GENERAL GYNECOLOGY

Transdermal hormonal contraception: benefits and risks

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Transdermal drug delivery systems have been available in the United States for >20 years. Since the introduction of the first transdermal patch (scopolamine) for the treatment of motion sickness, >35 transdermal patch products have been approved by the US Food and Drug Administration for a variety of indications that include hormone replacement therapy, nicotine replacement therapy, chronic pain (fentanyl), angina (nitroglycerin), hypertension (clonidine), and more recently, overactive bladder (oxybutynin), and contraception (ethinyl estradiol/norelgestromin). Clinical data demonstrated the efficacy and safety of the contraceptive patch; however, concerns regarding estrogen levels and reports of venous thromboembolism led to the development of 2 epidemiologic studies and, subsequently, revised product labeling. Despite this, the contraceptive patch may be an appropriate option for some patients.

Key words: contraceptive patch, hormonal contraception, transdermal delivery

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Transdermal drug delivery has a number of advantages (Table 1).[1-6] Transdermal delivery systems provide continuous administration of drug through the skin, which maintains constant plasma drug levels and avoids the peaks and troughs that are seen with oral administration.[1-3] Losses of bioavailability because of first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract that are seen with oral drug administration are avoided, which makes it possible to use lower doses of drug to achieve the therapeutic effect.[5,7] Continuous delivery of drug may reduce systemic side effects, particularly side effects that are associated with high plasma levels.[1,2,5] The multiday dosing that is made possible by the sustained delivery of drugs with short half-lives, which would require frequent dosing if given orally, improves patient compliance.[1,2] Other advantages of transdermal patches include a nonoral route of administration for patients who are unable to take oral medications and the immediate cessation of drug administration with removal of the patch.[1]

Unfortunately, the number of drugs that can be delivered by passive diffusion from a patch is limited by the barrier properties of the skin. At the present time, only low molecular weight substances with the correct balance of lipophilic and hydrophilic properties can be delivered effectively through the skin, although chemical permeation enhancers and other technologies are under investigation.[1-3,8,9] The drug molecule itself has to be potent, because the patch size limits the amount that can be delivered.[1,9] Although there was a high incidence of local skin reactions and problems of adhesion with the first generation of patches that used a reservoir system, the newer matrix systems have reduced these problems substantially.[6,7] It is important to recognize that, once a matrix patch is fully detached, it cannot be taped back on. Because the contraceptive hormones are an integral part of the adhesive system, the ability of the patch to deliver appropriate concentrations of hormones is lost when the patch is detached fully.

★ EDITORS' CHOICE ★

Transdermal Hormonal Contraception

The first transdermal contraceptive patch, a matrix system that contained a combination of 6.0 mg norelgestromin (formerly called 17-deacetylnorgestimate) and 0.75 mg ethinyl estradiol (EE; ORTHO EVRA; Ortho Women's Health & Urology, Raritan, NJ) was approved by the Food and Drug Administration in November 2001. Norelgestromin is the primary active metabolite of norgestimate, which is a progestin that has been used in combination with EE as an oral contraceptive (OC) since 1986.[10] One patch is applied once weekly for 3 consecutive weeks, followed by a patch-free week. During the 7-day wear period, the patch delivers constant, continuous levels of hormones and avoids the peaks and troughs seen with OCs (Figure 1).[11,12] The patch is more forgiving of dosing errors than an OC. Even if a scheduled patch change is missed for 2 days during weeks 2 and 3 of a 4-week cycle, clinical efficacy is maintained, and backup contraception is not needed.[12] The transdermal delivery of norelgestromin and EE avoids the enzymatic degradation in the gastrointestinal tract and possible first-pass metabolism in the liver that occurs with oral administration.[13] In a study that involved 5 premenopausal and 9 postmenopausal women that compared oral with vaginal administration of EE, a first-pass effect was not demonstrated.[14] However, little data exist about the transdermal route and other contraceptive steroids that are relative to this issue.

Prescribing Information Update

The manufacturer of the ORTHO EVRA patch, together with the Food and Drug

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TABLE 1
Advantages and disadvantages of transdermal drug delivery systems[1-6]

Advantage	Disadvantage
Continuous, sustained release of drug	Only small, lipophilic drugs can be delivered currently through the skin*
Avoids peak and trough drug levels	Drug molecule must be potent because patch size limits amount that can be delivered
Longer, multiday dosing interval	Not suitable for high drug doses
Avoids first-pass hepatic metabolism and enzymatic degradation by gastrointestinal tract	Adhesion may vary with patch type and environmental conditions
Less frequent dosing improves patient compliance	Skin irritation and hypersensitivity reactions may occur
Alternate route for patients who are unable to take oral medications	
Drug administration stops with patch removal	
Dose delivery unaffected by vomiting or diarrhea†	

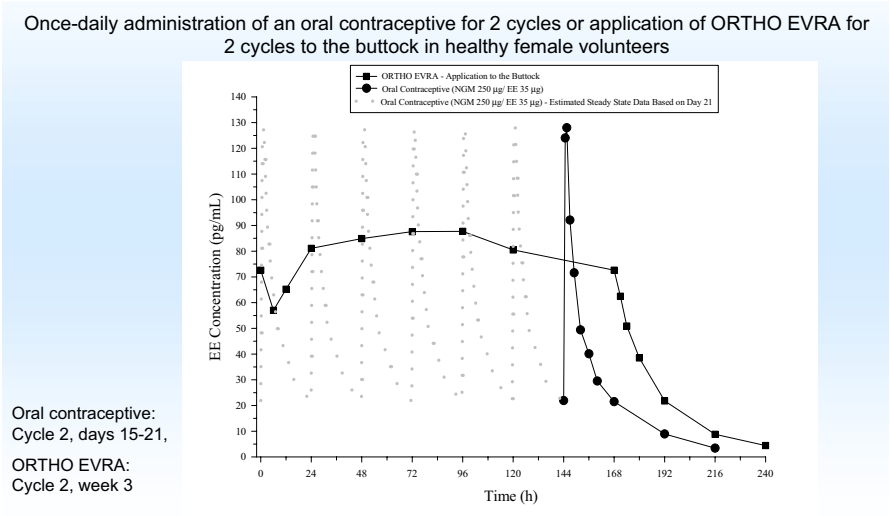
* Chemical permeation enhancers may permit transdermal delivery of a wider variety of drugs.[8]

† ORTHO EVRA PI.

Administration, has amended the prescribing information on the basis of pharmokinetic data and results from 2 separate epidemiologic studies that were designed to evaluate the risk of experiencing serious adverse events when using this method of hormonal contraception. The revised product labeling now includes the following bolded warning:

"The pharmacokinetic (PK) profile for the ORTHO EVRA patch is different from the PK profile for OCs in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA compared with women using an OC containing EE 35 mcg. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA. Inter-subject variability results in increased exposure to EE in some women using either ORTHO EVRA or OCs. However, inter-subject variability in women using ORTHO EVRA is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in pharmacokinetic profiles of EE in women using ORTHO EVRA compared with women using OCs containing 35 μg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism."[11]

FIGURE 1
Mean serum concentration-time profiles of EE: OC and ORTHO EVRA[11]



Once daily administration of an OC for 2 cycles or application of ORTHO EVRA for 2 cycles to the buttock in healthy female volunteers. Reprinted from the ORTHO EVRA package insert with permission from Ortho Women's Health & Urology, a Division of Ortho-McNeil Pharmaceuticals, Inc.

EPIDEMIOLOGIC STUDIES

Results from 2 separate case control epidemiologic studies that evaluated the risk of venous thromboembolism (VTE) and heart attack and stroke in contraceptive patch users compared with women who used an norgestimate OC that contained 35-μg EE have been reported recently.[15,16] Jick et al[15] provided results on the risk of nonfatal VTE in a nested case-control study using data from PharMetrics (Watertown, MA), a US-based company that collects information about insurance claims that are paid by managed care plans. The main outcome measures for this study were odds ratios and incidence rates that compared the risk of nonfatal VTE in new users of either the transdermal contraceptive patch or norgestimate OCs that contained 35-μg EE. Sixty-eight cases of VTE were identified in women aged 15-44 years (n = 31 for the patch; n = 37 for the OCs); 266 control subjects (women without VTE) were matched by year of birth and index date of the case. The odds ratio for the comparison of the patch with the OC was 0.9 (95% CI, 0.5-1.6). The overall incidence rate for VTE was 52.8 per 100,000 women-years (95% CI, 35.8-74.9) among patch users and 41.8 per 100,000 women-years for users of norgestimate-containing OCs (95% CI,