Maturitas 65S (2009) S3–S11

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Progestational effects of dydrogesterone *in vitro*, *in vivo* and on the human endometrium

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ARTICLE INFO

Article history:
Received 28 October 2009
Accepted 28 October 2009

Keywords:
Dydrogesterone
Progestational effect
Progesterone
Hormone replacement therapy
Endometrium

ABSTRACT

Dydrogesterone has a molecular structure closely related to that of natural progesterone, but it has enhanced oral availability compared with progesterone. The hormonal profile and the progestational potency of dydrogesterone has been determined *in vitro*, *in vivo* and in humans, in combination with estrogens or without. It showed varying affinity for progesterone-binding proteins in uterine tissue *in vitro*, depending on the species. It exerted a clear progestational response in the rabbit *in vivo*, although the potency was influenced somewhat by the route of administration. When used in hormone replacement therapy, 10 mg dydrogesterone given sequentially provides adequate protection against endometrial hyperplasia in postmenopausal women using 2 mg estradiol. Similarly, a dydrogesterone dose of 5 mg also protects the endometrium when continuously combined with 1 mg estradiol. Dydrogesterone also has beneficial effects in women with amenorrhea/oligomenorrhea, dysfunctional uterine bleeding and irregular cycles. In conclusion, having a similar profile to progesterone but with better oral availability, dydrogesterone has been used successfully to treat disorders related to absolute or relative progesterone deficiency.

1. Introduction

The characteristic progestational effects, common for all progestogens, are well known for progesterone, the main endogenous progestational steroid hormone. Progesterone is synthesized primarily by the corpus luteum in the ovary and by the placenta. Thus, a physiological increase in progesterone secretion occurs during the luteal phase of the menstrual cycle and during pregnancy. The decrease in progesterone secretion in the years preceding menopause is the first sign of oncoming ovarian failure. Small quantities of progesterone are also excreted by the adrenal cortex [1]. Progesterone formation appears to be regulated by a range of factors including β-adrenergic signals, follicular stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), dehydroepiandrosterone (DHEA) and estrogens [2–7].

The number of cellular pathways regulated by progesterone reflects the complexity of its physiological role. Progesterone acts on the uterus, the mammary glands and the brain. It is required in embryo implantation, maintenance of pregnancy and the development of mammary tissue for milk production. It interacts both synergistically and antagonistically with estrogens; however, the ratios of the two hormones vary widely in different target organs. Thus, depending on the cell or tissue context, progesterone can either stimulate cell proliferation (e.g. in the breast) or inhibit proliferation and induce differentiation (e.g. in the uterine endometrium) [8].

Progesterone protects the allogenic fetus from immunological rejection, inhibits contractions of the uterine myometrium by decreasing myometrial sensitivity to oxytocin stimulation and controls cervical competence [8–10]. It is required for rupture of the mature oocyte from the ovarian follicle, promotes mucus formation in the vagina and prepares the uterus for implantation by antagonizing the mitogenic activity of estrogen, reducing the levels of estrogen and progesterone receptors and transforming the estrogen-primed proliferated endometrium into a differentiated, decidualized secretory lining [8,11]. In menstruating women, progesterone is necessary to effect secretory transformation of the endometrium; normal menstrual bleeding is therefore progesterone withdrawal bleeding.

Progesterone exerts its progestational activity not only by binding to the two isoforms (A and B) of the nuclear progesterone receptor (PR), but also by interacting with membrane progesterone receptors (mPRα, mPRβ, and mPRγ), which may be responsible for mediating rapid, nongenomic actions of progestogens in a variety of target tissues, and with other steroid hormone receptors such as androgen, glucocorticoid and mineralocorticoid receptors. In contrast to some progestogens, progesterone does not interact with estrogen receptors (Table 1).

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doi:10.1016/j.maturitas.2009.10.011

Table 1
Relative binding affinities of progestogens to steroid receptors [1].

	Relative binding affinity [% of reference steroid]					
	Progesterone receptor	Androgen receptor	Estrogen receptor	Glucocorticoid receptor	Mineralocorticoid receptor	SHBG
Pregnanes						
Progesterone	50	0	0	10	100	0
Dydrogesterone	75	0	–	–	–	–
MPA	115	5	0	29	160	0
Norsteroids						
Norethisterone	75	15	0	0	0	16
Gestodene	90	85	0	27	290	40
Promegestone	100	0	0	5	53	0
Levonorgestrel	150	45	0	1	75	50
Androstanes						
Drospirenone	35	65	0	6	230	0
Reference steroid with 100% receptor binding affinity	Promegestone	Metribolone	Estradiol-17β	Dexamethasone	Aldosterone	Dihydro-testosterone

SHGB = sex hormone binding globulin; MPA: medroxyprogesterone acetate.

In accordance with its main function, a relative or absolute deficiency of progesterone (luteal insufficiency) leads to reproductive failure or menstrual disorders. A deficiency of progesterone relative to estrogens may lead to endometrial hyperplasia and an increased risk of endometrial carcinoma, e.g. in postmenopausal women who use estrogens to treat climacteric symptoms or to prevent postmenopausal osteoporosis.

States of relative or absolute progesterone deficiency can be treated with synthetic progestogens. These are currently used in a variety of gynecological indications such as infertility, threatened/recurrent miscarriage, amenorrhea, dysfunctional uterine bleeding, dysmenorrhea, premenstrual syndrome, endometriosis and endometrial hyperplasia. In infertility or threatened/recurrent miscarriage, only progesterone, dydrogesterone or 17α-hydroxyprogesterone caproate should be used in order to avoid some of the partial side effects associated with other progestogens (Table 2). In hormone replacement therapy (HRT), progestogens are added to oppose the proliferative effects of estrogens on the endometrium as the use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial carcinoma [12].

1.1. Differences between progestogens

Not all progestogens are equally suitable to be used as a replacement for endogenous progesterone as they differ not only with respect to their potency but also in their hormonal profile.

Because oral progesterone is rapidly metabolized by first-pass effects in the liver, oral administration is not so effective and the administration of therapeutically effective amounts generates a significant metabolite load, some of which cause well-known side effects such as drowsiness. Synthetic analogs of progesterone have been developed to improve oral availability and to produce longer lasting and more potent uterine effects than would be available from natural progesterone itself. In addition, progestogens differ significantly from each other and from progesterone with respect to the pattern of their partial effects [1].

Depending upon the route of administration, progestogens manifest different biological effects that are due to differences in metabolism and binding affinities to the PR and other steroid receptors. There are also differences in binding to serum proteins (e.g. sex hormone binding globulin (SHBG) or corticosteroid binding globulin) [1].

Derivatives of 19-nortestosterone, such as norethisterone and dl-norgestrel, which are widely used in some countries in combination with estrogens for HRT, possess androgenic activity. They increase plasma insulin levels, reflecting impaired glucose tolerance, and lower the levels of high density lipoprotein (HDL)-cholesterol, thereby increasing cardiovascular risk. Androgenic progestogens also have marked hepatocellular effects, i.e. they increase insulin like growth factor-I (IGF-I), a strong mitogenic factor, and decrease SHBG levels (Table 1) [1]. For relatively long-term use, such as in HRT, a progestogen without these androgenic effects is therefore desirable.

Some progestogens have been shown to bind to other classes of receptors apart from PRs. However, evidence has been accumulating to indicate that the biological activities of progestogens are not always in parallel with their receptor binding and the levels of RNA synthesis. The differences in biological effects may be due to

Table 2
Pharmacological properties of progestogens [1].

		Dydrogesterone	Testosterone and 19-nortestosterone derivatives	Progesterone derivatives	Progesterone
Blocking of ovulation	Human	–[a]	+	+	+
Estrogenic	Human/animal	–	+	–	±
Androgenic	Animal	–	+	+	–
Masculinization of fetus	Animal/human	–	+	+	–
Relaxation of uterine tissue	Animal/human	+	–	±	+
Adrenal atrophy	Animal	–	+	+	–
Thermogenicity	Human	–	+	+	+
Blood clotting	Human	–	+	+	–
Blood lipids	Human	–	+	–	–

+ = effect, – = no effect, and ± = equivocal.
[a] At normal dosage.