Pharmacologic Characteristics of Progestins Used for Contraception and Hormone Replacement Therapy, Including New Transdermal Technologies

Based on a presentation by Ronald T. Burkman, MD

Presentation Summary

Structural differences among progestins account for their unique properties. Pharmacologic principles should be used when considering the appropriate progestational agent to achieve both clinical and economic outcomes. Use of the same progestin in oral contraceptives (OCs) and hormone replacement therapy (HRT) allows for a seamless transition from OCs to HRT, while maintaining the health benefits of the OC. A pharmacologically based approach also has been used in developing the first transdermal contraceptive system, which is expected to be on the market in early 2002.

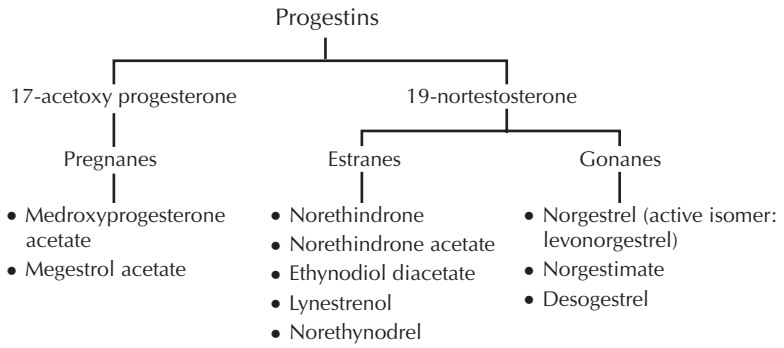
Ronald T. Burkman, MD, began his presentation by stating that pharmacologic principles should be used when considering the appropriate progestational agent to achieve both clinical and economic outcomes. Among women of reproductive age, including perimenopausal women, the desired progestational properties include ovulation inhibition; good cycle control with control of abnormal/undesired bleeding; a low side-effect profile; a range of noncontraceptive health benefits, and an absence of antiestrogenic effects, particularly as they relate to sex hormone-binding globulin (SHBG) levels. In postmenopausal women, the desired properties are somewhat different. For these patients, the goals are to achieve endometrial protection; noninterference with positive estrogenic effects, such as the beneficial effects on lipids and the cardiovascular system; a low side-effect profile with no undesired bleeding; and additional health benefits.

Differences in Activity

Progestins are classified on the basis of structural differences. The first progestins to be synthesized were the 17-acetoxy progesterone derivatives, or pregnanes, followed by the 2 types of 19-nortestosterone derivatives, estranes and gonanes (**Figure 1**).[1] The structural differences between progestins result in significant differences in their activity, as can be seen in their effects on various target organs. All of the synthetic progestins are far more potent inhibitors of ovulation than progesterone, with gonanes being somewhat more potent than estranes.[1,2] Gonanes are also substantially more potent than estranes in terms of endometrial transformation.[2] Equally important, the gonanes have a longer half-life, which makes possible lower doses or less frequent dosing, which in turn may reduce side effects and facilitate greater compliance.[3]

Different progestins also have different effects on plasma SHBG, a protein produced by hepatocytes that transports testosterone and estradiol in the blood. SHBG limits the clearance of sex steroids and regulates their access to target cells. Estrogen and thyroid hormone exert a beneficial effect on SHBG by increasing plasma levels, whereas androgenic progestins decrease SHBG levels and produce androgenic side effects. "Norgestrel and gestodene have a very high binding affinity for SHBG compared with the major

Figure 1. Clinical Classification of Progestins



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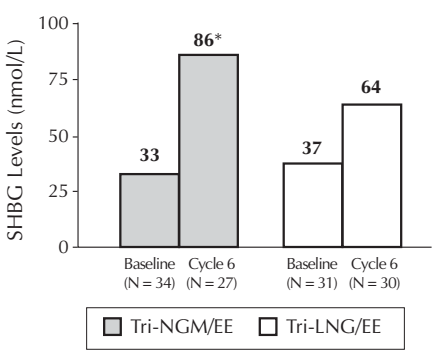
active metabolite of desogestrel," Dr. Burkman noted. "However, norelgestromin, the major metabolite of norgestimate, which is distributed by albumin rather than SHBG, has essentially no binding affinity for SHBG."[4]

A study comparing triphasic oral contraceptive (OC) formulations containing norgestimate (NGM) or levonorgestrel illustrates the implications of these differences.[5] Plasma levels of SHBG were increased significantly (P =.0005) by the norgestimate-containing OC (**Figure 2**), supporting its minimal androgenicity (Based on the results of 2 randomized trials, a triphasic NGM OC was approved by the Food and Drug Administration as an indication for the treatment of acne.[6,7]).

Different progestins also vary in their effects on lipids. Unlike estranes, gonanes, such as desogestrel and NGM, have favorable effects on lipids. As an example, Dr. Burkman cited a study in which OCs containing either desogestrel or NGM were assessed for efficacy, safety, and metabolic effects.[8] A rise of 13% and 10% in high-density lipoprotein (HDL) levels and a reduction of 2% and 0.2% in low-density lipoprotein (LDL) levels were observed, respectively, for desogestrel and NGM (**Figure 3**).[8] "These changes in lipids are responsible for some of the potential protective cardiovascular effects of HRT in postmenopausal women," Dr. Burkman noted, adding that this is not a result of direct action of the progestin but because the progestins do not interfere with the positive effects of estrogen on lipids.

Figure 2. Androgenicity of Progestin Component Affects SHBG Levels



EE = ethinyl estradiol; LNG = levonorgestrel; NGM = norethindrone acetate; SHBG = sex hormone-binding globulin.
*Between-regimen difference: P = .0005.
Source: Reference 5.

Use of the Same Progestin in OC and HRT Formulations

"Use of the same progestin in HRT allows for a seamless transition from OCs to HRT while maintaining the cardiovascular and dermatologic benefits of the OC," Dr. Burkman said, adding, "the NGM/17β-estradiol HRT formulation takes advantage of the low androgenicity of NGM, its optimal progestational profile, and favorable metabolic effects. Its successful long-term use in OC formulations increases its acceptance among menopausal women, ensuring compliance with a continuum of hormonal care."

Low-Dose and Transdermal Contraceptives

Dr. Burkman shifted his focus to a more specific discussion of the impact of the pharmacology of 3 new contraceptives—2 low-dose oral preparations and a novel new transdermal contraceptive system—on their efficacy, side effects, and dosing/delivery. In a comparative trial[9] of the

2 low-dose OCs, NGM/25 µg ethinyl estradiol (EE) versus norethindrone acetate (NETA)/20 µg EE, far more breakthrough bleeding (BTB)/spotting occurred with the NETA-containing OC than with the NGM-containing OC. Yet, BTB/spotting was no greater with the NGM low-dose OC than with triphasic NGM, a preparation containing a higher dose of estradiol (35 µg) and the same amount of NGM (**Figure 4**). Dr. Burkman noted, "As estrogen is reduced, a more potent progestin, NGM, is necessary to maintain endometrial stability."

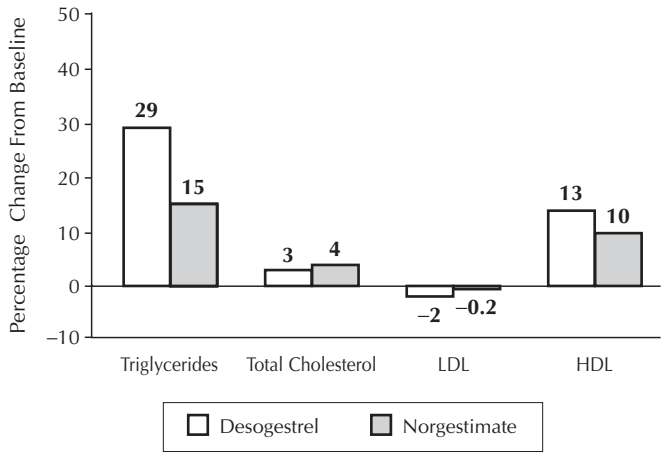
On the other hand, patients find regular withdrawal bleeding reassuring and an indication that they are functioning normally. Thus, amenorrhea can be disconcerting for many women. In this study, amenorrhea was very uncommon with the NGM compound, but occurred in 8% to 15% of cycles with the estrane compound.[9] Efficacy and side-effect profiles of the 2 agents were similar. The NGM/25 µg EE preparation is expected to be on the market in the latter part of 2002.

A similar pharmacologically based approach has been used in developing the first transdermal contraceptive system, which is expected to be on the market in early 2002. It provides continuous delivery of a daily dose of 150 µg norelgestromin (NGMN), the primary active metabolite of NGM, plus 20 µg EE through the skin for 7 days. Serum levels are within the range necessary for adequate contraception and are maintained for 7 days or longer. Dr. Burkman commented that the transdermal contraceptive system does not have the wide swings in serum concentration observed with OCs. He also noted that some degree of patient error may be covered by the extended protective effect of the 2-day forgiveness period; serum concentrations are maintained within levels needed for contraception for 9 days, while the patch is to be replaced every 7 days (**Figure 5**).[10]

The transdermal contraceptive system can be applied to 4 therapeutically equivalent sites—the buttocks, the abdomen, the torso (excluding breasts), or the upper outer arm.[11] In Phase 3 trials, women who wore it while on treadmills and while taking whirlpool baths had less than 2% of the patches detach completely.[12] Moreover, it was well tolerated, with less than 2% of patients removing it because of irritation.

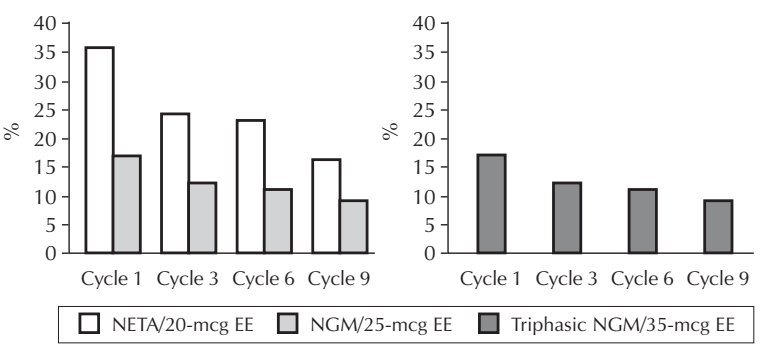
A recently published, randomized trial comparing the transdermal contraceptive

Figure 3. Lipid Effects of Low-Androgenic Progestins



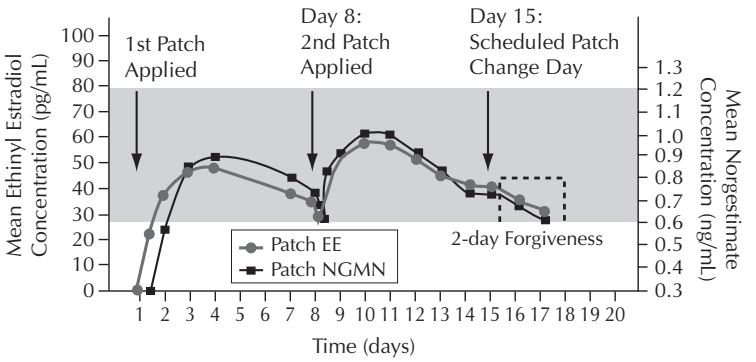
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Source: Speroff L, DeCherney A, and the Advisory Board for the New Progestins. Evaluation of a new generation of oral contraceptives. *Obstet Gynecol* 1993;81:1034-1047. Reprinted with permission from the American College of Obstetricians and Gynecologists.

Figure 4. Oral Contraceptives: Breakthrough Bleeding Comparisons



EE = ethinyl estradiol; NETA = norethindrone acetate; NGM = norgestimate.
Source: Reprinted from Hampton RM, Short M, Bieber E, et al. Comparison of a novel norgestimate/ethinyl estradiol oral contraceptive (Ortho Tri-Cyclen Lo) with the oral contraceptive Loestrin Fe 1/20. *Contraception* 2001;63:289-295 with permission from Elsevier Science.

Figure 5. Transdermal Contraceptive System: Serum Concentrations



EE = ethinyl estradiol; NGMN = norelgestromin.
Source: Reference 10.

system with an oral levonorgestrel triphasic preparation showed the number of pregnancies with the transdermal contraceptive system (5) was comparable with that of the OC (7), as were the overall Pearl Indexes (user failure plus method failure; 1.24 and 2.18, respectively) and the method scores (failure when taken as directed; 0.99 and 1.25, respectively).[13]

However, the 2 forms differed dramatically in terms of compliance. In this trial, a rate of 78% compliance, with correct or perfect use, was observed in the group receiving OCs. In contrast, more than 88% of the women in the transdermal contraceptive system group achieved perfect compliance—which should translate to reduced unintended pregnancy rates. Further, the incidence of BTB was comparable between the 2 treatments at all cycles.

Efficacy and rates of BTB observed with the transdermal contraceptive system are comparable with that of oral preparations, and a variety of anatomic sites (buttocks, abdomen, torso, and upper outer arm) are therapeutically equivalent. Of particular interest, compliance with the weekly transdermal contraceptive system is superior to that of the daily OC regimen; the transdermal contraceptive system delivers constant hormonal levels, unlike the peaks and troughs associated with oral contraception; and it maintains serum concentrations within levels needed for contraception for 9 days, affording women with an increased margin for error.

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