

Drospirenone 4 mg in a 24/4 regimen maintains inhibition of ovulation even after a 24-h delay pill intake – Pharmacological aspects and comparison to other progestin-only pills

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Abstract. – This review focuses on the pharmacological and inhibition of the ovulation of progestin-only, estrogen-free contraceptive containing drospirenone in a dosage of 4 mg in a regimen 24/4. The USA and European regulatory authorities have approved it.

The molecule has anti-gonadotropic, anti-mineralocorticoid, anti-estrogenic, and antiandrogenic properties. This regime improves the bleeding profile, maintains the plasma E2 levels comparable to the menstrual cycle's early follicular phase, avoids hypoestrogenism, and preserves efficacy despite forgetting the tablet intake as drospirenone has a half lifetime of 30-34 hours.

Clinical studies have shown good efficacy, very low cardiovascular side effects, and high acceptability and maintenance of ovulation inhibition after scheduled 24-h delays in pill intake.

The molecule is compared to other POP like levonorgestrel or desogestrel.

Key Words:

Estrogen free contraception, Progestins, Inhibition of ovulation.

Introduction

Drospirenone, a derivative of 17 α -spiro lactone, is an analogue of the aldosterone antagonist, spironolactone, and is a unique progestogen¹. The pharmacologic profile of drospirenone is more closely related to that of progesterone, especially regarding anti-mineralocorticoid and antiandrogenic activities than that of any other synthetic progestogen²⁻⁵.

It has a similar chemical structure to the aldosterone antagonist spironolactone. It has a low to moderate binding capacity to the PR, excellent binding properties to the mineralocorticoid re-

ceptor, and a low binding affinity to the androgen receptor⁶. Drospirenone has, in relation, only 10% of the progestogenic activity of levonorgestrel on the human endometrium.

Of note, (1) drospirenone demonstrated a relative binding affinity of 19% to the human and 40% to the rabbit progesterone receptor; (2) drospirenone and progesterone have high relative binding affinities for the min mineralocorticoid receptor (500% and 1000% for the human receptor for drospirenone and progesterone, respectively; both 100% for the rat receptor); (3) both progestogens have a 3% relative binding affinity to the androgen receptor in all models; (4) drospirenone exhibits a low relative binding affinity to the glucocorticoid receptor (1% and 3% for the animal and human receptor, respectively), whereas progesterone has some binding affinity to this receptor (11% and 35% for the animal and human receptor, respectively); and (5) neither drospirenone nor progesterone demonstrates significant binding to the estrogen receptor¹.

Inhibition of ovulation by drospirenone alone or in combination with ethinylestradiol 30 μ g has been demonstrated in humans⁷. Patients had documented normal ovulatory function in their pretreatment cycle. In a low dose-ranging study, drospirenone alone was assessed over three treatment cycles in 48 women randomized to dosages of 0.5, 1, 2, and 3 mg. The study showed a dose-dependent efficacy in ovarian suppression. The incidence of ovarian ripening was 9% and 42% in 3 mg and 2 mg drospirenone groups, respectively. The incidence of complete ovarian suppression was 91% and 50% in the 3 mg and 2 mg groups, respectively. All subjects in the 3 mg group were anovulatory, whereas one patient in each of the lower dosage groups ovulated⁷.

Pharmacokinetic studies of drospirenone in man demonstrated that its absorption is rapid and complete, with peak plasma concentrations of drospirenone occurring within 1 to 2 hours after oral administration. The absolute bioavailability of drospirenone after oral administration to young, healthy women was on average 76%. There is a linear relationship between the low dose of drospirenone (range 1 to 10 mg) and the pharmacokinetics of drospirenone. Steady state was achieved after about seven daily drospirenone 3 mg combined with ethinylestradiol 30 µg. The average maximum drospirenone plasma concentration ranges between 60 and 87 ng/mL, and the mean drospirenone trough level ranges between 20 and 25 ng/mL. Plasma levels of drospirenone decline biphasically. After oral administration, the mean half-lives are about 2 hours for the distribution phase and range from 25 to 33 hours for the disposition phase. Approximately 95% to 97% of drospirenone is bound to serum protein, thought to be albumin. Drospirenone does not bind to sex-hormone-binding globulin or corticosteroid-binding globulin and does not attenuate the Ethinyl oestradiol-induced increase in these proteins. Following oral or intravenous administrations, drospirenone is extensively metabolized. The primary plasma metabolites of drospirenone are the acid form of drospirenone generated by the opening of the lactone ring and the 4,5-dihydro-drospirenone-3-sulfate. The primary metabolites are generated independently of the cytochrome P450 enzyme system. Excretion of drospirenone is nearly complete after ten days, with trace amounts of drospirenone excreted unchanged in urine and feces. At least 20 different metabolites are observed in urine and feces. Less than 10% of the metabolites in urine are freely extractable, while about 38% to 47% are excreted as glucuronide and sulfate conjugates. About one-third of the metabolites in feces are freely extractable, and about 17% to 20% are excreted as glucuronides and sulfates⁸.

Traditional progestin-only pills (POP) like levonorgestrel or norethindrone inhibit ovulation in only 60-70% of the users. The reason is that both compounds are sold in a dosage of 0.03 mg per tablet per day, being lower than the established dosage of inhibition of ovulation⁹. The efficacy is dependent on other mechanisms of action, as the effects on cervical mucus penetrability, endometrial receptivity, and the ciliary activity in the fallopian tubes¹⁰⁻¹². These

short-lasting effects are greatly diminished by 24 hours after tablet intake¹⁰. Therefore, the POPs levonorgestrel or norethindrone tablet intake allows a delay intake of maximally 3 hours. In contrast, the allowed intake delay is 12 or, in some cases, 24 hours for combined pills. Delays of more than 3 hours are likely to occur frequently, the risk of reducing the contraceptive reliability is a real-life problem.

For a more recent POP containing 75 µg desogestrel, it has been shown that ovulation inhibition is maintained after three 12-hour delays in tablet intake, allowing for more flexibility in the intake regimen¹³. This effect is due to the higher dosage than the minimal ovulation inhibition dosage⁹.

New Developments with a 4 mg Drospirenone-only Pill

Since 2019 a new POP has been approved in all EU countries, the USA and many Middle and South America, Middle East Asia, and the Pacific region.

It contains non micronized drospirenone (DRSP) in a dosage of 4 mg per day in a 24/4 regimen. The efficacy has been demonstrated in large clinical trials resulting in a Pearl Index (PI) of 0.73¹⁴.

The effective inhibition of ovulation of 4 mg DRSP could be demonstrated in phase 2 clinical trials.

The efficacy assessment of the first clinical trial was the Hoogland Score (composite parameter of follicle size, oestradiol, and progesterone levels), LH and FSH levels, endometrial thickness, and bleeding pattern.

The primary endpoint was the Hoogland Score over two treatment cycles (FAS), resulting in a total of 50 (100.0%) observations. In the DRSP 4 mg group, there were 48 (96.0%) observations of Hoogland Scores < 5 (corresponding to ovulation inhibition). Two DRSP 4.0 mg subjects had Hoogland Scores of "6" (one in cycle 1, another in cycle 2). The ovulation in cycle two was possibly assessed by concomitant vomiting. However, the progesterone levels (maxima 5.34 nmol/L, 5.34 nmol/L, and 6.17 nmol/L, respectively) were not persistent and below normal luteal phase levels (Table I).

In cycle 1, the proportion of women with Hoogland Score ≤3 was 10 (40.0%) in the DRSP 4.0 mg group, whereas in cycle 2, the proportion of women with Hoogland Score ≤3 was 11 (44.0%).

Table I. Hoogland Scores over both cycles.

Hoogland score	Statistic	DRSP 4.0 mg (N = 50)
1 (No activity)	n (%)	8 (16.0%)
2 (Potential activity)	n (%)	13 (26.0%)
3 (Non active FLS)	n (%)	
4 (Active FLS)	n (%)	27 (54.0%)
5 (LUF)	n (%)	0
6 (Ovulation)	n (%)	2 (4.0%)
Missing	n (%)	0
Chi-square*	p-value	

The follicle diameter was measured during the two treatment cycles. The mean follicle diameter (SD) was 14.89 (4.45) mm in Cycle 1 and 16.66 (6.64) mm in Cycle 2. Despite the 4-day hormonal break, the maximum follicle size did not increase markedly.

The proportion of subjects having three consecutive measurements of a follicular diameter ≥ 15 mm was 28.0% in cycle 1 and 36.0% in cycle 2. The mean progesterone levels (SD) maximum levels per cycle were 3.89 (1.10) nmol/L in cycle 1 and 3.74 (1.01) nmol/L in cycle 2.

With the DRSP 4.0 mg regimen, the median maximum oestradiol values per cycle were 287.0 pmol/L in cycle 1 and 309.0 pmol/L in cycle 2.

The activity of follicles increases with their size and with the simultaneous serum oestradiol levels. Therefore, in further analysis, follicular size and serum oestradiol levels were combined: among women with follicular size > 13 mm, the proportion of women with E2 levels 275 pmol/L or above was in cycle 1: eight [32.0%] women and in cycle 2: 11 [44.0%] women.

Concerning endometrial thickness in cycle 1, the mean (SD) maximum endometrial thickness was 6.33 [1.23] mm. In cycle 2, by contrast, the mean (SD) maximum endometrial thickness per cycle was 6.60 [1.38] mm.

The serum LH levels were clearly below the ovulatory phase threshold value of 14.0 U/L throughout both treatment cycles. Mean (SD) serum LH levels in the DRSP 4.0 mg group were at a maximum of 6.30 (1.78) U/L on Day 3/Cycle 1).

The mean (SD) serum FSH levels ranged from 4.67 (1.75) U/L (day 9 in cycle 2) to 6.50 (2.43) U/L (day 3 in cycle 1).

These data were then re-confirmed in a second clinical trial where the inhibition of ovulation was compared to desogestrel.

In this trial, in cycle 1, the maximum score in each treatment group was 4; in cycle 2, one subject in each treatment group scored 6. In both cycles, the proportion of subjects who scored 4 was lower in the drospirenone group (24/4 regimen) than in the desogestrel group (continuous regimen). The odds ratio for having a lower Hoogland Score, indicating more significant ovarian suppression, in the drospirenone group compared with the desogestrel group was 2.42 in cycle 1 and 1.96 in cycle 2. The confidence intervals told that the results were not statistically significant.

In both cycles, the mean maximum follicular diameter tended to be smaller in the drospirenone group compared with the desogestrel group.

E2 levels were lower during both treatment cycles in the drospirenone group than in the desogestrel group, reflecting more potent ovarian suppression. Mean (\pm SD) E2 levels in cycles 1 and 2 were 184.34 (\pm 92.53) and 184.97 (\pm 85.57) pmol/l in the drospirenone group, compared with 374.95 (\pm 284.03) and 255.68 (\pm 146.58) pmol/l in the desogestrel group. E2 levels were not profoundly suppressed in both groups and remained comparable to normal early or mid-follicular phase levels (Table II).

This second study concluded that despite the 4-day treatment-free period, ovulation inhibition was as effective as with the desogestrel-only pill. The ovulation rate with the desogestrel-only pill was comparable to that in previous reports¹⁵.

Following these clinical trials, a third study¹⁶ was performed to investigate if ovulation inhibition with the drospirenone-only pill taken for 24 days followed by four days of placebo treatment was maintained after four scheduled 24-hour delays in tablet intake. More than 120 patients were evaluated in this study¹⁶.

The ovulation incidence was defined as the percentage of subjects ovulating during the treatment period. Ovulation was defined as the disappearance or persistence of a follicle larger than 13 mm and P levels higher than five ng/mL (16 nmol/L) on the day of sonographically suspected ovulation and 2 and 4 days after that. The progesterone criterion was based on the definition of regular luteal activity by Landgren et al¹⁷, i.e., progesterone levels higher than five ng/mL during at least five consecutive days. The follicular size was measured using vaginal sonography.

The overall ovulation rate was 0.8%, with a CI of 0.0% - 4.4%, showing very effective inhibition of ovulation. The acceptance criterion for

Table II. Serum levels of estradiol (pmol/L) by visit.

		Test (N = 27)	
	Statistic	Cycle 1	Cycle 2
Day 3	Mean (SD)	147.1 (55.4)	264.5 (189.8)
	Median	135.0	181.0
	Min/Max	85/353	67/986
Day 6	Mean (SD)	136.6 (55.6)	193.0 (117.5)
	Median	133.0	155.5
	Min/Max	37/285	37/461
Day 9	Mean (SD)	164.6 (79.8)	161.6 (151.7)
	Median	145.0	116.0
	Min/Max	60/349	37/645
Day 12	Mean (SD)	186.3 (136.8)	160.3 (138.9)
	Median	148.0	113.0
	Min/Max	73/592	37/620
Day 15	Mean (SD)	190.5 (132.7)	172.7 (97.4)
	Median	153.0	154.0
	Min/Max	59/648	37/414
Day 18	Mean (SD)	208.3 (189.1)	142.1 (73.7)
	Median	131.0	128.0
	Min/Max	37/767	37/322
Day 21	Mean (SD)	194.0 (144.9)	161.7 (83.0)
	Median	150.0	145.0
	Min/Max	62/698	37/376
Day 24	Mean (SD)	203.4 (155.9)	181.5 (99.0)
	Median	156.0	150.0
	Min/Max	79/796	74/434
Day 27	Mean (SD)	228.4 (122.8)	228.7 (166.3)
	Median	189.0	181.0
	Min/Max	91/615	53/694

maintenance of ovulation inhibition was met. Only one subject fulfilled the ovulation criteria in cycle 2. This subject ovulated in the pre-treatment cycle between days 13 and 15, followed by a progesterone concentration of 18.2 ng/mL (57.9 nmol/L) on day 19. During treatment, a large follicle-like structure vanished between days 2 and 7 of cycle 2. Progesterone levels were 5.7, 5.3, and 6.9 ng/mL (18.1, 16.9, and 21.9 nmol/L) on days 7, 9, and 11, respectively, so the Landgren criteria were met.

Table III depicts the data.

Even after delayed tablet intake, the mean follicle sizes per cycle showed adequate ovarian suppression. Mean and median values of the maximum follicular diameter per treatment cycle were between 13 and 8 cm, respectively. In both groups, mean progesterone levels were low (< 4 nmol/L) throughout the treatment cycles, reflecting the efficient inhibition of ovulation both in the regular and in the delayed-intake cycles.

The results of this study showed that occasional delays in tablet intake for up to 24 hours would

not compromise the contraceptive efficacy of the drospirenone-only pill, even if they occur around the pill-free period.

Conclusions

The maintenance of ovulation inhibition after multiple intake delays is essential from a clinical point of view. Forgotten pill intake occurs very frequently in clinical practice. Up to 50% of oral contraceptive users reported missing one or more pills per cycle, often in the riskiest period, the first week after the pill-free interval^{18,19}. Studies^{20,21} in which electronic devices were used to monitor compliance showed that on average, 2.6 and 4.7 pills were missed per cycle, respectively.

The development of an estrogen-free pill containing DRSP improves this condition as not only from the clinical point of view an inhibition of ovulation even after the delayed intake of 24 hours was shown but also due to the pharmacological profile of this drug.

Table III. Ovulation inhibition despite the delayed intake of 24 hours and four missed pills in 2 cycles.

		Group A (N=62) n (%)	Group B (N=65) n (%)	Total (N=127) n (%)
Cycle 1	Ovulation Rate n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Lower CI Limit (%)	0.000	0.000	0.000
	Upper CI Limit (%) [a]	5.950	5.675	2.905
Cycle 2	Ovulation Rate n (%)	1 (1.6)	0 (0.0)	1 (0.8)
	Lower CI Limit (%)	0.041	0.000	0.000
	Upper CI Limit (%) [a]	8.987	5.675	4.387
Overall Treatment Period	Ovulation Rate n (%)	1 (1.6)	0 (0.0)	1 (0.8)
	Lower CI Limit (%)	0.041	0.000	0.000
	Upper CI Limit (%) [a]	8.987	5.675	4.387

Group A: regular intake in cycle 1; delayed intake in cycle 2
Group B: delayed intake in cycle 1; regular intake in cycle 2

Ovulation was defined as the disappearance or persistence of a large follicle and progesterone levels higher than 5 ng/ml (16 nmol/L) for ≥ 5 consecutive days.

After a single administration of 3 mg DRSP, a 35 ng/ml peak serum level is reached within 1-2 h. After that, the levels decline, but after 24 h, DRSP concentrations of 20-25 ng/ml can still be measured. Consequently, DRSP accumulates in blood during multiple dosing, and treatment with DRSP in combination with a potent estrogen leads to a peak serum concentration of 60 ng/ml after 7-10 days. The half-lives are 1.6 h ($t_{1/2}$ alpha) and 27-36h ($t_{1/2}$ beta). The main metabolic pathways are the opening of the lactone ring leading to an acid group and the reduction of the 4-double bond^{8,22}.

In combination with an ovulation inhibiting dosage of 2 g for drospirenone²³ and a small placebo free interval of 4 days, it can be concluded that the 4 mg DRSP pill maintains the contraceptive efficacy even after a delay of the tablet intake for up to 24 hours representing this a step forward in the increase of contraceptive efficacy.

Conflict of Interest

Both authors are employees of Exeltis.

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