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Levels of Flurithromycin in Female Genital Tissue

PIO M. FURNERI,[1]* ANTONIO CIANCI,[2] LAURA CAMPO,[1] LUCIA S. ROCCASALVA,[2] GIANNA TEMPERA,[1] GAETANO FIORE,[2] GIUSEPPE PALUMBO,[2] ANNA MARIA LEPORE,[3] AND GIUSEPPE NICOLETTI[1]

Institute of Microbiology[1] and Institute of Obstetrical and Gynecological Pathology,[2] University of Catania, Catania, and Clinical Research and Development, Pierrel S.p.A., Milan,[3] Italy

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The levels of flurithromycin in gynecological tissue in 20 female patients were studied after preoperative administration. The tissue flurithromycin levels obtained were comparable to those obtained in serum at 3 and 4 h but were frequently higher than those in serum at 6 and 12 h. Flurithromycin reached the highest concentrations in ovary at 4 h and in endometrium at 6 h.

Flurithromycin [(8*S*)-8-fluoroerythromycin A (P-0501A)] is a 14-membered macrolide drug which is obtained when (8*S*)-8-fluoerythronolide A is added to the fermentation broth of *Streptomyces erythreus* ATCC 31772, a blocked mutant of an erythromycin-producing strain (19). The first in vitro studies demonstrated that this drug has activity similar to that of erythromycin (8, 10–13, 17); moreover, in mouse protection tests, flurithromycin is equal to or threefold more active than erythromycin (7). Flurithromycin, unlike erythromycin A, showed high stability at acidic pH values, better bioavailability, and lower liver toxicity in experimental animals. Pharmacokinetic parameters and oral absorption have also been described for humans, and flurithromycin showed a longer half-life and higher tissue concentrations than erythromycin (2, 3, 14, 16).

TABLE 1. Individual concentrations of flurithromycin in the genital tissues of 20 patients

Patient no.	Time (h)	Flurithromycin concn in:						
		Serum (μg/ml)	Vagina (μg/g)	Cervix (μg/g)	Endometrium (μg/g)	Myometrium (μg/g)	Uterine tubes (μg/g)	Ovary (μg/g)
1	3	0.90	0.30	0.40	0.10	0.50	0.30	0.19
2		1.20	0.36	0.21	0.90	0.75	0.50	0.30
3		1.40	0.55	0.35	0.70	0.80	0.21	0.10
4		1.60	0.60	0.30	0.20	0.41	1.00	1.00
5		1.30	0.45	0.32	0.80	0.40	0.77	0.56
Mean ± SD		1.28 ± 0.26	0.45 ± 0.13	0.32 ± 0.07	0.54 ± 0.36	0.57 ± 0.19	0.56 ± 0.33	0.43 ± 0.36
6	4	1.00	0.30	0.70	0.30	0.71	0.83	0.5
7		1.03	1.30	0.35	0.95	0.39	1.1	0.83
8		0.71	0.25	0.22	0.35	0.22	0.17	1.52
9		0.90	1.01	1.09	1.14	0.69	1.03	2.06
10		0.81	0.60	0.63	0.71	0.88	0.77	1.1
Mean ± SD		0.89 ± 0.13	0.69 ± 0.46	0.60 ± 0.33	0.69 ± 0.37	0.578 ± 0.27	0.78 ± 0.37	1.20 ± 0.61
11	6	0.60	0.51	0	1.2	0.65	0	0.70
12		1.00	0.41	0.39	0.98	0.67	0.81	0.71
13		0.70	0.40	0.78	0.93	0.62	0.99	0.73
14		0.90	0.48	0.81	1.32	0.73	0.60	0.83
15		0.79	0.41	0.55	1	0.71	0.90	0.85
Mean ± SD		0.80 ± 0.16	0.44 ± 0.05	0.51 ± 0.33	1.09 ± 0.17	0.68 ± 0.04	0.66 ± 0.40	0.76 ± 0.07
16	12	0.03	0.16	0.83	0.13	1.14	0.37	2.00
17		0.51	0.12	0.70	0.09	1.00	0.18	0.67
18		0.30	0.09	0.25	0.11	0.14	0.13	0.35
19		0.15	0.15	0.14	0.10	0.31	0.10	0.33
20		0.43	0.10	0.30	0.09	0.70	0.10	0.63
Mean ± SD		0.28 ± 0.20	0.12 ± 0.03	0.44 ± 0.30	0.10 ± 0.02	0.66 ± 0.43	0.18 ± 0.11	0.80 ± 0.69

* Corresponding author. Mailing address: Istituto di Microbiologia, Università di Catania, Via Androne 81, 95124 Catania, Italy. Phone: 39 95 316038 or 316201. Fax: 39 95 325032 or 316214.

TABLE 2. Tissue/serum flurithromycin ratios at different times

Time (h)	Tissue/serum flurithromycin ratio					
	Vagina	Cervix	Endometrium	Myometrium	Uterine tubes	Ovary
3	0.35	0.25	0.42	0.45	0.44	0.34
4	0.78	0.67	0.78	0.65	0.88	1.35
6	0.55	0.64	1.36	0.85	0.83	0.95
12	0.60	1.57	0.36	3.57	0.64	2.86

Moreover, flurithromycin's ethylsuccinate ester, adopted for a recently developed tablet preparation, gives an improved bioavailability relative to the previously described preparation (5).

Therefore, we investigated the penetration into female genital tissues of this new flurithromycin formulation. To accomplish this, tissue samples, obtained in the course of gynecological surgery from patients who had been given flurithromycin preoperatively, were tested for their antibiotic concentrations.

Twenty female patients undergoing gynecological surgery (hysterectomy and oophorosalpingectomy) were studied to evaluate concentrations of flurithromycin in genital tract tissues. Each patient had a normal clinical examination, normal hematological findings, and normal renal and liver function tests. None of the subjects had taken other drugs or antibiotics for at least 2 weeks before surgery. Informed consent was obtained from each patient before flurithromycin administration. No surgical prophylaxis was used.

The patients were then divided into four groups on the basis of the scheduled sampling time.

Patients enrolled in the study received 375 mg of flurithromycin ethylsuccinate orally every 12 h (1) for a total of seven doses. On the day of surgery, the last dose of flurithromycin was administered either 3, 4, 6, or 12 h before surgery.

Genital tissue samples (vagina, cervix, endometrium, myometrium, uterine tube, and ovary) were collected 3, 4, 6, and 12 h after drug administration under aseptic conditions during surgery, rapidly rinsed in phosphate buffer (0.1 M [pH 8.0]), and immediately put in cold phosphate buffer and processed within 2 h. Tissue samples were maintained at 4°C during transportation in the laboratory and until assayed (not more than 2 h). The tissue samples were first homogenized in an equal volume of phosphate buffer. Ultrasonic treatment was carried out to avoid clumps, and then the homogenized tissues were centrifuged at 3,000 × *g* at 4°C. The supernatant, sterilized by filtration, was used in the assay. For each patient, a blood sample was taken at the same time as that of the genital tissue. Serum was obtained by centrifugation immediately after collection of blood and maintained at 4°C during transportation and until assayed (not more than 2 h).

All samples were assayed by a microbiological method, with antibiotic medium 11 and *Micrococcus luteus* ATCC 9341 as the indicator organism. Serum and tissue samples were assayed against standards containing flurithromycin prepared in serum and tissues from subjects who had received no antibiotic therapy. The limit of detection of the assay was 0.01 μg/ml. The assay had a coefficient of variation of 5.95% (calculated at 1 μg/ml or 1 μg/g of tissue) and a mean relative error of 7%. The assay of hemoglobin in tissue and correction of flurithromycin concentrations for blood contamination were performed according to the method of Kroening et al. (15). Table 1 illustrates the concentrations obtained in genital tissue at different times compared with those obtained in the serum of the same patients at the same times. Table 2 shows the mean values for each group of patients by means of the time of sampling and their respective tissue/serum drug ratios. Table 3 shows the inhibitory quotients of flurithromycin (ratios between tissue or serum drug levels and MICs for the microorganisms tested [the numerical value of inhibitory quotients should be >1 to have clinical significance]) (6, 18). The MICs for some genital pathogens were obtained by means of a microdilution method,

TABLE 3. Inhibitory quotients of flurithromycin against some genital pathogens

Microorganism	Time (h)	Inhibitory quotient in[a]:						
		Serum	Vagina	Cervix	Endometrium	Myometrium	Uterine tubes	Ovary
C. trachomatis[b]	3	2.56 (10.67)	0.90 (3.75)	0.64 (2.67)	1.08 (4.50)	1.14 (4.75)	1.12 (4.67)	0.86 (3.58)
N. gonorrhoeae[c]		1.28 (2.56)	0.45 (0.90)	0.32 (0.64)	0.54 (1.08)	0.57 (1.14)	0.56 (1.12)	0.43 (0.86)
S. agalactiae[d]		10.67 (21.33)	3.75 (7.50)	2.67 (5.33)	4.50 (9.00)	4.75 (9.50)	4.67 (9.33)	3.58 (7.17)
M. genitalium[e]		160	56.25	40	67.50	71.25	70	53.75
C. trachomatis[b]	4	1.78 (7.42)	1.38 (5.75)	1.20 (5.00)	1.38 (5.75)	1.16 (4.83)	1.56 (6.50)	2.40 (10.00)
N. gonorrhoeae[c]		0.89 (1.78)	0.69 (1.38)	0.60 (1.20)	0.69 (1.38)	0.58 (1.16)	0.78 (1.56)	1.20 (2.40)
S. agalactiae[d]		7.42 (14.84)	5.75 (11.50)	5.00 (10.00)	5.75 (11.50)	4.83 (9.66)	6.50 (13.00)	10.00 (20.00)
M. genitalium[e]		111.25	86.25	75	86.25	72.50	70	150
C. trachomatis[b]	6	1.60 (6.67)	0.88 (3.67)	1.00 (4.25)	2.18 (9.08)	1.36 (5.67)	1.32 (5.50)	1.52 (6.33)
N. gonorrhoeae[c]		0.80 (1.60)	0.44 (0.88)	0.51 (1.02)	1.09 (2.18)	0.68 (1.36)	0.66 (1.32)	0.76 (1.52)
S. agalactiae[d]		6.67 (13.33)	3.67 (7.33)	4.25 (8.50)	9.08 (18.16)	5.67 (11.33)	5.50 (11.00)	6.33 (12.66)
M. genitalium[e]		100	55	63.75	136.25	85	82.50	95
C. trachomatis[b]	12	0.56 (2.33)	0.24 (1.00)	0.88 (3.67)	0.20 (0.83)	1.32 (5.50)	0.36 (1.50)	1.60 (6.67)
N. gonorrhoeae[c]		0.28 (0.56)	0.12 (0.24)	0.44 (0.88)	0.10 (0.20)	0.66 (1.32)	0.18 (0.36)	0.80 (1.60)
S. agalactiae[d]		2.33 (4.67)	1.00 (2.00)	3.67 (7.33)	0.83 (1.67)	5.50 (11.00)	1.50 (3.00)	6.67 (13.33)
M. genitalium[e]		35	15	55	12.50	82.50	22.50	100

[a] Values in parentheses are inhibitory quotients determined by means of MIC_{50}s.
[b] MIC_{90}, 0.5 μg/ml; MIC_{50}, 0.12 μg/ml (11).
[c] MIC_{90}, 1 μg/ml; MIC_{50}, 0.5 μg/ml (8, 12).
[d] MIC_{90}, 0.12 μg/ml; MIC_{50}, 0.06 μg/ml (12).
[e] MIC, 0.008 μg/ml (10, 11).

agar plate method, or cell culture assay and were previously reported (8, 10–12).

The highest concentrations of flurithromycin were recovered in ovary (4 h after the last administration) and in endometrium (6 after the last administration), with means ± standard deviations of 1.20 ± 0.61 and 1.09 ± 0.17 μg/g, respectively.

Tissue/serum drug ratios are tissue dependent and frequently are lower than 1, with the exception of ovary at 4 h; endometrium at 6 h; and cervix, myometrium, and ovary at 12 h (Table 2).

The present study was carried out to evaluate whether flurithromycin reaches sufficient concentrations in female genital tissues to be effective against microorganisms involved in genital infections. Some organisms most commonly responsible for both upper, lower, and sexually transmitted disease genital tract infections, such as *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Streptococcus agalactiae*, and *Neisseria gonorrhoeae*, are included in the antibacterial spectrum of flurithromycin (7, 8, 10–13). The breakpoint MIC is reported to be 0.5 μg/ml, and the MICs at which 90% of the isolates are inhibited (MIC_{90}s) are no higher than 0.5 μg/ml, with the exception of *N. gonorrhoeae*, for which the MIC_{90} is reported to be equal to 1 μg/ml and of which only 50% of the strains can be considered susceptible (12). As is apparent from the present study, the breakpoint MIC is reached or exceeded in most of the genital tissue from 3 to 12 h after the last administration, while it is maintained in the serum for up to 6 h.

Inhibitory quotients (based on tissue/MIC ratios) are favorable for *C. trachomatis*, *M. genitalium*, and *S. agalactiae*, while they have little or no clinical significance for *N. gonorrhoeae*. Moreover, erythromycin and many of its derivatives are not indicated for the therapy of gonococcal infections (4), although for patients with chlamydial-gonococcal mixed infections who cannot take tetracycline (e.g., pregnant women), erythromycin or its derivative flurithromycin can be suggested as a substitute (4).

In conclusion, flurithromycin showed a moderate tissue penetration, for at least 6 h after the last administration, with tissue/serum drug ratios below 1, except in ovary at 4 h and endometrium at 6 h, for which the ratio was >1; moreover, a small improvement at 12 h after the last administration was recorded for cervix, myometrium, and ovary, for which the ratios were above 1. However, the intracellular concentration of the compound should be considered, because this is an important feature of this class of compounds, conditioning their in vivo activity on intracellular pathogens such as *C. trachomatis* and *N. gonorrhoeae*. In this respect, flurithromycin reaches intracellular levels 10-fold higher than the extracellular ones, at least in polymorphonuclear leukocytes (9). Other cell models, such as fibroblasts, etc., should be studied.

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