with a one-compartment first-order-lag-time-first-order-elimination model (Fig. 1) as follows: $C(T) = D^* K_{01}/V(K_{01} - K_{10})^* [\text{EXP}(-K_{10}^* T) - \text{EXP}(-K_{01}^* T)]$, where C is concentration, T is time (in hours), D is dose, K_{01} is absorption rate constant, K_{10} is elimination rate constant, and EXP is exponent. The area under the concentration-time curve from 0 h to T (AUC_{0-T}) was calculated by the trapezoidal method. Thus, $\text{AUC}_{0-\infty} = \text{AUC}_{0-T} + C_T/k_{el}$, where $\text{AUC}_{0-\infty}$ is the area under the concentration-time curve from 0 h to infinity, C_T is the concentration detected in the plasma at the final time point, and k_{el} is the elimination rate constant).

RESULTS

The drug concentrations in serum and each genital tissue after intravenous administration of 150 mg of fluconazole are shown in Table 1 and Fig. 1 and 2.

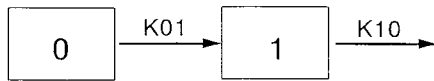
The maximum concentration of fluconazole in serum was observed to be 6.1 µg/ml at 1.0 h after the drip infusion was begun (Table 2). The peak concentrations in tissues from the portio vaginalis, cervix uteri, myometrium, endometrium, ovary, and oviduct ranged from 6.4 to 9.5 µg/g around 1.0 h after the drip infusion was begun. The levels of penetration of fluconazole into gynecological tissues appeared to be similar to or slightly above those in serum samples.

No abnormal symptoms or laboratory findings attributable to fluconazole were observed in the study.

DISCUSSION

Systemic fungal infections and superficial fungal infections have been increasing in recent years, because of the increasing population of compromised hosts: patients with immune deficiencies due to diseases, immunosuppression as a result of host

* Corresponding author. Mailing address: Department of Obstetrics and Gynecology, School of Medicine, Gifu University, 40, Tsukasamachi, Gifu-City, Gifu 500-8705, Japan.



$$C(T) = D \cdot K_{01} / V / (K_{01} - K_{10}) \cdot (EXP(-K_{10} \cdot T) - EXP(-K_{01} \cdot T))$$

FIG. 1. Diagram of the one-compartment first-order-lag-time-first-order-elimination pharmacokinetic model. See Materials and Methods for an explanation of the abbreviations.

reactions to organ transplants, and neutropenia from cancer or cancer chemotherapy (1–3, 17, 18).

In humans, the volume of distribution approximates that of total body water (0.8 liter/g). In contrast to the protein binding capacities of other azole antifungals, that of fluconazole is low (approximately 11%), and therefore most fluconazole circulates as a free form (4, 5, 10, 20, 22). Alternatively, fluconazole can penetrate into gynecological tissues in concentrations equivalent to those in serum, as shown in this study. The peak concentrations in each gynecological tissue, such as the uterus, ovaries, and oviducts, were 6.4 to 9.5 µg/g around 1.0 h after

TABLE 1. Drug concentrations in serum and each genital tissue after oral administration of 150 mg of fluconazole

Patient	Time after administration (h)	Concn (µg/ml) in serum from:		Concn (µg/g) in tissue from:					
		Uterine artery	Antecubital vein	Portio vaginalis	Cervix uteri	Endometrium	Myometrium	Oviduct	Ovary
1	1.83	3.6	3.7	3.0	3.1	3.2	3.4	3.4	NT ^a
2	2.08	3.0	2.7	2.6	2.7	2.6	2.5	2.6	NT
3	2.50	4.1	4.1	4.1	4.6	4.2	4.3	3.9	4.0
4	2.57	3.7	3.8	3.6	3.6	3.8	4.3	4.4	4.3
5	2.57	2.1	1.9	2.1	1.7	1.8	2.2	1.9	NT
6	2.58	3.9	3.8	3.2	3.2	NT	2.8	4.5	4.3
7	2.67	3.5	3.6	4.1	3.2	4.5	3.8	4.4	NT
8	2.67	2.3	2.5	2.3	2.3	NT	2.3	4.2	2.6
9	2.75	4.3	4.3	3.8	4.5	NT	4.6	4.2	4.7
10	2.83	3.3	3.2	2.3	2.8	3.5	3.0	3.4	3.2
11	3.08	1.5	1.5	1.2	1.4	1.3	1.5	1.2	1.3
12	3.17	4.0	4.1	4.2	3.8	5.3	4.7	5.2	4.6
13	4.25	3.1	3.5	3.3	3.7	4.2	3.2	4.3	3.4
14	6.00	3.7	3.8	3.9	3.3	3.6	3.8	4.1	NT
15	9.33	4.1	4.0	4.0	3.6	NT	4.3	NT	3.2
16	10.42	3.4	3.5	3.2	3.2	3.3	3.4	3.6	NT
17	11.50	3.0	2.9	2.4	2.6	2.8	2.8	NT	NT
18	13.00	4.5	4.5	4.5	3.1	5.7	5.4	4.9	NT
19	13.00	3.4	3.2	3.4	2.8	3.6	3.2	4.4	3.4
20	13.50	3.2	3.4	3.4	3.1	NT	3.4	3.6	3.3
21	14.00	3.7	3.7	4.0	3.5	NT	3.7	4.4	3.6
22	14.50	3.4	3.3	NT	3.2	3.8	3.5	4.1	3.7
23	17.25	3.7	3.7	3.5	3.3	3.4	3.5	3.8	NT
24	19.25	NT	3.6	NT	NT	NT	NT	NT	NT
25	21.50	3.6	3.4	3.3	NT	NT	3.2	3.7	3.4
26	21.50	3.5	NT	2.9	NT	NT	3.4	2.8	3.8
27	22.67	3.2	3.2	3.0	NT	NT	2.9	3.7	NT
28	23.17	2.0	2.2	1.9	2.0	2.3	2.2	2.3	2.1
29	24.25	2.6	2.7	2.7	2.6	2.9	2.9	NT	NT
30	24.57	2.3	2.3	2.4	2.4	2.6	2.7	2.4	NT
31	24.83	2.5	2.5	2.0	2.4	2.4	2.7	NT	NT
32	26.00	2.8	2.8	3.2	2.4	2.6	2.9	3.3	NT
33	26.33	2.8	2.6	2.4	2.4	2.6	2.5	2.8	NT
34	27.50	NT	3.5	4.3	NT	NT	5.1	4.1	3.4
35	31.25	2.2	2.2	2.1	2.2	NT	2.2	2.1	1.9
36	37.00	1.9	1.8	2.1	2.0	NT	2.4	2.2	2.1
37	37.50	2.3	2.2	NT	2.1	NT	2.3	2.9	2.4
38	37.50	1.6	1.5	1.5	1.8	1.3	1.5	1.4	1.5
39	39.50	NT	1.6	1.6	1.4	1.7	1.5	1.5	1.5
40	41.50	1.4	1.3	1.3	1.5	1.5	1.4	1.7	1.6
41	41.50	2.3	2.1	NT	NT	NT	1.9	2.1	2.0
42	41.67	1.5	1.5	1.5	1.4	NT	1.7	1.6	1.5
43	41.83	2.2	2.2	1.6	2.2	1.9	2.1	2.4	2.0
44	42.00	3.8	3.5	3.2	NT	NT	3.5	4.1	3.9
45	43.50	1.5	1.4	1.6	1.6	NT	1.8	1.8	1.6
46	45.50	NT	NT	1.2	1.3	1.3	1.5	NT	NT
47	46.17	NT	2.0	NT	NT	NT	NT	NT	NT
48	49.50	NT	1.2	1.2	1.2	1.5	1.3	1.3	1.4
49	50.00	1.4	1.5	1.2	1.1	1.3	1.3	1.3	1.5
50	52.25	1.5	1.5	1.0	1.1	1.1	1.7	1.3	1.1
51	64.50	NT	1.8	2.1	1.8	1.5	1.6	1.6	1.4
52	68.50	1.1	1.0	0.8	0.8	NT	1.3	1.1	1.1

^a NT, not tested.

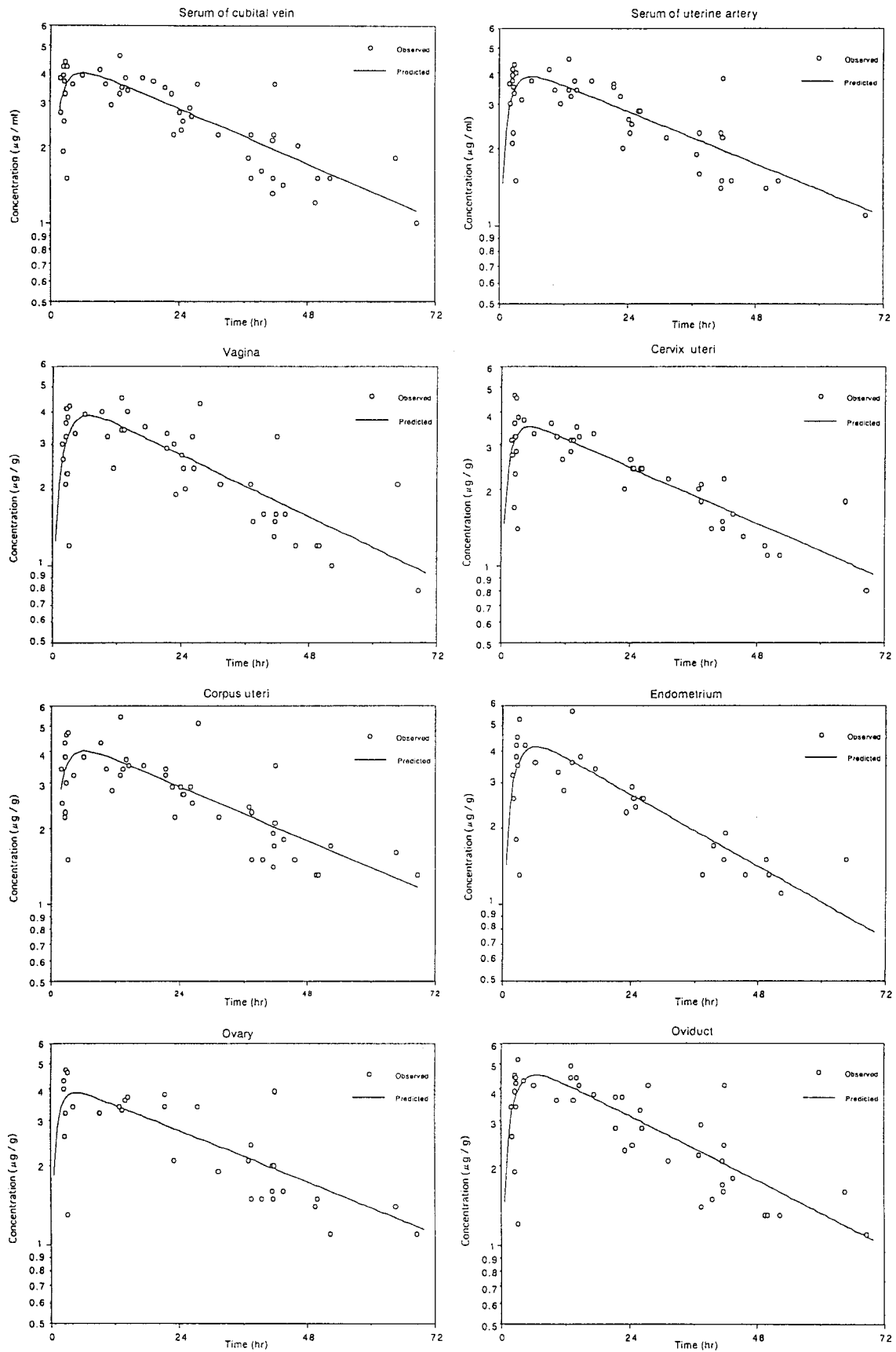


FIG. 2. Drug concentrations in serum and each genital tissue after oral administration of fluconazole (150 mg).

TABLE 2. Pharmacokinetic parameters of 150 mg of orally administered fluconazole

Tissue	Pharmacokinetic parameter ^a			
	C _{max} (h)	T _{max} (h)	t _{1/2} (h)	AUC _{0-∞} (μg · h/ml or g)
Serum from cubital vein	3.9	6.1	33.5	214
Serum from uterine artery	3.8	6.0	35.4	221
Vagina	3.8	6.8	30.0	194
Cervix uteri	3.5	5.3	33.0	186
Corpus uteri	4.0	6.2	33.9	223
Endometrium	4.1	6.2	25.5	180
Oviduct	4.5	6.6	29.1	222
Ovary	3.9	4.7	36.5	221

^a C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; t_{1/2}, half-life; AUC_{0-∞}, area under the concentration-time curve from 0 h to infinity.

the drip infusion was begun, levels which were similar to or slightly above those in serum. The penetration of fluconazole appears to occur rapidly from serum to each genital tissue.

Fluconazole inhibited hyphal branching almost totally at concentrations of 0.2 mg/liter in a morphology study of *C. albicans* (23). The MICs of fluconazole for pathogenic yeasts fell within achievable concentrations in serum and gynecological tissues even around 50 h after drug administration.

The presented penetration of oral fluconazole into gynecological tissues suggests that fluconazole has a considerable potential for treatment of not only human systemic fungal infections but also vaginal candidiasis with excellent activity.

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