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Pharmacological profile of progestins

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Abstract

The synthetic progestins used so far for contraception and menopausal hormone therapy are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH progesterone derivatives and 19-norprogesterone derivatives). Among the 19-nortestosterone derivatives, the estrane group include norethisterone (NET) and its metabolites, and the gonane group include levonorgestrel (LNG) and its derivatives. The later, including desogestrel (DSG) and its derivative etonogestrel, gestodene (GES) and norgestimate (norelgestromin), have been referred to as third-generation progestins. Several new progestins have been synthesized in the last decade and may be considered as a fourth-generation of progestins. Dienogest is referred to as a hybrid progestin being derived from the estrane group with a 17α-cyanomethyl group, and drospirenone derives from spirolactone. These two progestins have no androgenic effect but a partial antiandrogenic effect. The later exerts anti-mineralocorticoid effects. This property leads to a decreased salt and water retention and a lowering in blood pressure in users of pills containing this progestin. The 19-norprogesterone derivatives appear more specifically progestational and do not possess any androgenic, estrogenic or glucocorticoid activity. They are referred to as "pure" progestational molecules as they bind almost exclusively to the progesterone receptor (PR) and do not interfere with the other steroid receptor. This category includes, trimegestone, nomegestrol acetate and Nestorone® is not active orally but proved to be a potent anti-ovulatory agent when given in implants, vaginal rings or percutaneous gel. Non-androgenic progestins would appear neutral on metabolic factors and on the vessels and would have the advantage of avoiding acnea. Progestins with antiandrogenic properties may also be used for the treatment of women with preexisting androgen related conditions. The progestins available for therapy exhibit profound differences according to their structure or metabolites and it is inappropriate to consider the various effects of the old and new molecules as class-effects.

Keywords: Progestins; Menopause; Progesterone

1. Introduction

Progesterone (P) and synthetic progestins interact not only with the progesterone receptor (PR), but also with other steroid receptors. Depending on the derivative molecule (either P or testosterone, T) some progestins bind to androgen receptors (AR) as well, inducing either androgenic or anti-androgenic effects. Molecules similar to the native hormone P may exert a competitive inhibition to the mineralocorticoid receptor and some derivatives of 17-hydroxy progesterone or testosterone may exert glucocorticoid-like effects.

When considering the comparative potency of progestins, it is necessary to note their specific actions: i.e. whether (1) the progestin has progestational

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activity with the ability to maintain pregnancy and transform the endometrium into the secretory phase; (2) the progestin is anti-estrogenic with the ability to down regulate the estrogen receptors and to decrease the thickness of the estrogen-primed endometrium; or (3) the progestin has anti-androgenic activity, i.e., it opposes androgen-induced prostate growth, as observed in animal experiments or counteracts the effects of endogenous androgen in humans.

The effects of progestins relate to their interactions with receptors: AR (e.g., acnea, lipid effects); glucocorticoid receptors (GR) (e.g., salt and water retention, bloating); or mineralocorticoid receptors (e.g., decreased water retention and weight). Anti-androgenic progestins may act in several ways. They can exert competitive inhibition of the AR, or bind to the enzyme 5-alpha reductase and hence interact with the conversion of testosterone into dihydrotestosterone (its active metabolite). When combined with estrogen the non-androgenic progestins do not oppose the estrogen-dependent increase in SHBG. The later effect results in more binding of the circulating androgens and less free T available for action at the receptor level. Thus, anti-androgenic progestins may have beneficial effects (e.g., controlling endogenous androgen and decreasing acnea or hirsutism).

The synthetic progestins used in clinical practice are derived either from T (19-nortestosterone derivatives) or from P (17-OH progesterone derivatives and 19-norprogesterone derivatives) [1].

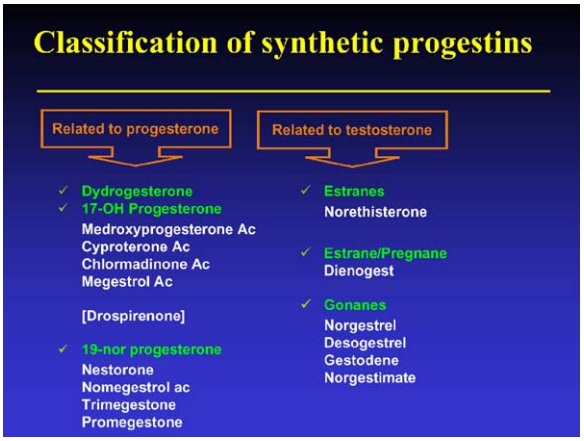
Among the 19-nortestosterone derivatives is the first generation progestin, norethynodrel (the first progestin synthesized) [1]. The second generation is categorized into two groups: the estrane group includes norethisterone (NET) and its metabolites, and the gonane group includes levonorgestrel (LNG) and its derivatives. Norethynodrel, lynestrenol and ethynodiol acetate are prodrugs of NET and convert into NET for exerting their action. The third generation of progestins, derived from the latter group are: desogestrel (DSG) with its active metabolite 3-keto-desogestrel also named etonogestrel, gestodene (GES) and norgestimate (and its active 17-deacetylated metabolite, norelgestromin). These testosterone-derived molecules have been used in most of the contraceptives available to date and some have androgenic activity.

2. Specific activities of new progestins

Several new progestins have been synthesized in the last decade [2]. Dienogest, referred to as a hybrid progestin, is derived from the estrane group with a 17α-cyanomethyl radical [3]. However it is considered to be close to the pregnane group as it does not exert the androgenic effects of the testosterone derivastives. In contrast it has a significant anti-androgenic activity. Drospirenone is derived from spirolactone [4]. The 19-nor derivatives of progesterone are referred to as ‘pure’ progestational molecules as they bind more selectively to the progesterone receptor (PR) and interfere very little with other steroid receptors [2]. This category includes, promegestone (R5020), demegestone, trimegestone, nomegestrol acetate (NOMAc), and Nestorone®, as well as a new compound related to Nestorone with a methyl radical in C18 [2,5–7] (Table 1).

Very small structural changes may account for considerable difference in the effects of progestins. The addition of a double bond in the C6–7 position of the hydroxyprogesterone skeleton, as well as a deletion of the CH_3 radical in position C19, confers to the molecule of NOMAc a higher progestational potency than medroxyprogesterone acetate (MPA), both being 17-OH progesterone derivatives [6]. By contrast, Nestorone, another 19-norprogesterone with no CH_3

Table 1
Classifications of progestins



Synthetic progestins are classified according to the steroid from which they derive, either from testosterone (estranes and gonanes) or from progesterone (pregnanes and norpregnanes).

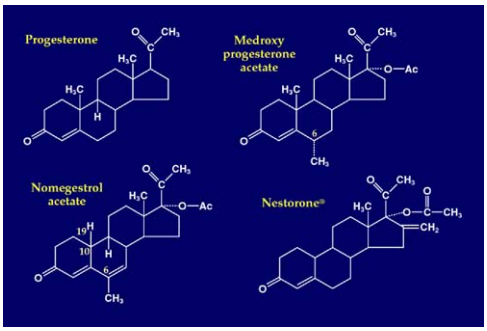


Fig. 1. Chemical structure of two 19-norprogesterone derivatives, nomegestrol acetate and Nestorone as compared with the native hormone progesterone and with medroxyprogesterone acetate, a 17-hydroxy progesterone derivative.

radical in position 6, is far more potent than NOMAc but is not active orally; Nestorone must be administered parenterally due to its rapid hepatic metabolism [7] (Fig. 1).

2.1. Comparative progestational activity of various gestagens

Progestational activity is usually tested using the McPhail Index in immature rabbits and pregnancy maintenance assessment in female rats. According to these in vivo bioassays, Nestorone appears to be one of the most potent progestins. Nestorone is 3–10 times more potent than LNG and 100 times more potent than P itself when the molecules are administered subcutaneously [7]. When given orally, NET, MPA and drospirenone are more potent than P but less than LNG [1,4]; NOMAc is four times more active than MPA [6]. Trimegestone, which has been recently synthesized, appears more potent than Nestorone [8].

The ovulation inhibition tests in rats have been used to measure the biological anti-ovulatory potency of these steroids. In this model, Nestorone is three times more potent than LNG when administered parenterally [7].

The binding affinity of the various progestins to the sex steroid receptors, such as the estrogen receptor (ER) or the AR, indicate considerable difference between the molecules (Table 2). However, the binding affinity does not always correlate with the in vivo tests of estrogenic or androgenic potency.

2.2. Androgenic activity of progestins

In a study using the rat ventral prostate as a source of AR, the relative binding affinity (RBA) of LNG and desogestrel was 70 and 40% that of T, respectively. In contrast Nestorone and P did not show significant binding [7].

The in vivo biological assay of androgenicity usually considers the effect of a given compound on the weight increase of the ventral prostate and other male sex organs in immature male rats. Using these models, LNG and 3-keto-desogestrel express androgenicity and increase the weight of the ventral prostate in a dose-dependent manner, while Nestorone and P do not induce such effects [7]. In similar experiments, Bullock and Bardin [9] demonstrated that MPA was androgenic at high doses, while Duc et al. [10] showed no androgenic effect of NOMAc, even when administered at very high doses.

Table 2
Relative binding affinities of some progestins, expressed in percent and compared with 100% binding for the native hormone to its target receptor

Binding of progestins with human steroid receptors in vitro					
Receptor	Relative binding affinity (%)				
	TMG	MPA	NET	GES	LNG
Progesterone	588	298	134	864	323
Androgen	2.4	36	55	71	58
Glucocorticoid	13	58	104	38	7.5
Mineralocorticoid	42	3.1	2.7	97	17
Estrogen	<0.02	<0.02	0.15	<0.02	<0.02

Abbreviations: TMG: trimegestone; MPA: medroxyprogesterone acetate; NET: norethisterone; GES: gestodene; LNG: levonorgestrel; adapted from [8].

2.3. Estrogenic activity of progestins

Examination of the estrogenic activity of progestins revealed that the uterine weight of ovariectomized immature female rats was significantly increased by LNG but not by Nestorone at similar doses [7]. Neither compound demonstrated binding to the estrogen receptor.

2.4. Summary of the various activities of T and P derivatives

Considering activities other than progestational action, the 19-nor-testosterone derivatives exert some androgenic activity, while only a few of these progestins have an estrogenic effect. The 17-hydroxy progesterone derivatives, however, exhibit varying activities: cyproterone acetate (CPA) is a potent anti-androgenic compound. MPA has slight androgenic action [9] and exerts glucocorticoid activity when given at high doses [11]. Megestrol acetate has 50% less glucocorticoid effects than MPA. Drospirenone derived from spirolactone, more recently synthesized in this class of compounds is essentially an anti-mineralocorticoid progestin and exerts some anti-androgenic action [4].

The 19-norprogesterone derivatives appear more specifically progestational and do not possess any androgenic, estrogenic or glucocorticoid activity at therapeutic doses [7,10]. Nestorone binds to the GR but does not exert glucocorticoid activity in the in vivo assays showing no increase in liver glycogen and tyrosine transaminase TAT which increase significantly under dexamethasone [7]. However, in the ovariectomized female rats, Nestorone, only at a high dose showed significant effects on thymus regression [7].

Most of the progestins available to the prescriber exert the expected activity, namely the progestational effect, and all progestins are able to oppose the proliferative effect of estrogens on the endometrium. However, their progestational potency varies, and the dose required to achieve the effect on the endometrium differs from a few micrograms to several milligrams. The relevance of such difference resides in the ability to use the more 'potent' molecules at very low doses in long-acting delivery systems, including gels or patches. According to their structure and the steroid from which they derive, different molecules will exert additional activities, some considered beneficial and others deleterious leading to side effects. Given these differences, it appears inappropriate to claim the side effects of 'progestins' to be a class-effect.

3. Pharmacokinetic differences between gestagens

Other important considerations in evaluating progestagen action are pharmacokinetic properties and binding of progestins to serum proteins. A comparison of radioactivity recovered in urine and feces after oral and IV administration of a labelled compound indicates the absolute bioavailability of that compound and determines its absorption via the oral route. The compounds with the highest oral bioavailability are gestodene, desogestrel and cyproterone acetate (CPA) [12,13]. The new progestins dienogest and drospirenone exhibit also a high oral bioavailability [3,14,15].

The half-life of a compound is modulated by its binding to plasma proteins. Compared with T as a reference, LNG and 3-keto-desogestrel exhibit a significant but lower affinity to the sex hormone binding globulin (SHBG) [7]. While both NET and LNG bind to SHBG, their elimination half-lives vary: the terminal half-life ($\beta_{t1/2}$) is approximately 7–8 h for NET and up to 26 h for LNG. In contrast, CPA has a $\beta_{t1/2}$ of 48 h [2] and NOMAc of about 50 h [16]. Dienogest, a newly synthesized hybrid progestin, has a shorter half-life of 6–12 h. The longer half-life of the progesterone derivatives may be related to their retention and storage in the fatty tissue [12].

Progesterone, drospirenone, dienogest and Nestorone do not bind to SHBG, and the free fraction of each should be greater than most of the 19-nortestosterone-derived progestins. The oral bioavailability of Nestorone is only about 10% with a shorter half-life than progestins that bind to SHBG. However, a much slower elimination rate is observed with the sustained-release subdermal implant [17].

4. New progestins used in contraception and HRT

Drospirenone, which has pharmacodynamic properties very similar to progesterone [14,15], has been developed as an oral contraceptive in pills containing

3 mg of the progestin and 30 μg of ethynylestradiol (EE) (Yasmin®) [4,18] and also for HRT in a combination containing oral estradiol (Angeliq®). Drospirenone has anti-mineralocorticoid and progestogenic properties not found in most synthetic progestins. The main feature of this combination resides in the ability of the progestin to counteract the effect of EE, a potent estrogen, on liver synthesis of angiotensinogen leading to aldosterone increase. Due to its anti-mineralocorticoid properties, the progestin antagonizes the aldosterone effect. Water and salt retention is therefore counteracted by the anti-mineralocorticoid activity of the progestin, and weight loss, rather than weight gain, has been observed [4,15,18]. In a 6-month study [4,15] of 3 mg drospirenone plus EE (20, 15 or 30 μg) or 150 μg LNG plus 30 μg EE, the EE/LNG group exhibited 0.7 kg increase in body weight while all three drospirenone groups showed reduction of 0.7–1.7 kg. As expected, the largest reduction appeared in those receiving 15 μg EE due to drospirenone's antagonism of EE's sodium-retaining effect. Likewise, slight increases in blood pressure were seen in the LNG/EE group and decreases in the drospirenone groups, a non-significant difference attributed to reduction in extracellular volume.

Large multicenter trials [19,20] evaluating drospirenone/EE, showed good ovulation inhibition, cycle control, tolerability and safety profile. Results of the two studies [19,20] comparing EE/DRSP (Yasmin®) to EE/desogestrel (Marvelon®) exhibited significant weight reduction in both groups. The difference in weight reduction between the two treatments was also statistically significant in both studies $P < 0.0072$ (13 cycle study) and $P = 0.0009$ (26 cycle study), with greater reduction in the drospirenone group. Huber et al found that the drospirenone regimen decreased acne and seborrhea from 21.5% at baseline to 7.8% at cycle 13 due to the progestin's anti-androgenic activity.

Dienogest (DNG) is an anti-androgenic progestin with strong progestational activity and when combined with ethinyl estradiol (EE) (30 μg/day EE/2 mg/day dienogest) is an effective oral contraceptive (Pearl Index ∼0.2). This COC has good bleeding control and improves androgenic symptoms [21,22].

All the progestins may indeed block ovulation whatever their anti-ovulatory potency. However the more potent molecules may be used at much lower doses and, hence, in long-acting delivery systems such as vaginal rings, implants, gels or transdermal patches.

5. Progestins and cardiovascular disease

Many of the progestins used in contraception, as well as HRT, are derived from T, and their main side effects are related to androgenic properties or to their glucocorticoid effects. Improvement of OCs has been attempted by decreasing the androgenic potency of the steroids. However, the third generation progestins, having fewer androgenic effects than the second generation, have lost some of the ability to oppose the effects of the ethinyl estradiol component of the OCs. Whether this property has resulted in lower arterial risk but a higher risk in venous thromboembolism is still debated.

Studies have also shown that estrogen has beneficial effects on blood vessel walls; estrogen and progesterone binding sites have been found in blood vessel walls and in endothelial cells lining the walls. Estrogen increases the release of nitric oxide causing relaxation of smooth muscle cells and vasodilation. In monkeys, neither natural progesterone nor NOMAc inhibits estrogen's beneficial effect on coronary dilator response. However, when MPA was combined with estrogen the positive response was inhibited by 50% [23,24].

Another study in monkeys, showed that estrogen given either alone or with natural progesterone had anti-atherogenic effects irrespective of HDL total cholesterol levels. The addition of natural progesterone did not diminish this effect [25].

5.1. Venous thromboembolism (VTE)

The risk of VTE observed in users of OCs, particularly during the first year of use, has generated controversy. Some studies have noted increased VTE risk in users of third generation OCs. In a recent meta-analysis, the odds ratio for the risk of VTE was 1.7 (C.I. 1.4–2.0) when third and second generation OC use was compared. The odds ratio was 3.1 (C.I. 2.0–4.6) in first-time OC users, 2.5 (1.6–4.1) in short-term users, and 2.0 (1.4–2.7) in long-term users [26]. Other studies that had been carefully adjusted for duration of use (or studies of first-time OC users

only) showed no statistically significant difference in VTE risk in users of OCs containing different types of progestins [27].

Odlind et al. [28] have shed some light on the role of third generation progestins and VTE risk with COC use. Although it is the estrogen dose that is associated with VTE risk, in combined oral contraceptives, the degree of estrogenicity and thus VTE risk also depends on the androgenic and anti-estrogenic effects of the progestin.

Odlind and coworkers have studied sex hormone binding globulin (SHBG) as a marker for estrogenicity and as a surrogate marker for VTE risk. SHBG, highly sensitive to estrogen, has shown dramatic dose-dependent increases with oral intake of ethynylestradiol [28,29] alone. With combined contraceptives, SHBG increases to varying degrees depending on the anti-estrogenic activity of the progestin used. Odlind and coworkers found a relationship between the reported risk of VTE in various COC studies and reported average increase in SHBG levels, which the authors identify as a measure of total estrogenicity. Monophasic levonorgestrel-containing COCs (+30 μg EE) have an approximate 50% SHBG increase while desogestrel or gestodene-containing COCs (+30 μg EE) have a 200–300% rise in SHBG. In triphasic preparations containing LNG, e.g., gestodene or desogestrel, the increase in SHBG is 100, 150 and 200%, respectively. Cyproterone acetate with a higher VTE risk than gestodene or desogestrel has a 300–400% SHBG increase. Percent increase in levels of SHBG for COCs (+30–35 μg EE) having no epidemiologic data for VTE risk are as follows: norgestimate, 150% increase; drospirenone or dienogest, 250–300%. The combined contraceptive vaginal ring (NuvaRing, Organon, Inc.) releasing 15/20 μg/day EE/etonogestrel results in a 150% increase in SHBG and the new contraceptive patch, releasing 20/150 μg/day EE/norelgestromin, a 260% increase. Whether such surrogate marker is used to predict the risk is far from being accepted. However as none of the clotting factors seem to be valid as a predictor of VTE risk, only long-term surveillance and observational studies will give use some answer about the new OC combinations.

As far as hormonal therapy used after the menopause is concerned, the progestins are associated with estrogen much less potent that ethinyl estradiol, and derivatives of progesterone are preferred to the androgenic progestins used in COC. However, MPA is the most prescribed progestin in the USA in contrast with European countries. The Women's Health Initiative (WHI) study evaluating the effects of conjugated equine estrogen plus MPA as a progestin in healthy postmenopausal women was prematurely halted due to an increased risk of breast cancer and a lack of overall benefit [30]. Surprisingly the expected decrease in cardiovascular disease was not observed and the reverse was found with a hazard ratio of 1.29 for coronary heart disease. The study tested a specific combination of conjugated equine estrogen and MPA given continuously. Although it has been claimed that HRT increased the CHD risk, it would be inappropriate to extend the finding to all HRT preparations as the doses and type of molecules is of importance in term of their pharmacological action. While other progestins might exert a better action than MPA on the CHD, this is not documented by large RCT. Also whether the findings are due to the type or dose of molecules used, or to the age of the population studied is actively debated.

In conclusion, the progestins available for oral contraception and for HRT are not similar and may have profound differences according to their structure, metabolites and pharmacodynamic actions. Therefore it is inappropriate to consider the various effects of the old and new molecules as class-effects.

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