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An investigation into the effect of tenidap sodium on the pharmacokinetics of a combined oral contraceptive

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1 The effects of tenidap sodium and placebo on the pharmacokinetics of a combined oral contraceptive (Microgynon 30®) were evaluated in 18 healthy premenopausal women in a double-blind, cross-over study lasting two menstrual cycles.

2 Tenidap (120 mg day^{-1}) or placebo was given for 11 days, starting within 4 days of menstruation and Microgynon 30®, containing levonorgestrel (150 μg) and ethinyloestradiol (30 μg), was administered on day 10 of tenidap therapy.

3 The mean maximum plasma levonorgestrel concentrations (C_{max}), time to C_{max} (t_{max}) and area under the plasma time-concentration curves (AUC(0,t)) did not differ between subjects given tenidap or placebo. The C_{max}, t_{max} and AUC(0,t) values for ethinyloestradiol did not differ between tenidap and placebo recipients. Only the ethinyloestradiol C_{max} showed a significant difference (P = 0.02) between menstrual cycles 1 and 2 (252.9 pg ml^{-1} and 271.3 pg ml^{-1}, respectively).

4 Co-administration of tenidap and Microgynon 30® was well tolerated and no subject withdrew from the study because of side-effects. There were no side-effects considered to be related to tenidap and no clinically significant laboratory abnormalities were considered to be related to treatment.

5 The results of the study suggest that the pharmacokinetics of the oestrogen and progestin components of the oral contraceptive Microgynon 30® are unlikely to be affected by concomitant administration of tenidap.

Keywords tenidap sodium oral contraceptive levonorgestrel ethinyloestradiol pharmacokinetics

Introduction

Tenidap sodium is a novel cytokine-modulating anti-rheumatic drug that has been extensively studied in more than 5000 subjects including patients with rheumatoid arthritis and osteoarthritis. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), which are often used to treat rheumatoid arthritis, tenidap has been shown to reduce serum interleukin-6 (IL-6) levels *in vitro* [1] as well as levels of acute phase proteins [2, 3] which are secreted by the liver in response to IL-6 and other cytokines [4]. Tenidap has also been shown to inhibit cyclo-oxygenase activity [5].

Rheumatoid arthritis is a chronic inflammatory polyarthritis of unknown aetiology. Unlike other forms of arthritis, rheumatoid arthritis is much more likely to affect younger people, with a range of age of onset of 35–50 years [6]. It is also three times more prevalent in women than men [7]. Many of these women are of childbearing age and likely to be taking concomitant oral contraception.

Many formulations of oral contraceptive are available, either containing both an oestrogen and a progestin component, or only a progestin. The most widely used oral formulations contain 30 μg oestrogen and a synthetic progestin. Such preparations are not used exclusively for contraceptive purposes, they are also employed to treat menstrual disorders in women of reproductive age. Lower doses of combined oestrogen and progestin therapy, furthermore, are extensively used in peri- and post-menopausal women as hormone replacement therapy.

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The combined oral contraceptives are biologically inactivated in the liver and drugs that induce hepatic enzymes, such as phenobarbitone and rifampicin, alter the metabolism of oral contraceptives [8]. Such interactions are clinically important, since they render the contraceptives less reliable.

Some anti-rheumatic drugs, although chemically unrelated to tenidap, have been shown to interact pharmacokinetically with either the oestrogen or progestin component of oral contraceptives. These include aspirin [9], oxaprozin [10] and diflunisal [11]. It is therefore important that the effect of tenidap on the pharmacokinetics of a typical combined oral contraceptive (Microgynon 30® (150 μg levonorgestrel plus 30 μg ethinyloestradiol)) is studied to assess any potential change in contraceptive efficacy.

Methods

Subjects

The study was to be carried out in a minimum of 18 healthy premenopausal female volunteers. The study was designed to have 80% power to detect a 20% difference in AUC values for the oral contraceptives. All subjects gave written, informed consent prior to entry and ethical approval was obtained from the district ethics committee.

Only women with regular menstrual cycles were included in the study. A negative pregnancy test result was required at study entry and subjects of child-bearing potential must not have used hormonal contraception methods for the previous 3 months.

All subjects underwent clinical examination, standard laboratory tests of haematological, renal and hepatic function, 12-lead electrocardiography and pregnancy testing at screening. Subjects had to be within 15% of the ideal weight for age and height. No medications, including over-the-counter medications and recreational drugs, were to have been taken in the 4 weeks before enrolment, especially drugs extensively metabolised by the liver (e.g. propranolol, phenothiazines). Subjects with peptic ulcer disease, recurrent gastro-intestinal problems and malabsorption syndromes were excluded from the study.

Protocol

The placebo-controlled, double-blind, randomised, two-way cross-over study was conducted over two menstrual cycles. Subjects were assigned randomly to receive an oral dose of tenidap sodium (three 40 mg capsules) or matched placebo once daily for 11 days during the first cycle; during the second cycle, they received the alternative treatment. During both cycles, the first dose of tenidap or placebo was taken on the second, third or fourth day of the menstrual cycle and a single dose of the oral contraceptive tablet (Microgynon 30®, Schering) containing levonorgestrel (150 μg) and ethinyloestradiol (30 μg) was taken on day 10 of tenidap therapy. Study therapy was administered at the research centre under supervision.

Serum levonorgestrel and ethinyloestradiol measurements

Plasma samples were obtained on days 10 and 11 of tenidap or placebo treatment in cycles 1 and 2 at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24 and 36 h after dosing with the oral contraceptive. On each occasion, a 6 ml blood sample was collected in a heparinised tube, centrifuged and the separated plasma frozen at −20° C. Analysis was by radioimmunoassay with calibration ranges of 0.05–4 ng ml^{-1} for levonorgestrel and 10–600 pg ml^{-1} for ethinyloestradiol. The assays were performed as described by Dyas *et al.* [12]. Plasma concentration-time curves were plotted, and values of maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) for levonorgestrel and ethinyloestradiol were estimated directly from the data. Area under the concentration-time curve (AUC(0,t)) was calculated using the linear trapezoidal rule where t is the time of the last quantifiable concentration. The data were not susceptible for analysis of λ_z or $t_{1/2}$.

Plasma tenidap measurements

Measurement of plasma tenidap concentrations was carried out at 1 and 3.5 h post-dose on day 10 of tenidap dosing. A 10 ml blood sample was collected in heparinised tubes, centrifuged and the separated plasma was stored at −20° C prior to analysis using a validated high-performance liquid chromatography procedure with ultraviolet detection at 365 nm and a calibration range of 0.5–30 μg ml^{-1} as described by Wilner & Gardner [13].

Safety assessment

Side-effects observed or volunteered by the subjects at each review visit were detailed and designated as drug-related, possibly drug-related, or not drug-related with details of severity, time of onset, duration and any symptomatic therapy required.

Laboratory safety tests (haematology, serum chemistry and urinalysis) were performed at each review visit on days 1, 3, 8, 12 and 14 in menstrual cycles 1 and 2, and again on day 1 of the third menstrual cycle during a follow-up examination.

Statistics

Derived parameters were subjected, untransformed, to an analysis of variance appropriate to the two-period cross-over design [14]. Significance was considered to be reached at P values of ≤ 0.05.

Results

Subjects

All 18 subjects enrolled into the study completed therapy and were assessed for pharmacokinetics and safety (Table 1). Protocol violations included one subject with an abnormal electrocardiogram at

Table 1 Baseline demographics of healthy subjects treated concomitantly with Microgynon® and either tenidap (120 mg day^{-1}) or matching placebo in a cross-over study design

Number of subjects	18 (all female)
Age (years)	
Mean	30.4
Range	22–45
Weight (kg)	
Mean	59.7
Range	45.8–74.8
Ethnic origin	
White	12
Arab	6

screening that was considered not be be clinically significant. Another subject started therapy later than the day of the menstrual cycle specified in the protocol (1 day later in the first cycle, and 2 days later in the second cycle). A blood sample was not taken from one subject at 1 h post-dose on the second cycle and one subject had insufficient blood taken at 2 h post-dose for the levonorgestrel assay.

Pharmacokinetics

Maximum plasma concentrations of levonorgestrel and ethinyloestradiol were followed by a biphasic decline in concentrations for the two treatments. Mean levonorgestrel C_{max} values were 3.35 and 4.10 ng ml^{-1} after co-administration with tenidap and placebo, respectively, and t_{max} occurred 1.19 and 1.17 h, respectively, after contraceptive dosing (Table 2). The mean values for AUC(0,t) were 20.40 ng ml^{-1} h for subjects receiving tenidap plus Microgynon 30® and 23.57 ng ml^{-1} h for subjects treated with placebo plus Microgynon 30® (Table 2). There was no significant difference in the mean values of C_{max}, t_{max} or AUC(0,t) between the groups. The sequence in which tenidap and placebo were administered in the two menstrual cycles studied did not influence any levonorgestrel pharmacokinetic parameter.

The mean ethinyloestradiol C_{max} values of 255.7 pg ml^{-1} for the subjects treated with tenidap plus Microgynon 30® and 268.4 pg ml^{-1} for subjects dosed with placebo plus Microgynon 30® occurred at 1.11 and 0.97 h, respectively, after Microgynon 30® dosing (Table 2). There were no statistically significant differences between the mean values for C_{max} and t_{max} for the two treatments. There was a significant ($P = 0.02$) period effect for the C_{max} values: 252.9 and 271.3 pg ml^{-1}, respectively, for periods 1 and 2. No other pharmacokinetic parameters showed statistically significant effects related to the menstrual cycle and sequence in which tenidap and placebo were given. The AUC(0,t) values were 1605 pg ml^{-1} h and 1686 pg ml^{-1} h for subjects treated with tenidap plus Microgynon 30® or placebo plus Microgynon 30®, respectively; the difference between these values was not statistically significant.

The concentrations of tenidap sodium in plasma on day 10 of the treatment were 16.64 ± 9.90 μg ml^{-1} at 1 h after dosing and 24.80 ± 8.03 μg ml^{-1} at 3.5 h after dosing.

Safety

None of the subjects withdrew from the study or discontinued treatment because of side-effects. Tenidap was well tolerated with no side-effects considered to be related to the drug. Of the 18 subjects, one presented with moderate metrorrhagia while receiving placebo. Menstrual irregularities, which were attributed to the effect of single oral contraceptive doses, were reported by five subjects. There were no clinically significant laboratory abnormalities considered to be related to treatment. Electrocardiographic abnormalities not considered to be clinically significant were recorded in two subjects: one at screening that was unchanged at baseline; and one at the final visit. No clinically significant changes in heart rate and blood pressure were detected.

Three subjects presented with an intercurrent illness during the cycle when they received tenidap. One subject suffered from odontalgia for 1 day which was treated with niflumic acid, another suffered from influenza-like symptoms for 5 days for which no treatment was given and the third suffered from bleeding of the right ear for 12 h on day 3 and 0.5 h on day 4 of the cycle; no treatment was given.

Table 2 Mean pharmacokinetic parameters for the constituents of Microgynon 30® with and without concomitant administration of tenidap 120 mg to healthy volunteers

Component	*Parameter*	*Tenidap (T)* (n = *18*)	*Placebo (P)* (n = *18*)	*Difference (T–P)**
Levonorgestrel	C_{max} (ng ml^{-1})	3.35	4.10	−0.74
	t_{max} (h)	1.19	1.17	−0.03
	AUC(0,t) (ng ml^{-1} h)	20.40	23.57	−3.18
Ethinyloestradiol	C_{max} (pg ml^{-1})	255.7	268.4	−12.7
	t_{max} (h)	1.11	0.97	0.14
	AUC(0,t) (pg ml^{-1} h)	1605	1686	−81

*None of these differences is statistically significant.

Discussion

The pharmacokinetic data from this placebo-controlled, double-blind, two-way cross-over study showed no statistically significant differences in the pharmacokinetic parameters, C_{max}, t_{max} and AUC(0,t), for levonorgestrel and ethinyloestradiol in plasma when concurrent tenidap was given compared with placebo. Although a statistically significant variation between the two menstrual cycles was detected for ethinyl-oestradiol C_{max}, the difference was not consideredto be clinically significant. There were no statistically significant variations between the two cyclesstudied for any of the other pharmacokinetic parameters.

Interactions between oral contraceptives and other drugs have been previously demonstrated. For example, the antibiotic rifampicin has been shown to increase the hydroxylation rate of oestradiol and 17α-ethinyloestradiol fourfold and it is postulated that this is the cause of the reduced contraceptive efficacy seen when rifampicin is co-administered with oral contraceptives [15]. The plasma clearance of the analgesic diflunisal has been shown to be increased in women taking oral contraceptives compared with controls. The time to maximum plasma concentration (t_{max}) was significantly longer in women not taking oral contraceptives compared with those on oral contraceptives [11]. Gomaa *et al.* [9] showed that aspirin decreased the oral bioavailability and AUC0(0,t) value for the oral contraceptive norethindrone.

The implications of these findings with tenidap are especially important because rheumatoid arthritis is three times more prevalent in women than men [7]. Rheumatoid arthritis also often has an early onset, and thereby affects young women who are likely to use oral contraception. A therapy to be used for rheumatoid arthritis therefore should be able to be taken by women of child-bearing age without concern that either they may not be able to use oral contraception or that the effectiveness of oral contraception may be impaired.

The results of this study suggest that there is no pharmacokinetic interaction in subjects receiving concomitant tenidap and Microgynon 30®. It appears unlikely, therefore, that concomitant tenidap administration would lead to decreased oral contraceptive efficacy.

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