Maturitas 71 (2012) 337–344

Contents lists available at SciVerse ScienceDirect

Maturitas

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

Review

The pharmacology of dienogest

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ARTICLE INFO

Article history:
Received 10 January 2012
Received in revised form 17 January 2012
Accepted 19 January 2012

Keywords:
Dienogest
Pharmacology
Estradiol
Ethinyl estradiol

ABSTRACT

Dienogest (DNG) is a 19-nortestosterone derivative (a C-19 progestogen) with a cyanomethyl instead of an ethinyl group at the C-17 position, which may make the compound elicit fewer hepatic effects than other C-19 nortestosterone derivatives. Its similarity to norethisterone is reflected in its high endometrial efficacy, which could explain the high stability of the menstrual cycle women achieve when they use DNG in combination with ethinyl estradiol (EE) or with estradiol valerate (E2V). Its strong endometrial efficacy underlies the use of DNG (on its own) to treat endometriosis, and gives it antiproliferative and anti-inflammatory effects in the treatment of endometriotic lesions. Properties derived from its C-19 derivative structure include its short plasma half-life, of about 10 h (which means the drug is not accumulated), and its high oral bioavailability, of more than 90%. However, DNG also has some of the properties of typical of progesterone derivatives, including a lack of effect on the metabolic and cardiovascular systems, and considerable antiandrogenic activity, the latter increased by its lack of affinity to the sex-hormone binding globulin (SHBG), in contrast to other C-19 progestogens.

DNG has no glucocorticoid and no antimineralocorticoid activity. It also has no antiestrogenic activity, which suggests that it should not antagonize estradiol's beneficial effects. This is important for its use in the treatment of endometriosis, because, due to DNG's low gonadotropic activity, E2 levels are not decreased to zero, in contrast to treatments with gonadotropin-releasing hormone (GnRH) analogues. This maintenance beneficial E2 effects is of particular importance for the general tolerability of the first contraceptive pill to use E2V instead of EE, although clinical endpoint studies are still ongoing. These studies are expected, on the basis of its pharmacology, to demonstrate the cardiovascular safety of the new pill.

Contents

DOI of original article: 10.1016/j.maturitas.2012.01.007.
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0378-5122/$ – see front matter
doi:10.1016/j.maturitas.2012.01.018

1. Introduction

Dienogest (DNG) is a progestogen that for many years has been used in combination with other compounds for both hormonal contraception and hormone replacement therapy (HRT) [1,2]. For both indications, DNG is used as the progestogenic component, at a dosage of 2 mg/day: in combination with estradiol valerate (E2V) at a dosage of 1 or 2 mg/day for HRT; and in combination with ethinyl estradiol (EE) at a dosage of 30 μg/day for hormonal contraception. Two new developments, however, make it timely to review the main pharmacological properties of this special progestogen: DNG (not in combination with another compound) has recently been launched for the treatment of endometriosis [3,4]; and it is included as the progestogenic component of the first combined oral contraceptive (COC) to contain E2V rather than EE [5,6]. Since the valerate ester is split off during the gastrointestinal absorption of orally administered E2V, the new COC pill is the first hormonal contraceptive to use 'natural estradiol' in place of the synthetic estrogen EE [7].

In the treatment of endometriosis, a dose-finding study has found that the minimum effective dosage of DNG is the same as that for its use in HRT, namely 2 mg/day [8]. In the novel COC the dosage of DNG is also in this range, for example at about 2.4 mg/day in the new four-phase ("dynamic estrogen step down, progestin step up") 26/28-day regimen (Fig. 1).

Extensive clinical data on the use of DNG in the treatment of endometriosis have been published [3,4], and similarly the novel COC has been described in detail, including its contraceptive efficacy and safety [5,6]. The aim of the present review is to summarize the general pharmacological properties of DNG.

2. Chemical classification and functional structural elements

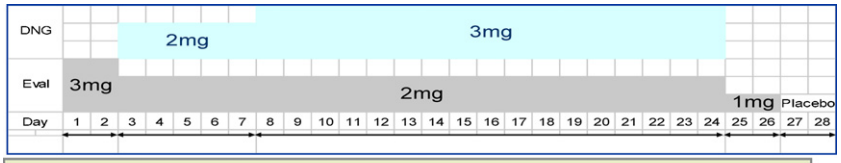
Progestogens are commonly classified according to their chemical structure. Most have a skeleton comprising 21 carbon atoms; these are the C-21 progestogens (the pregnanes). Derivatives of the C-19 compound nortestosterone (NET) are also classified as progestogens; these include the estranes (with a methyl group at position C-13) and the gonanes (with an ethyl group at C-13). Finally, spirolactone is also a progestogen, with its derivative drospirenone (Fig. 2). According to this classification, DNG is an estrane, a derivative of NET, but instead of having an ethinyl group at position C-17 (as do the other estranes) it uniquely has a cyanomethyl group ($CNCH_3$) in that position (Figs. 3 and 4).

Another of DNG's special structural features is the double bond in the steroidal B-ring, which leads to a so-called "conjugated double-bond system" over steroid rings A and B, with the pharmacological consequence of strong affinity to progesterone receptors.

Thus, DNG's unique chemical structure gives it the pharmacodynamic properties of both C-19 norprogestins and progesterone derivatives. But DNG also has its own specific properties. In particular, the cyanomethyl group that replaces the ethinyl group at C-17 endows it with only low activity in the up-regulation of mitochondrial cytochrome P450 (CYP) enzymes [9]. Indeed, it presents only low activity in its reaction with hepatic proteins in general. This is in sharp contrast to the progestogens that feature the ethinyl group, which not only react with mitochondrial P450 but can even destroy those enzymes. The results from a variety of experimental studies have led to the suggestion that with DNG the risk of drug interactions caused via up- or down-regulation of the P450 enzyme system is reduced or even eliminated, again in contrast to the ethinylated progestogens. This may be of especial importance for combinations of DNG with E2, because E2 similarly has no relevant drug interactions caused via its P450 enzyme activity, in contrast to EE [10]. Nevertheless, a weak interaction of the cyanomethyl group cannot be excluded [9], and for legal reasons users of medicines containing DNG have to be informed of possible drug interactions with other sex steroids. Studies are ongoing that are likely to demonstrate the lower risk of clinically important drug interactions with DNG compared with those arising with ethinylated progestogens.

3. Pharmacokinetics and steroid receptor activities

Table 1 summarizes the pharmacokinetics of DNG according to the "ADME classification" [11,12]. Regarding *absorption*, its similarity to other NET derivatives may explain its high bioavailability (>90%), in contrast to some progesterone derivatives. Likewise,



- 26 active tablets
- 22 E2V/DNG days per cycle (days 3–24)
- 4 E2V only days (days 1–2 and 25–26)
- 2 hormone-free tablets per cycle (placebo, days 27–28)

E2V Estradiol valerate; DNG Dienogest

Fig. 1. Regimen of the fourphasic combined oral contraceptive pill: E2-valerate/dienogest (E2V/DNG).