ELSEVIER

Contraception 89 (2014) 242 – 252

Contraception

Review article

Gestodene: A review of its pharmacology, potency and tolerability in combined contraceptive preparations☆

Frank Z. Stanczyk[a,*], David F. Archer[b]

[a]University of Southern California Keck School of Medicine, Los Angeles, CA, USA
[b]Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA, USA

Received 24 June 2013; revised 28 November 2013; accepted 5 December 2013

Abstract

Combined progestin–estrogen pills are an established and reliable contraceptive option used by women worldwide. Combined oral contraceptives (COCs) containing the progestins – gestodene, desogestrel or norgestimate – were developed to minimize androgenic side effects and are considered an effective, well-tolerated contraceptive option. Gestodene achieves contraceptive efficacy with the lowest dose of any progestin in a COC, and has an established and favorable short- and long-term tolerability profile. In this review we present an overview of the pharmacology, potency and tolerability of gestodene.

Keywords: Gestodene; Combined oral contraceptives; Ethinyl estradiol; Pharmacology; Review

1. Introduction

Combined progestin–estrogen contraceptive pills are used by women throughout the world and provide a reliable, reversible method of contraception [1,2]. Orally active, synthetic progestogens (progestins) that provide suppression of ovulation have been developed, beginning in the 1950s; they included norethynodrel and norethindrone (norethisterone). These progestins were initially used with mestranol, a synthetic estrogen, to produce the first combined oral contraceptives (COCs). Since mestranol is rapidly converted to ethinyl estradiol after its ingestion, the latter estrogen eventually replaced mestranol in COCs. Subsequently, the pharmaceutical industry began investigating the use of progestins with high progestational activity, which led to the development of COCs containing the progestin levonorgestrel. Following this, gestodene, desogestrel and norgestimate were developed and used in COCs to minimize the androgenic side effects seen with progestins such as levonorgestrel [3]. After that, COCs containing dienogest or drospirenone as the progestational component achieved regulatory approval and were marketed.

Following the publication of epidemiologic data in the mid-1990s on the risk of venous thromboembolism (VTE) among users of COCs containing gestodene or desogestrel [4–7], a thorough examination was conducted on the safety profile of these formulations. COCs containing gestodene or desogestrel were compared with levonorgestrel to establish whether they conferred a greater risk of VTE. Although the initial data suggested an elevated risk of VTE with gestodene- or desogestrel-containing COCs, later analyses conducted by the European Drug Safety and Advisory Committee and led by the European Commission stated that they posed no greater risk to public health than other COCs [8]. Overall, COCs containing gestodene or desogestrel are now considered a safe, effective, well-tolerated contraceptive option [9].

Gestodene – a progestin in the 19-nortestosterone series – today is widely used across Europe. Gestodene differs from

☆ David F. Archer is a consultant to Agile Therapeutics, Abbott, Bayer Pharma AG, CHEMO, Endoceutics, Ferring, HRA Pharma, Pfizer, and has been a consultant for Warner Chilcott within the past calendar year. He currently receives research grant support from CONRAD, NICHD, Warner Chilcott, and Abbott. He has received speaker fees from Besins and Merck within the past year, and has stock options from Agile Therapeutics. Frank Z. Stanczyk has no financial disclosures pertaining to the current review, but has received honoraria from Bayer Pharma AG within the last 3 years for services unrelated to this publication. Editorial assistance for this paper was funded by Bayer Pharma AG, Berlin, Germany.

* Corresponding author. Tel.: +1 323 226 3220; fax: +1 323 226 2850.
E-mail address: fstanczyk@socal.rr.com (F.Z. Stanczyk).

0010-7824/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.contraception.2013.12.003

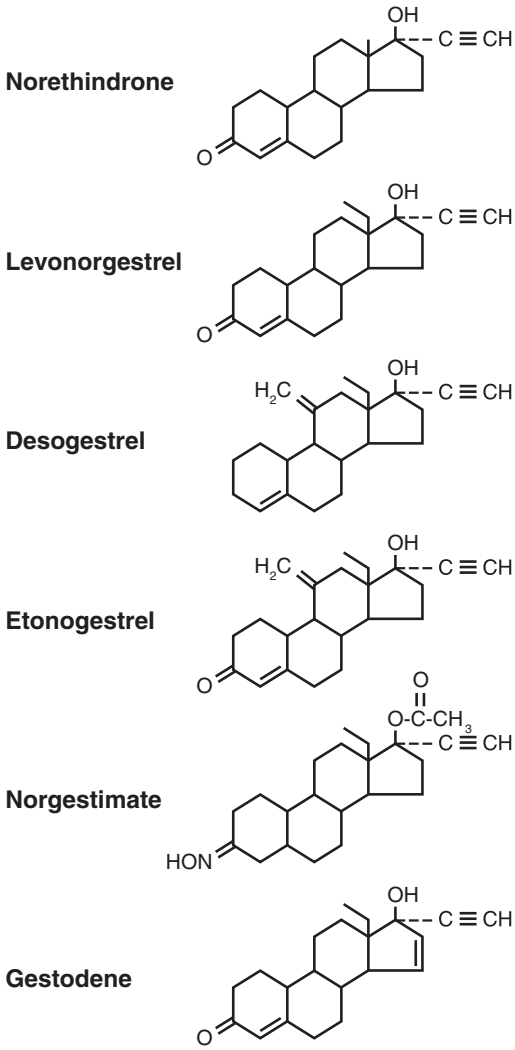

Fig. 1. Chemical structures of the progestins norethindrone, levonorgestrel, desogestrel, etonogestrel, norgestimate and gestodene.

levonorgestrel by a double bond between carbons 15 and 16 in the D-ring (Fig. 1) [10]. This variation in chemical structure results in a shift in the conformational location of the 18-ethyl group and accounts for differences in the pharmacokinetics of the two steroids [10].

The purpose of this paper is to review and evaluate the published literature on gestodene, and provide a comprehensive profile of its properties and actions when administered as a COC in conjunction with ethinyl estradiol. Key themes include the pharmacokinetics and potency of gestodene, its effect on cycle control, its short- and long-term safety profile, and its tolerability. The collated literature will then be summarized and used to evaluate the place of gestodene in the current contraceptive landscape.

2. Potency

All progestins bind with relatively high affinity to the progesterone receptors and vary in their affinity for other receptors, including the androgen, glucocorticoid and mineralocorticoid receptors. The affinity of a progestin for a particular receptor is determined from binding studies performed using a wide range of models, including human and animal tissues and cell lines. Binding assays are usually performed using a constant concentration of radiolabeled reference progestin, such as promegestone, incubated with varying concentrations of an unlabeled competitor test progestin to obtain an IC_{50} for the competitor. The IC_{50} is the concentration of the unlabeled progestin that corresponds to 50% inhibition of the total binding of the radiolabeled reference progestin. Affinities are usually expressed as percent relative binding affinity (% RBA = IC_{50} competitor/IC_{50} reference × 100%). RBAs are often only an approximate measure of binding affinity because the IC_{50} can vary with concentration of receptor and/or radiolabeled reference progestin, and whether or not equilibrium has been reached in the assay. In one review, RBAs of a variety of progestins to the progesterone receptors were compiled from several competitive binding studies by cross-comparison [11]. The analysis showed that levonorgestrel and etonogestrel had higher binding affinity than gestodene, and that gestodene had higher affinity than norethindrone and drospirenone, the latter of which demonstrated the lowest affinity of the progestins mentioned here. However, another study found that when comparisons of binding affinities were determined using recombinant human progesterone receptor binding, in vitro, gestodene demonstrated the highest affinity, followed by levonorgestrel and norethindrone [12].

The affinity of a progestin for a steroid receptor is a major contributor to its potency since the concentration of the progestin, competing endogenous hormone and receptor concentrations, in conjunction with the progestin's affinity, determine the fractional occupancy of the receptor; this in turn affects the percentage of the progestin's maximal response, i.e., its efficacy [13]. The term "potency" has been widely used in in vitro animal and clinical studies to describe many different biologic actions of progestins. Pharmacologically, the potency of a drug is defined as the concentration of the drug required for half of its maximal biologic response (EC_{50}) under defined experimental conditions. However, potency alone does not describe the biologic effect of a drug; efficacy must also be determined. Efficacy of a drug refers to the maximal biologic effect that the drug can elicit under defined experimental conditions. Both potency and efficacy can only be accurately determined by performing a dose–response analysis in which dose–response curves are constructed using cells in culture, tissue, animals or humans. A variety of responses can be measured, including enzyme/activity, mRNA levels, and physiologic functions, e.g., ovulation inhibition.

Although dose–response analysis was performed in some studies, usually only three doses are chosen arbitrarily and full curves are not generated. In most instances, the assays used to determine the "potency" are based on the progestational effects of the progestogens on delay of menses, inhibition of