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Improving cycle control in progestogen-only contraceptive pill users by intermittent treatment with a new anti-progestogen

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BACKGROUND: The safety and efficacy of the anti-progestogen Org 31710 in improving cycle control in healthy women using the desogestrel progestogen-only pill was investigated in this randomized, double-blind, placebo-controlled study. METHODS: A total of 103 women using the 75 μg desogestrel progestogen-only pill daily also received either 150 mg Org 31710 or placebo once every 28 days, starting on day 1, for a duration of 4–7 treatment cycles. RESULTS: The percentage of women with bleeding or spotting (B/S) every day in the placebo group was on average 30% during the whole treatment period and no days without reported B/S occurred. In contrast, a cyclic pattern was observed for the Org 31710 group; a peak incidence of B/S was observed on day 3 or 4 of each cycle, followed by a sharp decrease on cycle days 9–15. Compared with controls, less subjects in the Org 31710 group reported irregular, frequent or prolonged bleeding. These differences were clearly observed in the initial cycles, but were somewhat less pronounced during the later cycles of the treatment period. A relatively high incidence of B/S episodes starting in the second section of the cycle was also observed. CONCLUSION: The addition of Org 31710 once a month improved cycle control in women using daily treatment with 75 μg desogestrel.

Key words: anti-progestogens/cycle control/progestogen-only pill

Introduction

Poor cycle control (Broome and Fotherby, 1990) is the most troublesome side-effect of progestogen-only oral contraception and contraceptive implants. Menstrual disturbance is by far the most common reason for discontinuation of these methods (Belsey, 1988; Glasier, 2002). However, the avoidance of an estrogen component has many advantages, in particular for those women at higher risk for venous thrombosis (Alving and Comp, 1992). In addition, for breast-feeding women or those with complaints associated with the use of combined oral contraceptives, a progestogen-only pill (POP) may be the preparation of first choice.

Daily administration of 75 μg desogestrel (Cerazette; Organon, Oss, The Netherlands) has been shown to be a safe and reliable contraceptive method with an efficacy comparable with low-dose combined oral contraceptives (Collaborative Study Group on the Desogestrel-Containing Progestogen-Only Pill, 1998). However, irregular bleeding remains a major clinical problem and satisfaction and long-term compliance may improve if these bleeding problems can be reduced.

Org 31710 is a synthetic 19-nor steroid possessing strong anti-progestogenic and weak androgenic/anti-androgenic activity. It has less anti-glucocorticoid activity than, for example, mifepristone. Org 31710 did not show any agonistic progestogenic activity in the Clauberg test, even in doses 4- to 8-fold higher than the progestogen norethisterone (Kloosterboer *et al*., 1988, 1994). If administered during the mid-luteal phase of the menstrual cycle at sufficiently high dosages, Org 31710 will, as with other anti-progestogens, induce bleeding and shedding of the endometrium (Kloosterboer *et al*., 1988; Swahn *et al*., 1988). Org 31710 appeared to be more potent than mifepristone for induction of menses in monkeys, since the monkeys started to bleed 1–2 days earlier than following mifepristone (Kloosterboer *et al*., 1988). In an earlier study it was shown that a single dose of 150 mg Org 31710 was the lowest dose that would induce a bleeding within 24–28 h after ingestion (data on file, Organon).

It has been demonstrated that the addition of an anti-progesterone to progesterone-only contraception reduces the incidence of unscheduled bleeding in monkeys, and that the

supplementary administration of an anti-progestogen to a POP regimen may improve cycle control, possibly as a result of blocking progesterone receptors in the endometrium (Hodgen *et al*., 1994; Heikinheimo *et al*., 1996). Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel (Norplant) (Cheng *et al.*, 2000). The improvement in bleeding pattern could be either by a direct effect of anti-progestin on the endometrium, as suggested by the effect on steroid receptor expression, or by inducing ovulation (Glasier *et al.*, 2002). An increased ovulation rate may jeopardise contraception; however, no pregnancies occurred when mifepristone was administered to Norplant users (Cheng *et al*., 2000)

This study was designed to determine if the addition of the new anti-progestogen, Org 31710, at regular 28 day intervals to a POP regimen of 75 μg desogestrel daily would improve cycle control in women using this form of contraception. As part of this study the effect on endocrine parameters was studied. These data have been published separately (Van Heusden *et al*., 2000)

Subjects and methods

Study design and medication

The study was performed in six centres in Edinburgh, Hull, Paris, Rotterdam, Santiago and Stockholm with ethical approval obtained from the supervisory body of each centre. The study was designed as a randomized, double-blind, placebo-controlled study with a duration of minimally four and maximally seven consecutive treatment periods of 28 days. This range in the treatment period was related to a fixed clinical completion date.

Eligible subjects were given a continuous POP regimen consisting of 75 μg desogestrel daily and then randomized by computer code to receive in addition either a single dose of 150 mg (three tablets containing 50 mg each) of the anti-progestogen, Org 31710, or visually indistinguishable placebo tablets once every 28 days in a double-blind fashion. The first desogestrel and Org 31710/placebo tablets were both given on the first day of menstruation and therapy continued for between 16 and 28 weeks (four to seven cycles of 28 days). Therefore, Org 31710/placebo tablets were given on a maximum of seven occasions (mean 5.8) on days 1, 28, 56, 84, 112, 140 and 168.

Subjects

Women were eligible for participation in the study if they were healthy, 18–45 years old, had normal menstrual cycles with a mean length of 24–35 days (with an intra-individual variation of ±3 days) and a body mass index between 18 and 29 kg/m^2. The menstrual history was asked for in detail at the screening visit. The volunteers were advised to use barrier methods of contraception during the whole treatment period unless they had undergone sterilization. Women who had taken recent steroid contraceptive therapy (orally 1 month, parental 6 months), who were lactating, had abnormal haematological or biochemical values at screening, hypertension, PAP smear class III or higher and undiagnosed vaginal bleeding were excluded from participation.

Vaginal bleeding pattern

The occurrence of vaginal bleeding was documented on a daily basis on a diary card by the women themselves. Vaginal bleeding was indicated as spotting (requiring maximally one pad/tampon per day) or bleeding (requiring two or more pads/tampons per day). Analysis of bleeding patterns was performed, excluding women with major protocol violations, as a per protocol group, by cycle and reference period (RP). Major protocol violations were defined as serious non-compliance with the study drugs, missing data on the diary cards or deviations from inclusion/exclusion criteria (i.e. injectable hormonal contraception within 6 months or other hormonal contraception within 4 months prior to the start of the study).

For the cycle analysis, treatment cycles were defined as the days between Org 31710/placebo intake. Based on the hypothesis that Org 31710 induces a regular bleeding pattern, each cycle was subdivided in two sections: a first section of the first 7 days (day 1–7: period of expected bleeding) and the other section (day 8–28, when bleeding was not expected). The percentage of women with bleeding or spotting (B/S), the number of B/S days, and the occurrence of B/S episodes starting in a certain period of the cycle were calculated per woman, per cycle and per RP.

Reference period analysis was performed as described by the World Health Organization using 90 day RPs (Rodriguez *et al*., 1976; Belsey *et al*., 1986; Belsey and Farley, 1988). Bleeding was categorized in five bleeding pattern indices (amenorrhoea, infrequent bleeding, frequent bleeding, prolonged bleeding and irregular bleeding) following standard World Health Organization definitions (Belsey *et al*., 1986), with a modification for infrequent bleeding.

Amenorrhoea was defined as no B/S throughout a RP; infrequent bleeding was defined as less than three B/S episodes starting within an RP excluding amenorrhoea; frequent bleeding was defined as more than five B/S episodes starting within a RP; prolonged bleeding was defined as at least one B/S episode starting within a RP and lasting >14 days, and irregular bleeding was defined as a range of the length of bleeding-free intervals <17 days. Bleeding patterns were analysed for a shifted RP which was defined as a period of 90 days, starting 28 days after the first day of treatment, i.e. day 29–118. This period was chosen to exclude the bleeding episode at the start of the study, noted for all women since the study started on the first day of menses. This shifted RP was considered more useful in comparing bleeding patterns between treatment groups.

Safety

Evaluation of safety was performed at screening, 1–3 days after each Org 31710/placebo intake and 1–3 days after the last desogestrel POP intake. Safety evaluation included assessment of haematology parameters, biochemistry and enzymes, urinalysis and vital signs. The numbers and nature of adverse events were recorded throughout the study period. For safety variables, only descriptive statistics were used.

Data analysis

For the cycle analysis, treatment cycles were defined as the treatment period starting on the day of Org 31710/placebo intake and ending on the day before the next Org 31710/placebo intake. These cycles were subdivided into the first period of 7 days ('expected bleeding') and the remaining part of the cycle ('non-expected bleeding').

Variables (such as mean number of B/S days, occurrence of B/S episode) were calculated per subject, per cycle and per period. Treatment group comparison was performed using the Wilcoxon test stratified for centre. In addition, the variables were summarized for each subject across cycles 2–7. These intra-subject variables are presented and analysed using the Wilcoxon test, stratified for centre.

The RP analysis as described by the World Health Organization using 90 day RPs was performed with inter-group comparison using the Wilcoxon test, stratified for centre. Differences between the treatment groups in the number of subjects who discontinued the study were analysed using the Cochran–Mantel–Haenszel test.

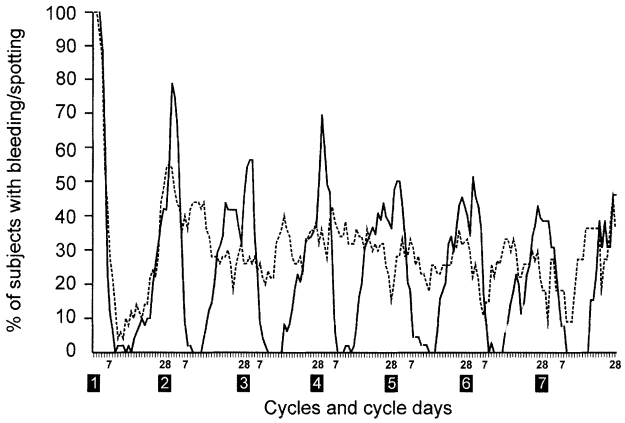

Figure 1. Percentage of subjects with bleeding/spotting in both treatment groups. Per protocol group. Dotted line: 75 μg desogestrel POP alone. Solid line: 75 μg desogestrel POP + 150 mg Org 31710 once every 28 days.

Table I. Demographic data and menstrual bleeding characteristics [mean (range)] at baseline for all treated subjects

	75 μg DSG + Org 31710 (n = 52)	75 μg DSG + placebo (n = 51)
Age (years)	31.6 (20–44)	32.8 (22–45)
Height (cm)	164.4 (145.0–184.0)	164.6 (148.0–179.0)
Weight (kg)	63.8 (49.0–85.0)	63.6 (48.0–93.0)
Body mass index (kg/m^2)	23.6 (19.0–29.0)	23.5 (18.0–29.0)
Cycle length (days)	28.3 (24–35)	28.6 (25–35)
Usual duration of flow (days)	4.6 (3–8)	4.6 (2–8)

DSG = desogestrel progestogen-only pill.

For safety parameters, descriptive statistics were used. Results were considered statistically significant if $P < 0.05$.

Results

Subjects

A total of 103 women was randomized, 52 to the Org 31710 group and 51 to the placebo group. The per protocol group consisted of 102 women (51 in each group). Three women (5.8%) in the Org 31710 group and nine (17.6%) in the placebo group discontinued the study (P = 0.048, Cochran–Mantel–Haenszel test). The most frequently reported reasons for discontinuation were occurrence of unacceptable adverse events (three in the Org 31710 group and four in the placebo group), 'not willing to or cannot co-operate further' (three in the placebo group) and bleeding irregularities (two in the placebo group). All women dropping out because of adverse effects did so after at least two treatment cycles. The mean treatment duration with 75 μg desogestrel POP was 161 days for the Org 31710 group and 152 days for the placebo group. Demographic data and menstrual bleeding characteristics at baseline were comparable for both groups (Table I).

Bleeding pattern

The percentage of women who reported B/S is graphically presented in Figure 1. Since all women started treatment on the first day of menses, a 100% B/S incidence was observed for both treatment groups on the first days of cycle 1. From cycle 2 onwards, the percentage of women with B/S per day in the placebo group was on average 30% during the whole treatment period and no days without reported B/S occurred. In contrast, a cyclic pattern was observed for the Org 31710 group; a peak incidence of B/S was observed on day 3 or 4 of each cycle, followed by a sharp decrease to almost 0% of the women on cycle days 9–15, and again a gradual increase in B/S incidence up to the next Org 31710 intake (Table II). When only bleeding (no spotting) was taken into account, incidences were lower but followed the same pattern.

In the placebo group, two women (3.9%) as compared with none in the Org 31710 group discontinued because of an unacceptable bleeding pattern.

Cycle analysis

The median percentages of days with recorded B/S per cycle (and period of the cycle) are presented in Table II for cycle 1, 3, 6 and for cycles 2–7 combined. B/S on cycle days 1–7 (period of expected bleeding) was more frequent in the Org 31710 group compared with the placebo group. In the second period of the cycle (days 8–28), significantly less B/S was reported by the Org 31710 group compared with placebo in the first three cycles, whereas in cycles 4–7 no clear difference was observed. Similarly, more women reporting B/S episodes starting in, or with a part in cycle days 1–7 were observed in the Org 31710 group compared with the placebo group (Table III), except for cycle 7. The percentage of women reporting B/S episodes starting in the second period of a cycle (days 8–28) was comparable for both treatment groups.

Reference period analysis

The RP analysis divides the bleeding information into consecutive periods of 90 days (Table IV). The treatment duration allows only the evaluation of the first RP (day 1–90) and the RP starting 28 days after the first treatment administration (i.e. day 29–118, presented as Ref. per #). Except for the number of B/S episodes, statistically significant differences between the two treatment groups were present for all the parameters, i.e. the number of B/S days, the mean length of B/S episodes (days) and the range of the length of bleeding-free intervals (days) were less for the Org 31710 group than for the placebo group. Although no significance was shown (P = 0.31 and 0.42), the median number of BS episodes was smaller within the Org 31710 group than in the placebo group in both RPs. The range of the length of bleeding intervals is a measure for the variation in bleeding patterns. Amenorrhoea did not occur.

Safety

A total of 65% of the subjects in the Org 31710 group and 59% in the placebo group reported at least one adverse event, the most frequent of which were headache, emotional lability, acne and breast pain. Differences in incidence occurred mainly for acne (3.8% for Org 31710 and 11.8% for the placebo group) and breast pain (15.4 versus 5.9%). Three subjects (5.8%) in the Org 31710 group, two classified as possibly related [headache (n = 1) and ovarian cyst (n = 1)] and one unlikely to be related to the treatment (cystitis), discontinued

Table II. Percentage of days with recorded bleeding and/or spotting (means)

Cycle	75 μg DSG + Org 31710			75 μg DSG + placebo		
	n	Cycle day 1–7	Cycle day 8–28	*n*	Cycle day 1–7	Cycle day 8–28
1	50	70.0	11.5[a]	50	72.3	17.2
3	48	42.9[b]	13.0[b]	50	27.1	29.5
6	35	38.4	15.9	27	22.8	26.0
2–7 comb.[d]	51	45.0[c]	17.4[c]	50	31.2	29.5

[a]$P \leqslant 0.05$; [b]$P \leqslant 0.01$; [c]$P < 0.001$ (comparison between treatment groups).
[d]Within-subject summarization over cycles 2–7.
Note: Cycles with major protocol violations were excluded from analysis.

Table III. Percentage of subjects with a bleeding/spotting (B/S) episode either starting in, or being part of, the cycle periods

Cycle	75 μg DSG + Org 31710				75 μg DSG + Placebo			
	n	B/S episode starting day 1–7	B/S episode part of day 1–7	B/S episode starting day 8–20	*n*	B/S episode starting day 1–7	B/S episode part of day 1–7	B/S episode starting day 8–28
1	50	100.0	100.0	52.0	50	100.0	100.0	62.0
3	48	52.1[b]	79.2[b]	58.3	50	26.0	48.0	72.0
6	35	34.3[a]	71.4[a]	77.1	27	11.1	40.7	59.3
2–7 comb.[c]	51	49.9[b]	78.4[b]	69.8	50	28.8	55.0	62.5

[a]$P \leqslant 0.05$; [b]$P < 0.001$ (comparison between treatment groups).
[c]Within-subject summarization over cycles 2–7.
Note: Cycles with major violations were excluded from analysis.

Table IV. Per protocol group, reference period analysis

Variable	Ref. period	75 μg DSG + Org 31710		75 μg DSG + placebo		*P*-value
		n	Median	*n*	Median	
No. of B/S days	1	44	21.5	46	28.0	0.023
	#	41	23.0	38	31.0	0.007
No. of B/S episodes	1	44	3.0	46	4.0	0.31
	#	41	4.0	38	4.5	0.42
Mean length of B/S	1	44	5.0	46	6.5	0.031
episodes (days)	#	41	5.0	38	6.7	0.016
Range length of	1	44	14.5	46	22.5	0.001
bleeding-free interval (days)	#	41	19.0	38	22.5	0.023

Note: Reference period 1 is from day 1–90; reference period # is from day 29–118.
B/S = bleeding/spotting episode.

due to unacceptable adverse events. This was also the case for four subjects (7.8%) in the placebo group, all of which were classified as probably related to treatment. These were emotional lability ($n = 1$), decreased libido ($n = 1$), increased weight ($n = 1$) and hypertrichosis ($n = 1$). One of the women in the Org 31710 group had a serious adverse event (appendectomy).

No clinically relevant changes from baseline were observed for any of the measured haematology, biochemistry and urinalysis parameters. A difference between the Org 31710 and placebo groups was observed for body weight: 10 women in the Org 31710 group (19.2%) had an increase ($n = 6$) or decrease ($n = 4$) in body weight of >7% compared with one woman (2.0%) in the placebo group.

Discussion

The most common side-effect and reason for discontinuation with progestogen-only contraception is bleeding disturbance (Broome and Fotherby, 1990). This may be caused by a direct effect of the progestogen on the endometrium and/or disturbed ovarian hormone production (Kim Björklund *et al*., 1992; Lau *et al.*, 1996; Faundes *et al.*, 1998; Glasier *et al.*, 2002). The present study represents the first pilot study investigating the effects of an anti-progestogen, Org 31710, on an oral progestogen-only regimen. A dose of 150 mg Org 31710 was selected based on its menses-inducing effect when administered during the mid-luteal phase in women with a regular menstrual cycle as observed in earlier studies. A single oral dose of 150 mg Org 31710 induced vaginal bleeding within 48 h,

whereas a dose of 75 mg Org 31710 demonstrated only a moderate anti-progestational effect, as shown by the induction of menses in only two out of six women (Kloosterboer *et al*., 1994). The strength of the study is that it is a randomized, placebo-controlled, multicentre trial which includes a significant number of subjects who were carefully supervised. A drawback is that according to the study design, a majority of women were not followed for 7 months but for a mean of 5.8 months. Therefore, a lower number of subjects were included in the analysis for the last 3 months. However despite few subjects during this part of the study, all data were analysed and reported to give some information on prolonged treatment.

In the present study, we showed that the bleeding pattern of women using the 75 μg desogestrel POP was significantly improved by the administration of 150 mg Org 31710 once every 28 days. A cyclic bleeding pattern was observed in the Org 31710 treatment group with a bleeding-free period in all subjects and in all treatment cycles following the addition of Org 31710. The incidence of B/S was significantly higher during day 1–7 (period of expected bleeding) in the Org 31710 group compared with the control group, accompanied by a significantly lower incidence of B/S in the remaining part of the cycle (day 8–28, period of unscheduled bleeding). These differences were clearly observed in the initial treatment cycles, but were somewhat less pronounced during the later cycles of the treatment period. Thus, cycle control in the Org 31710 group was not yet optimal, as also evidenced by the relatively high incidence of B/S episodes starting in the second period of the cycle. The seemingly better cycle control in the initial treatment cycles could reflect a decrease in effect over time, but such a trend needs to be confirmed in larger studies.

A similar improvement in bleeding pattern has been reported (Cheng *et al*., 2000) in women using a levonorgestrel-releasing subdermal contraceptive implant in whom 50 mg mifepristone was given once every 4 weeks.

The mechanism behind the improvement in bleeding pattern is not known. As part of this study, the effect of the treatment on pituitary–ovarian activity was also studied (Van Heusden *et al.*, 2000). The results further support the previously published finding that 75 μg desogestrel daily in contrast to 30 μg levonorgestrel daily (Collaborative Study Group on the Desogestrel-Containing Progestogen-Only Pill, 1998) completely inhibited ovulation. When Org 31710 was added to the desogestrel POP treatment, increased serum progesterone level (>10 nmol/l), indicating ovulation, was found in 29% of the subjects. However, changes in serum FSH, estradiol and progesterone levels could not predict ovulation and none of the measured parameters could be related to the observed bleeding pattern. Endometrial thickness as assessed by transvaginal sonography was also greater on cycle days 7–13 and 19 in the Org 31710-treated group (Van Heusden *et al*., 2000).

If sufficient doses of different anti-progestogens, including Org 31710, are administered during the mid-luteal phase, shedding of the endometrium and vaginal bleeding will occur (Swahn *et al.*, 1988; Kloosterboer *et al*., 1994; Cameron *et al*., 1996). It is likely that this effect is due to a direct effect on the endometrium since it is not associated with a decrease in ovarian steroid concentration and can be induced even when progesterone levels are artificially elevated by exogenous hCG administration (Croxatto *et al*., 1985). However, when given at the end of the secretory phase a luteolytic effect may also be of importance, which is the case with mifepristone (Swahn *et al.*, 1988). The reason for the improved cycle control with an Org 31710–POP regimen is not clear. Since more subjects bled during the first days following Org 31710 treatment, this indicates that shedding of the endometrium could be one explanation. Another possibility is an increased frequency in ovulatory cycles with Org 31710–POP treatment in comparison with POP alone (Van Heusden *et al*., 2000). In these subjects, a luteolytic effect of Org 31710 cannot be excluded.

It has previously been demonstrated that in ovariectomized cynomolgus monkeys in the presence of progesterone, mifepristone is antagonistic, but in its absence mifepristone exhibits endometrial progestational effects at low doses and an anti-proliferative (anti-estrogenic) effect at higher doses (Wolf *et al*., 1989; Chwalisz *et al*., 1991). Further results indicate that the anti-proliferative effect of the anti-progestogen is not due to a decrease in estrogen receptor concentration as occurs during progesterone treatment. On the contrary, both estrogen and progesterone receptor concentration increased significantly and to supra normal levels in ovariectomized monkeys on estradiol replacement therapy when treated with mifepristone. A possible explanation is that the over-expressed estrogen receptor might not activate the post-receptor mechanism responsible for endometrial tissue growth (Neulen *et al*., 1996). These effects support the suggestion that the action of anti-progestogen on the bleeding pattern with desogestrel POP is mainly due to an effect on the endometrium and the progesterone receptor (Heikinheimo *et al*., 1996).

The contraceptive mode of action of the desogestrel POP depends on the suppression of ovulation and the mid-cycle peaks of LH, as well as on effects on cervical mucus, Fallopian tube motility and endometrium (McCann and Potter, 1994). Since the addition of Org 31710 to the desogestrel treatment increases the rate of ovulation, a possible drawback may be an increased risk of contraceptive failure. However, the frequency of ovulation was similar to that observed with 30 μg/day levonorgestrel (Collaborative Study Group on the Desogestrel-Containing Progestogen-Only Pill, 1998) and in the study by Cheng *et al.* (Cheng *et al*., 2000), and in these studies, no pregnancy occurred.

In light of an improved but not yet optimal bleeding pattern associated with this regimen and the possible decreased contraceptive efficacy with Org 31710 added to POP, further investigations will be necessary for the clinical development of an optimal Org 31710–POP regimen.

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