Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial

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Aims Breakthrough bleeding or even unwanted pregnancies have been reported in women during concomitant therapy with oral contraceptives and St John's wort extract. The aim of the present study was to investigate the effects of St John's wort extract on oral contraceptive therapy with respect to ovarian activity, breakthrough bleeding episodes and the pharmacokinetics of ethinylloestradiol and 3-ketodesogestrel.

Methods Eighteen healthy females were treated with a low-dose oral contraceptive (0.02 mg ethinylloestradiol, 0.150 mg desogestrel) alone (control cycle) or combined with 300 mg St John's wort extract given twice daily (cycle A) or three times daily (cycle B). Ovarian activity was assessed by measuring follicle maturation and serum oestradiol and progesterone concentrations. The number of breakthrough bleeding episodes and the pharmacokinetics of ethinylloestradiol and 3-ketodesogestrel were assessed under steady-state conditions.

Results During concomitant administration of low-dose oral contraceptive and St John's wort, there was no significant change in follicle maturation, serum oestradiol or progesterone concentrations when compared with oral contraceptive treatment alone. However, significantly more subjects reported intracyclic bleeding during cycles A (13/17 (77%), $P < 0.015$) and cycle B (15/17 (88%), $P < 0.001$) than with oral contraceptives alone (6/17 (35%)). The AUC(0,24 h) and C_{max} of ethinylloestradiol remained unchanged during all study cycles, whereas the AUC(0,24 h) and C_{max} of 3-ketodesogestrel decreased significantly from 31.2 ng ml⁻¹ h to 17.7 ng ml⁻¹ h (43.9%; 95% confidence interval (CI) -49.3, -38.5, $P = 0.001$) and from 3.6 ng ml⁻¹ to 3.0 ng ml⁻¹ (17.8%; CI -29.9, -5.7, $P = 0.005$), respectively, during cycle A and by 41.7% (CI -47.9, -35.6; $P = 0.001$) and by 22.8% (CI -31.2, -13.3; $P < 0.001$) during cycle B respectively, compared with the control cycle.

Conclusions There was no evidence of ovulation during low-dose oral contraceptive and St John's wort extract combination therapy, but intracyclic bleeding episodes increased. Bleeding irregularities may adversely effect compliance to oral contraceptives and together with St John's wort-induced decreases in serum 3-ketodesogestrel concentrations, enhance the risk of unintended pregnancies.

Keywords: cytochromes, drug effects, interaction, oral contraceptives, P-glycoprotein, pharmacokinetics, St John's wort

Introduction

Extracts of *Hypericum perforatum* L. (St John's wort) have gained in popularity as an alternative treatment for mild

to moderate depression. Clinical trials and systematic reviews indicate that St John's wort is more efficacious than placebo, and as effective as conventional antidepressants, for the short-term treatment of mild to moderate depressive disorders [1–8]. The overall incidence of adverse drug reactions associated with St John's wort is similar to that reported for placebo, and lower than that associated with conventional antidepressant agents [9]. A number of clinically significant pharmacokinetic and pharmacodynamic interactions have been identified

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between St John's wort and other conventional drugs, such as cyclosporin [10–12], digoxin [13], indinavir and amitriptyline [14].

In other studies, it has been shown that St John's wort extract can induce the *in vitro* [15, 16] and *in vivo* [17, 18] expression of the drug metabolizing cytochrome P450 enzyme CYP3A4 and the drug efflux pump P-glycoprotein. This induction, and the consequential enhanced elimination of the affected drugs, is thought to be the basis for many of the herb-drug interactions mentioned above.

There have been reports of intracyclic bleeding episodes and unwanted pregnancies among women taking both St John's wort and oral contraceptives [19–22]. Preliminary data from another clinical trials in healthy female volunteers showed a higher incidence of breakthrough bleeding episodes after co-administration of St John's wort extract and an oral contraceptive, but endogenous hormone concentrations were not affected. From these results, the authors concluded that St John's wort should be used with caution in women taking oral contraceptives [23]. However, in this study compliance to therapy was not monitored. In general, the composition of St John's wort extracts varies with their origin and mode of extraction.

The aim of this study was to evaluate in a tightly controlled manner the effect of a standardized St John's wort extract (LI160) on the pharmacokinetics and pharmacodynamics of a combined low-dose oral contraceptive (ethinylloestradiol 0.02 mg, desogestrel 0.150 mg). Efforts were made to ensure total compliance to therapy.

Methods

The study was performed in accordance with the principles of the Declaration of Helsinki on human rights in clinical research and the European Guidelines on Good Clinical Practice [24]. The protocol and the informed consent forms were approved by the local Ethics Committee (Ethische Kommission beider Basel) prior to the start of the study.

Selection of participants

Eligible subjects were women aged between 18 and 35 years with regular menstrual cycles. Women were not admitted to the study if they were pregnant or lactating, had used oral contraceptives during the last 3 months or had had injections of hormonal contraceptives within the last 6 months prior to the screening visit, needed any ongoing drug therapy, were smokers, had contraindications or allergies to the study drugs, suffered from significant cardiovascular, hepatic or renal disease, had a history of insulin dependent diabetes mellitus, uncon-

trolled thyroid disorder or had signs of alcohol or drug abuse. The presence of an ovulatory cycle was assessed before the study by endosonographic examination (follicular diameter ≥ 12 mm on days 10–12) and hormone measurements in the follicular and luteal phase of oestradiol (> 90 pmol L⁻¹) and progesterone (> 4.9 nmol L⁻¹), respectively. All subjects were required to use barrier methods of contraception during the trial. Subjects abstained from consuming grapefruit products for the entire study period. They also abstained from xanthine-containing foods and beverages from 12 h before until 24 h after the beginning of the in-patient study day, and from alcohol from 72 h before until 24 h after the study day. All patients gave their written informed consent to participate in the trial.

Trial structure

The study took place in the clinical research centre of the University Clinic of Basel, Switzerland between July 2002 and March 2003.

Participants received no medication during the pre-study cycle. During the first (control) cycle, between days 1–21 of their menstrual cycle, subjects received a daily dose of the oral contraceptive (ethinylloestradiol 0.02 mg; desogestrel 0.150 mg) at 08.00 h. During the next two cycles, the subjects received in addition St John's wort extract standardized to 0.3% hypericin extracted in methanol 80% v/v (= LI160). This extract was supplied as 300 mg film coated tablets (Jarsin®, Medichemie, Switzerland). Since St John's wort is given in a dose range between 500 mg to 900 mg daily, two doses were investigated. The timing of administration was as recommended by the manufacturer (09.00 h, 13.00 h and 18.00 h). In cycles A and B, subjects received 300 mg St John's wort two and three times daily, respectively. In the lower dose group, only the morning and evening doses were given. After the control cycle, eligible subjects, namely those who had ovulated in the prestudy cycle and whose ovulation was suppressed in the control cycle, were randomly assigned to study cycle A or cycle B, and then crossed over. To monitor compliance, both study drugs were provided in their own electronically monitored package (MEMS V, Medication Event Monitoring System, Aardex, Switzerland). Medication-taking events were retrieved from the TrackCap using the MEMS Communicator (Aardex, Switzerland) and analysed with a Power View software system (Aardex, Switzerland). Each MEMS opening was recorded and the dose was presumed to have been taken. Participants were carefully instructed on their dosing regimen and were told that compliance was monitored during the study to detect omitted doses that, in turn, could affect therapy efficacy. The subjects were reminded to dispense each pill imme-

diately before consumption. The MEMS boxes were returned for analysis on each study day. We selected reasonable but arbitrary compliance criteria, based on the general recommendation in package inserts of oral contraceptives, i.e. the interval between two oral contraceptive drug ingestions should not exceed 36 h. If a missed dose was followed by intracyclic bleeding between 2 and 7 days later, the subject was excluded from the analysis for that cycle.

Pharmacodynamic measurements

With respect to ovarian activity, the primary endpoints were the mean diameter of the largest follicle-like structure (FLS) within the ovaries, as detected by endosonography on cycle days 11 or 12, and oestradiol serum concentration, measured on the same days. Progesterone serum concentrations were determined on day 23 of every cycle.

Secondary outcome measures were the appearance of intracyclic bleeding episodes and the area under the concentration-time curve ($AUC(0,24\text{ h})$), the maximum serum concentration (C_{max}) of ethinyloestradiol and 3-ketodesogestrel. The data from the control cycle were compared with those from cycle A and cycle B.

During all three phases, the participants were asked to note any intracyclic bleeding episodes (spotting and/or bleeding) in a special diary. Intracyclic bleeding was scored as either 0 (no bleeding, no sanitary protection necessary), 1 (spotting, no or little sanitary protection necessary), 2 (bleeding less than usual, sanitary protection necessary), 3 (bleeding as strong as usual, sanitary protection necessary) or 4 (bleeding stronger than usual, sanitary protection necessary).

Intracyclic bleeding was defined as all vaginal bleeding occurring between cycle day 3 to cycle day 21.

Endosonographic measurements

Vaginal endosonography (using an ATL HDI 5000, transvaginal transducer 5–9 MHz; Philips Medical Systems, Bothell, WA, USA) was performed by an experienced gynaecological sonographer (MS). The thickness of the endometrial layer was recorded and the size and location of the ovaries were visualized. The mean diameter of the largest FLS within the ovaries was determined from three measurements in perpendicular dimensions. Additionally, the occurrence of cystic structures with diameters >25 mm was documented. In these cases, regular follow-up was performed.

Blood sampling

Subjects attended the Clinical Research Centre of the University Hospital of Basel on the morning of the study

day, usually on cycle day 10. Because of weekends, the study was done on days 11 or 12 for some subjects. The volunteers arrived after an overnight fast of at least 12 h. At 12.00 h and 17.00 h, standard meals were served. Blood samples were drawn through an indwelling cannula inserted into a forearm vein.

Whole blood (7.5 ml) was collected into tubes (S-Monovette; Sarstedt, Nümbrecht, Germany) and kept at room temperature for 30 min. After centrifugation at approximately 1580 g for 10 min, serum was separated and frozen at -20°C until analysis. After administration of the oral contraceptive, blood was collected at the following time points: 0 (predose), 0.75, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 11, 14 and 24 h after dosing.

Measurement of ethinyloestradiol and 3-ketodesogestrel

Desogestrel is a prodrug and is converted by cytochromes CYP2C9/CYP2C19 and hydroxysteroid dehydrogenase rapidly and completely [25] to the active metabolite 3-ketodesogestrel [26]. Therefore, 3-ketodesogestrel and not desogestrel was measured in serum.

Determination of serum ethinyloestradiol and 3-ketodesogestrel was performed using a liquid chromatography-mass spectrometry assay. The assays were carried out by Analytisches Zentrum Biopharm GmbH Berlin, Bitterfelder Strasse 19, D-12681 Berlin, Germany (a commercial analytical laboratory) from whom further details can be obtained. In brief, 3-ketodesogestrel and the internal standard were extracted from human serum and the organic layer was removed and evaporated to dryness with nitrogen. Chromatography was performed on a reverse phased column and the eluents were detected with an electro spray interface in positive mode. The lower limits of quantification of ethinyloestradiol and 3-ketodesogestrel were 4 pg l^{-1} and 0.05 ng ml^{-1} , respectively. The intra-assay variability showed an imprecision of between 7.8% (at 4 pg ml^{-1}) and 3.7% (at 120 pg ml^{-1}) and between 5.5% (at 0.20 ng ml^{-1}) and 2.8% (at 17.50 ng ml^{-1}) for ethinyloestradiol and 3-ketodesogestrel, respectively ($n = 6$). The interassay variability showed an imprecision between 4.9% (at 10 pg ml^{-1}) and 2.6% (at 100 pg ml^{-1}) and between 10.2% (at 0.20 ng ml^{-1}) and 4.5% (at 17.50 ng ml^{-1}) for ethinyloestradiol and 3-ketodesogestrel, respectively ($n = 6$). This method was validated over the range 4 pg ml^{-1} to 120 pg ml^{-1} for ethinyloestradiol and 0.05 ng ml^{-1} to 20 ng ml^{-1} for 3-ketodesogestrel.

Serum peak concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained from raw data. The steady-state pharmacokinetics of ethinyloestradiol and 3-ketodesogestrel were characterized by the area under the serum concentration-time curve within one dosing interval ($AUC(0,24\text{ h})$). The latter and terminal half-life ($t_{1/2}$)

were estimated by nonlinear regression analysis using iteratively reweighted least squares (WinNonlin, version 4.0; Pharsight Corp., Mountain View, CA [27]), assuming multiple dosing and a two-compartment model with first order absorption, disposition and elimination kinetics.

Oestradiol and progesterone measurements

Serum oestradiol concentration was measured on day 11 or 12, and that for progesterone on day 23 of each menstrual cycle by the Hormone Laboratory of the University Clinic of Basel using commercial ECLIA kits (Estradiol II® and progesterone II®, Elecsys, Roche Diagnostics, Switzerland). The limits of determination of these methods were 44 pmol l⁻¹ and 0.48 nmol l⁻¹ for Estradiol II and Progesterone II, respectively. The maximum interassay coefficient of variation was 6.2% for the Estradiol II assay and 4.8% for the Progesterone II assay.

Statistical analysis

The incidence of breakthrough bleeding was compared using Pearson's Chi-square test or Fisher's exact test. Continuous variables were compared by general linear model analysis. When statistical significance was found, pair-wise comparisons were performed using Tukey's multicomparison test. For data that were not normally distributed, nonparametric comparison by the Wilcoxon signed ranks test was performed. *P* values were adjusted for multiple comparisons by Bonferroni's correction. All tests were two-sided and the level of significance was *P* = 0.05. Statistical analysis was performed using SPSS software (version 11.0).

Adverse events

All unfavourable changes in the condition of the subjects were defined as adverse events and were recorded on every clinic day and on the day of the last follow-up examination.

Results

Participants were recruited from July 2002 to December 2002. Subjects visited the clinic two or three times per cycle during four consecutive cycles. The age of the subjects ranged from 20 to 35 years (median 26 years). The subjects had body mass indices between 17.8 and 25.5 kg m⁻² (median 21.5 kg m⁻²). Two subjects were included who showed follicular maturation (follicle diameter = 18.5 mm and 14 mm, respectively) and low concentrations of progesterone, suggesting luteal insufficiency.

Based on data retrieved from the MEMSV Caps, seven subjects missed one and one subject three oral contraceptive doses. According to our criteria for acceptable compliance, none of the subjects was excluded from analysis.

On day 11 or 12 of the prestudy cycle, oestradiol concentrations in all the subjects were above 90 pmol l⁻¹ (Table 1), the lower limit of the normal range (LLN) for the follicular phase of the menstrual cycle.

Endosonographic examination showed FLSs having diameters >12 mm in all 17 subjects. On day 23, progesterone concentrations were within the normal range for the luteal phase of the menstrual cycle (4.9–72.0 nmol l⁻¹) in 15 subjects, whereas in the other two subjects, the progesterone concentration was below 4.9 nmol l⁻¹.

Table 1 The effect of St John's wort given twice daily or three times daily on the pharmacodynamics of oral contraceptive therapy.

	Pre-study cycle no medication	Control cycle oral contraceptive	Cycle A Oral contraceptive + St John's wort extract 300 mg twice daily	Cycle B Oral contraceptive + St John's wort extract 300 mg three times daily
<i>Primary outcome measures</i>				
Volunteers with follicle-like structure >12 mm	17	1	3	3
Oestradiol concentration (pmol l ⁻¹)	653 (411.4, 893.8)	46 ^a (35.2, 57.4)	237 (-17.1, 490.4)	151 ^b (5.0, 297.3)
Progesterone concentration (nmol l ⁻¹)	29.9 (17.8, 35.0)	1.3 ^a (1.0, 1.5)	1.3 (1.0, 1.5)	1.4 (0.9, 1.7)
<i>Secondary outcome measures</i>				
Intracyclic bleeding episodes	NM	6/17	13/17 ^c	15/17 ^d
Endometrial thickness (mm)]	6.7 (5.5, 8.0)	4.7 (3.3, 6.0)	4.2 ^e (3.2, 5.4)	4.7 (3.6, 5.8)
Cystic structures present	2	2	4	3

NM = not monitored; data represent means (95% confidence interval) ^asignificantly different from prestudy cycle (*P* < 0.001); ^bsignificantly different from control cycle (*P* = 0.011); ^cand ^dsignificantly different from control cycle (*P* = 0.037 and *P* = 0.004, respectively); ^esignificantly different from prestudy cycle (*P* = 0.011).

In two subjects, pre-existing cystic structures were observed. These cysts were monitored and their size remained constant throughout the entire study period.

Oestradiol concentrations were significantly decreased in the control cycle compared with the prestudy cycle ($P < 0.001$) to values below 90 pmol l^{-1} in all but one woman. The ethinyloestradiol concentration in this subject was at 99 pmol l^{-1} , but no FLS was observed.

Endosonographic examination on the same day showed no follicular growth in 16 out of the 17 subjects. In one subject, in whom the oestradiol serum concentration was suppressed, an FLS of 16.3 mm mean diameter was detected. Progesterone concentrations on day 23 were below 4.9 nmol l^{-1} (LLN) in all subjects. This decrease from the prestudy cycle was statistically significant ($P < 0.001$). No subjects developed new cystic structures in this cycle.

When compared with the prestudy cycle, serum concentrations of oestradiol and progesterone on day 11 or 12 were both significantly decreased after oral contraceptive treatment ($P < 0.001$). No statistically significant differences in hormone concentrations were observed between the three cycles of contraceptive treatment.

The two subjects who showed low progesterone concentrations in the prestudy cycle had sufficient ovarian suppression during the control cycle.

In cycle A on day 11 or 12, the oestradiol concentration was above 90 pmol l^{-1} in four subjects. In the others oestradiol concentrations were below this value. Concentrations showed no significant difference from those of the control cycle. In 14 out of the 17 women, no FLS was observed by endosonographic examination. Two subjects had FLSs of 21.6 mm and 21.3 mm diameter, which correlated with their elevated oestradiol serum concentrations. One subject with a suppressed oestradiol concentration had an FLS of 12.3 mm diameter. Progesterone concentrations on day 23 were below 4.9 nmol l^{-1} in all subjects and these values were not significantly different from those in the control cycle.

In cycle A two additional women developed cystic structures (mean diameter 25.3 mm and 25.5 mm, respectively).

In 5 of 17 women, oestradiol production was not suppressed (concentrations above 90 pmol l^{-1}) during cycle B. Concentrations were statistically different from those in the control cycle ($P = 0.011$). Three subjects had FLSs of 20 mm, 17.6 mm and 16.3 mm diameter and their oestradiol concentrations were above the LLN. The progesterone concentration on day 23 was suppressed in all women and values were not significantly different from those in the control cycle. One additional subject showed a cystic structure in this cycle.

The results of intracyclic bleeding episodes are shown in Table 1. During cycle A and cycle B significantly more subjects reported intracyclic bleeding episodes compared with the control cycle (*vs* cycle A $P < 0.015$ and *vs* cycle B $P < 0.001$).

The pharmacokinetic parameters for ethinyloestradiol and 3-ketodesogestrel are listed in Tables 2 and 3. The serum concentration *vs* time profiles are shown in Figure 2. When compared with the control cycle, the pharmacokinetics of ethinyloestradiol did not change significantly during all cycles. However, the AUC(0,24 h) of 3-ketodesogestrel decreased significantly during cycle A ($P < 0.001$) and cycle B ($P < 0.001$). The C_{max} of 3-ketodesogestrel also decreased significantly during cycle A ($P < 0.005$) and cycle B ($P < 0.001$) when compared with the control cycle – no statistical significance was seen in the pharmacokinetic parameters between cycle A and cycle B. The half-life of 3-ketodesogestrel also decreased significantly during cycle A ($P = 0.003$) and cycle B (0.009) when compared with the control cycle.

All recorded adverse events were of mild to moderate severity and resolved spontaneously. In the control cycle three subjects experienced mild gastrointestinal symptoms, five had headaches, one had fatigue, and one had mood changes. In one subject, symptoms of pre-existing acne

Table 2 The effect of St John's wort given twice daily or three times daily on the pharmacokinetics of 3-ketodesogestrel.

	Cycle A			Cycle B	
	Control cycle oral contraceptive	Oral contraceptive + St John's wort extract 300 mg twice daily	% difference vs control (95% confidence interval; P value)	Oral contraceptive + St John's wort extract 300 mg three times daily	% difference vs control (95% confidence interval; P value)
C_{max} (ng ml ⁻¹)	3.6 ± 1.3	3.0 ± 0.9	-17.8 (-29.9, -5.7; $P = 0.005$)	2.9 ± 1.0	-22.8 (-31.2, -13.3; $P < 0.001$)
t_{max} (h)*	1.5 (0.75–4.0)	1.5 (0.75–3.0)	5.6 (-35.8, 47.0; NS)	1.5 (0.75–1.75)	-15.1 (-33.1, 3.0; NS)
$t_{1/2}$ (h)	25.8 ± 7.8	15.9 ± 10.1	-32.8 (-55.8, -10.0; $P = 0.003$)	16.5 ± 7.4	-30.0 (-50.9, -9.0; $P = 0.009$)
AUC (ng ml ⁻¹ h)	31.2 ± 13.3	17.7 ± 6.4	-43.9 (-49.3, -38.5; $P = 0.001$)	18.4 ± 8.4	-41.7 (-47.9, -35.6; $P = 0.001$)

*Median (range); NS not significant.

Table 3 The effect of St John's wort given twice daily or three times daily on the pharmacokinetics of ethinyloestradiol.

	Control cycle oral contraceptive	Cycle A Oral contraceptive + St John's wort extract 300 mg twice daily	% difference vs control (95% confidence interval; P value)	Cycle B Oral contraceptive + St John's wort extract 300 mg three times daily	% difference vs control (95% confidence interval; P value)
C_{max} (pg ml ⁻¹)	53.7 ± 15.4	53.2 ± 12.3	0.3 (-11.1, 11.7; NS)	55.6 ± 13.9	3.2 (-7.0, 13.5; NS)
t_{max} (h)*	1.5 (0.75–2.25)	1.5 (0.75–2.0)	9.8 (-21.9, 41.6; NS)	1.5 (0.75–2.0)	-3.2 (-31.0, 24.7; NS)
$t_{1/2}$ (h)	45.5 ± 87.1	23.4 ± 13.5	66.1 (-87.1, 411.2; NS)	36.2 ± 64.8	162.1 (-87.1, 411.2; NS)
AUC (pg ml ⁻¹ h)	436.6 ± 185.4	393.9 ± 124.8	-5.0 (-16.4, 6.6; NS)	437.3 ± 137.2	4.8 (-7.6, 17.2; NS)

*Median (range); NS not significant.

Figure 1 Study design and number of subjects at each stage.

became aggravated. In cycle A two subjects experienced gastrointestinal discomfort, two had headaches, one had fatigue, one had pruritus and one complained of weight gain (2 kg). In cycle B two subjects experienced gastrointestinal disorders, three had headaches, one had fatigue, one had a phototoxic skin reaction and one had dizziness.

Discussion

The present study represents the first controlled trial investigating the potential influence of St John's wort LI160 on oral contraceptive therapy.

The results of this study showed that during all study cycles, sporadic FLSs were observed, which were partly accompanied by elevated serum oestradiol concentrations in the follicular phase. However, no increase in progesterone concentration during the luteal phase was detected, suggesting that no ovulation had occurred. The AUC(0,24 h) of 3-ketodesogestrel was decreased significantly during comedication with the oral contraceptive and St John's wort extract LI160 compared with the control cycle, whereas that of ethinyloestradiol remained unchanged.

Intracyclic bleeding episodes are a common problem among oral contraceptive users, particularly in the first

Figure 2 Mean $\pm$ SEM serum concentration vs time profiles for ethinyloestradiol (A) and 3-ketodesogestrel (B) after administration of low-dose oral contraceptive alone (○) or in combination with twice daily (BD) (●) or three times daily (TID) (■) 300 mg St John's wort (SJW).

treatment cycle. In the present study, the proportion of subjects with intracyclic bleeding episodes during the control cycle (6 out of 17 = 35%) is comparable with observations from other studies during the first month of oral contraceptive treatment, (43% in [28] and 56% in [29]). Usually, the incidence of intracyclic bleeding episodes decreases rapidly after the first treatment cycle [28, 29]. However in our study, the incidence increased significantly from 35% to 76% and 88% during study cycles A and B, respectively. This observation indicates a higher risk of intracyclic bleeding episodes during concomitant administration of low dose oral contraceptives (ethinyloestradiol 0.02 mg + desogestrel 0.150 mg) and St John's wort extract LI160.

Our pharmacokinetic findings conflict with previous observations of a significant decrease in ethinyloestradiol concentrations during concomitant administration of oral

contraceptives and other known CYP3A4 inducers [30, 31]. This decrease may be the result of direct induction of the oestradiol conjugation [32], rather than induction of its CYP3A4-mediated hydroxylation [33], the former being the major pathway of its metabolism. We assume that the induction of CYP3A4 and P-glycoprotein was insufficient to influence the pharmacokinetics of ethinyloestradiol.

In contrast to the oestradiol data, we observed a decrease in the AUC(0,24 h) of ketodesogestrel during treatment with St John's wort. Inhibition of CYP2C9/CYP2C19, which would lead to decreased formation of 3-ketodesogestrel from the prodrug desogestrel, and/or induction of CYP3A4 and resulting enhanced metabolism of 3-ketodesogestrel may be the basis of the findings. The St John's wort constituents I3,II8-biapiogenin and hyperforin are potent inhibitors of CYP2C9 *in vitro* [34].

Preliminary results of a study by Gorski [23] are in agreement with our findings. They showed no effect of St John's wort on the pharmacokinetics of ethinyloestradiol, although the clearance midazolam was enhanced, suggesting CYP3A4 induction. An increased rate of breakthrough bleeding episodes was also demonstrated and an elevated clearance of the gestagenic component of an oral contraceptive during concurrent administration of St John's wort extract was observed.

We found no evidence of ovulation during concomitant administration of low-dose oral contraceptives containing 0.02 mg ethinyloestradiol and 0.150 mg desogestrel, and St John's wort extract LI160. Additionally, the endometrial thickness was decreased in most participants during oral contraceptive treatment. Thus, even if ovulation had occurred, it is unlikely that a fertilized egg would be able to implant in the endometrium. However, the reported bleeding irregularities may have a negative effect on compliance to oral contraception and, together with the decrease in serum concentrations of 3-ketodesogestrel may increase the risk of unintended pregnancies.

The composition of St John's wort extracts may vary widely among the different brands [35]. Therefore, data from different brands or extracts may not be directly comparable.

A clear limitation of the present study is the small sample size. To confirm our observations, a large clinical trial with a longer follow-up period is required.

We have studied the interaction of St John's wort extract with only one preparation of oral contraceptive, which in Switzerland is the first choice for young women without any risk factors for thrombosis. Therefore, further interaction studies with other oral contraceptives consisting of different combinations of hormones should be performed.

In summary, St John's wort extracts should be used with caution in women taking oral contraceptives.

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