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DISTRIBUTION OF ORAL NIMESULIDE IN FEMALE GENITAL TISSUES

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ABSTRACT

Nimesulide is a non-steroidal anti-inflammatory agent which has proved to be effective in reducing menstrual discomfort in dysmenorrhoeaic women. To determine the concentrations of this drug in the uterus (fundus, cervix), oviduct, and ovaries and to correlate these findings with plasma concentrations, a single oral dose of 100 mg nimesulide was administered 1 to 6 h before surgery to 12 women undergoing hysterectomy and salpingo-oophorectomy, mainly for fibroids. Tissue samples were taken, concentration of nimesulide measured by HPLC, and findings compared with plasma concentrations. One patient not undergoing treatment served as control. Nimesulide concentration in the tissues studied was highest 3 h after administration, as expected from the drug's pharmacokinetic profile. The highest tissue/plasma ratio (0·5) was also found at that time. Average tissue concentrations at 1, 2, 3, and 6 h after drug intake ranged from 0·3 to 1·8 $\mu g\,g^{-1}$, and plasma concentrations from 2·6 to 4·1 $\mu g\,ml^{-1}$. Nimesulide was evenly distributed in the tissues studied.

KEY WORDS Nimesulide female genital tract tissue concentration HPLC

INTRODUCTION

Nimesulide (4-nitro-2-phenoxymethanesulphonanilide) is a recently developed non-steroidal anti-inflammatory agent (NSAID) which has good analgesic and antipyretic properties. *In vitro*, it inhibits the biosynthesis of prostaglandins by bovine seminal vesicle microsomes and arachidonic acid induced human platelet aggregation. Its activity is weaker than that of indomethacin, comparable with that of phenylbutazone, but stronger than that of acetylsalicylic acid.[1] It has been shown, moreover, that nimesulide influences the contractility and reactivity of the isolated rat uterus.[2]

A controlled clinical and pharmacological study, carried out on women suffering from primary essential dysmenorrhoea, demonstrated that nimesulide modifies pathological uterine activity positively, significantly decreasing resting and active pressure, as well as frequency of contractions. The treatment resulted in a significant reduction of menstrual fluid prostaglandin F levels and alleviation of pain.[3] Cross-over therapeutic trials on dysmenorrhoeaic women, with

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either placebo or active reference drugs as control, established that nimesulide is very effective in reducing menstrual discomfort.[4,5]

When orally administered, the drug is relatively slowly absorbed: mean C_{max} is reached 3 h after administration. Half-life is about 5 h, and elimination is completed within 24 h.[6] The aim of the present study was to determine the distribution of nimesulide in the uterus, oviduct, and ovaries after a single oral does and to correlate these findings with plasma levels. The observed time for maximal tissue concentrations, found in this study, are compared with earlier pharmacokinetic data.

METHODS

The study, which involved 13 female volunteers undergoing hysterectomy and salpingo-oophorectomy, was carried out according to an open design. Twelve of the subjects were given a single oral does of 100 mg of nimesulide at different time intervals before surgery, and the remaining one served as a control. The age of the subjects ranged from 45–67 years ($54 \pm 6{\cdot}7$ years SD) of which three were nulliparous, 10 previously had pregnancies (G $3{\cdot}4 \pm 0{\cdot}8$) and one to three deliveries (P $2{\cdot}4 \pm 0{\cdot}7$). Nine patients underwent surgery for uterine fibroids, two for endometrial hyperplasia, one for uterine prolapse, and one for cervical dysplasia.

Four subjects received the drug 1 h, three 2 h, four 3 h, and one 6 h prior to surgery.

In the evening before and in the morning of the operation day, the patients received an anxiolytic drug (diazepam 10 mg); seven subjects also received a prophylactic dose of metronidazole or tinidazole.

Subjects who were known to be hypersensitive to NSAIDs, suffering from gastrointestinal diseases, or hepatically or renally impaired, factors which may have affected metabolism or excretion, respectively, were excluded from the study. Concomitant medication related either to the surgical intervention or to the diseases of the patient (anxiolytics, anaesthetics, antibiotics or oestrogens) was allowed. The study was approved by the Ethical Committee of Turku University Hospital and informed consent was given.

During the operation, 2 g of tissue as well as 20 ml blood were collected. The serum samples were stored at $-20°C$. They were then analysed according to the method of Castoldi *et al.*[7]

Preparation of tissue samples

Two grams of muscle were homogenized in 10 ml acetonitrile p.a. and extracted twice with 20 ml of n-hexane. The n-hexane layer was discarded and the acetonitrile evaporated to dryness at 50° using a rotary evaporater. The

residue was dissolved in 100 µl of internal standard solution (2-tert-butyl-4-methoxyphenol, 150 µg ml^{-1}) and injected into the HPLC apparatus.

Preparation of serum samples

One millilitre of methanol and 0·6 ml of hydrochloric acid (1 M) were added to 1 ml serum. The nimesulide was extracted into benzene (2 × 5 ml) and back extracted into sodium hydroxide solution (2 × 2 ml, 0·2 M). The aqueous layer was re-acidified with hydrochloric acid (2 M) and the nimesulide re-extracted into benzene (2 × 3 ml). The organic layer was evaporated to dryness, under a stream of nitrogen, and the residue redissolved in 100 µl of internal standard solution for the HPLC injection.[7]

HPLC conditions

The analyses were carried out at room temperature with a high-pressure liquid chromatographic (HPLC) apparatus Spectra Physics SP, equipped with an Rp-18 µm-Bondapack column (5 µm, 300 × 4 mm). The eluent was acetonitrile/water (65/35) at a flow rate of 1·5 ml min^{-1}. The injection volume was 20 µl. The wavelength of the UV detector was 313 nm.

Table 1. Concentration of nimesulide in tissues (T, µg g^{-1}) and in serum (S, µg ml^{-1}) after a single oral dose of 100 mg. Sampling 140 min (average) after administration of drug

Patient no.	Cervix	Fundus	Oviduct	Ovary	Serum
1	1·56	0·51	0·94	1·04	2·95
2	1·46	1·46	2·47	1·92	0·84
3	1·19	1·80	1·83	2·61	4·99
4	1·41	0·68	1·19	1·59	2·77
5	0·14	0·13	0·11	0·07	1·56
6	1·01	0·75	1·17	0·68	3·29
7	1·72	1·18	1·17	0·92	3·88
8	0·58	0·75	0·91	0·31	3·46
9	0·48	0·44	0·36	0·37	1·88
10	0·50	0·90	0·50	0·45	3·32
11	0·76	0·37	0·62	0·75	4·08
12	0·19	0·15	0·08	0·15	0·72
Mean ±SD	0·92	0·76	0·95	0·91	2·81
	0·55	0·51	0·70	0·78	1·32
Ratio T/S	0·40	0·34	0·46	0·42	

Table 2. Concentrations of nimesulide in tissues (T, $\mu g\,g^{-1}$) and in serum (S, $\mu g\,ml^{-1}$) in relation to the time interval between drug administration and laparotomy

	1 h ($n = 4$)		2 h ($n = 3$)		3 h ($n = 4$)		6 h ($n = 1$)	
	1	2	1	2	1	2	1	2
Cervix	0·42 ±0·20	0·16	0·97 ±0·77	0·37	1·41 ±0·15	0·49	0·76 (–)	0·19
Fundus	0·55 ±0·34	0·22	0·70 ±0·52	0·26	1.11 ±0·62	0·39	0·37 (–)	0·09
Oviduct	0·47 ±0·33	0·18	0·80 ±0·63	0·31	1·61 ±0·69	0·56	0·62 (–)	0·15
Ovary	0·30 ±0·16	0·12	0·58 ±0·40	0·22	1·79 ±0·66	0·62	0·75 (–)	0·18
Serum	2.55 ±0·98	–	2.63 ±1·68	–	2·89 ±1·69	–	4.08 (–)	–

1 = Mean ± SD.
2 = T/S.

RESULTS

Nimesulide concentrations in the tissues and in serum are shown in Table 1. Tissue concentrations and T/S ratios in relation to the time of sampling are shown in Table 2. In the tissues analysed, the drug reached a concentration of about $1\,\mu g\,g^{-1}$ and in serum a level of $\approx 3\,\mu g\,ml^{-1}$. No trace of the compound ($< 0{\cdot}05\,\mu g\,g^{-1}$ or ml^{-1}) was found in the control patient. The maximum tissue concentrations were reached 3 h after drug intake (Figure 1). The distribution of the drug was similar in the different genital tissues analysed.

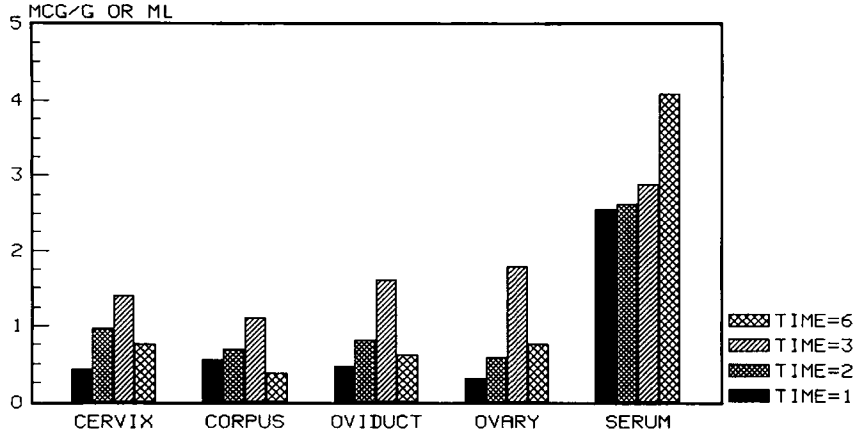

Figure 1. Concentration of nimesulide in tissues ($\mu g\,g^{-1}$) and in serum ($\mu g\,ml^{-1}$) in relation to the time interval (h) between drug administration and laparotomy

DISCUSSION

In the present study, plasma concentrations of nimesulide after a single oral dose of 100 mg are comparable with those reported for this NSAID by Ambrosini.[8] The 3 $mg\,l^{-1}$ concentration in the present study reflects the situation when the drug is taken in the fasting state before laporotomy. It has been shown that nimesulide is absorbed better on a full stomach, reaching a peak plasma concentration of 6 to 10 $mg\,l^{-1}$ instead of 2 to 6 $mg\,l^{-1}$. (See Ward and Brogden.)[9] This might partly explain the individual variations in serum concentration (Table 1, case 3; Table 2, the only instance at 6 h).

The results of the present study are in accord with the finding in rat studies that a dose of 1·5 $mg\,kg^{-1}$ yields a plasma concentration of 4·5 $mg\,l^{-1}$.[10]

Maximal tissue levels at 3 h accords with what is known about the absorption, distributions, and elimination of some NSAIDs. During absorption and distribution tissue concentrations of nimesulide lag behind those in plasma. However, after distribution is complete NSAID levels, for example in synovial fluid, can exceed those of plasma.[11]

There was no difference between the nimesulide levels in the different genital tissues studied. Although cervical tissue is mainly collagen and fundal uterine tissue smooth muscle, there was no significant difference in the distribution of nimesulide. With another NSAID, naproxen, the concentration reached in uterine tissue endometrium after a single oral dose of 500–750 mg was of the same order of magnitude as with nimesulide (3·7 $\mu g\,g^{-1}$ resp. 1·4 $\mu g\,g^{-1}$).[12]

The good clinical response to nimesulide in dysmenorrhoeic patients corresponds to the distribution of the drug in the genital tissues studied.

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