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Transdermal Application of Steroid Hormones for Contraception

Régine Sitruk-Ware

Medical and Clinical Development Department, CIBA-GEIGY Ltd, P.O. Box 4002, Basle and Division of Endocrinology, Department of Internal Medicine, University Hospital, Basle, Switzerland

The concept of transdermal delivery (TD) for steroid application has nowadays been largely accepted for hormone replacement therapy in the menopause. It is only recently that the same concept has been envisaged for contraception. The skin can be penetrated by both estrogens and progestins, provided they are delivered in an appropriate solvent. About 10% of the total dose applied topically is actually absorbed. The transdermal delivery systems (TDS) presently available are either of the reservoir type (membrane-moderated system) or of the matrix dispersion type where the drug is dispersed into a polymer matrix. Estradiol (E_2) is the most appropriate steroid for TD and can be combined with progestins to ensure a contraceptive effect. Only potent progestins should be used to achieve effective plasma levels with low doses in order to maintain an acceptable small surface of TDS. TDS changed weekly and delivering both E_2 and levonorgestrel (L-NG) at daily dosages of 38.4 ($\pm$7.5) and 28.8 ($\pm$7.2) μg/10 cm^2 per day respectively, showed ovulation suppression. Another progestin derived from norprogesterone (ST 1435) has been shown to penetrate the skin when suspended in acetylated lanolin or dissolved in a hydroalcoholic gel and to ensure ovulation suppression at a dose of 2 mg per day in a small number of cycles. These preliminary data demonstrate the feasibility of suppressing ovulation in women by transdermal absorption of steroids. Using TDS for contraception implies that such systems should be perfectly adhesive, well tolerated locally and achieve nearly 100% efficacy. These targets are very challenging, however, the potential advantages are so high that the concept deserves further development.

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INTRODUCTION

During the past decades, women have been trying to find alternatives to the pill for fertility regulation. It has been shown in western countries that an increasing number of women have stopped using the oral contraceptives in parallel with an increasing number of published articles in women's magazines and the lay press, questioning the safety of oral steroids.

One of the main drawbacks of oral contraceptives which affect compliance appears to be the need for daily intake with a high "price to pay" in case of a forgotten pill. Therefore long-acting delivery systems appear attractive to many women and to the prescribers. Non-oral delivery of steroids has been described through vaginal rings, implants and injectables which all offer a long-lasting effect and also a good tolerability profile due to the evidence of a first-pass liver effect usually responsible for metabolic drawbacks. Among these new non-oral methods transdermal delivery systems (TDS) offer a new way of delivering contraceptive steroids with two main advantages over the pills: they enable the use of a lower dose of steroids because the liver, where steroids are usually first metabolized, is by-passed; and they would act over a few days, avoiding the daily pill intake.

Although the use of TDS represents a growing sector of the industry in the treatment of menopausal symptoms and hormonal replacement therapy (HRT), the concept of TDS has been envisaged for contraception by several authors but is facing current technological limits [1, 2].

THE SKIN AS A ROUTE OF DELIVERING STEROIDS

Using the skin to deliver steroids into the systemic circulation would have appeared an unrealistic challenge at the turn of the 20th century. From that

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time, it has been shown that the skin is not totally impermeable to all substances but can be permeable to lipid-soluble substances [3]. It has been also widely recognized that the stratum corneum has the principal barrier function of the epidermis and acts as a reservoir and a diffusion barrier [4, 5].

The skin is a multilayered organ composed of the epidermis, characterized by the absence of capillary blood flow, the dermis and the hypodermis. The epidermis is five-layered and its outer layer, the stratum corneum, acts as the protecting barrier to the body. The horny external layer contains only 20% water, while the regenerative internal layer called the stratum germinativum contains about 70% water. The dermis contains the capillary plexus connected to the general circulation and the rate of blood perfusion through the skin is extremely rapid.

The diffusion of drugs through the skin is a complicated process not yet fully understood. Among the key factors for skin penetration, the physicochemical properties of the drug and the characteristics of the enhancers are crucial to determine the rate at which a molecule will diffuse across the skin [2, 3]. Small hydrophilic or polar molecules can be absorbed through the skin at a rate controlled by the stratum corneum. With occlusion of the skin as in a TDS, and the use of appropriate enhancers, the permeation of the skin increases greatly [3, 5].

In the absence of occlusion, when a substance is applied topically on the skin, according to its dissolution in an appropriate solvent, the molecules will be absorbed within the stratum corneum, then a diffusion process occurs through the epidermis and the capillary dermis until the molecules are transferred to the capillary plexus and the circulating blood [3].

When using transdermal devices the events involved in drug diffusion through the skin include: drug transport within the delivery system to the device/skin interface; partitioning of the drug from the delivery system into the stratum corneum; and then diffusion and transport as described above [2, 6].

Individual variations occurring at each of these important steps will affect the rate of absorption, and as well the thickness of the stratum corneum and its degree of hydration under occlusion will affect skin permeability.

TRANSDERMAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS (TDS)

The success of this method of delivering drugs depends on the optimization of the reservoir and of the barrier membrane which regulates the release of the drug. The reservoir should ideally hold the drug in a stable condition and not interact with the drug itself. It should also maintain its integrity at high humidity and at high body temperature, be self-adhesive, have a good surface contact with the skin and be non-irritant. In the field of contraception the perfect adhesiveness of such a system is of crucial importance as this prerequisite ensures the constant delivery of the active compounds. The user should indeed never run the risk of being unprotected whenever the system is lost. Also, the long-lasting delivery of the steroids over a week, as has been described [1], implies that the system should be strictly non-irritant. Nevertheless, the occlusion of the skin for more than 24 h is not a physiologic condition. Therefore, skin irritation and redness would be unavoidable in some sensitive skins.

The membrane-moderated system

In this approach, the drug reservoir is contained within a compartment delimited by a drug-impermeable metallic plastic laminate and a rate-controlling polymeric membrane. This membrane can be non-porous, with defined drug permeability properties, or microporous. On the external surface of the polymeric membrane, a thin layer of drug-compatible, hypo-allergenic adhesive polymer can be added to achieve intimate contact with the skin.

The adhesive diffusion-controlled system

This is a simplified version of the membrane-moderated system. Here, the drug reservoir consists of an adhesive polymer from which the drug is released. This medicated adhesive is spread onto a drug-impermeable metal-plastic laminate. A layer of non-medicated rate-controlling adhesive polymer is added to provide adhesion and diffusion control.

The matrix dispersion type system

This third system consists of a hydrophilic or lipophilic polymer matrix in which the drug is dispersed. Then the medicated polymer is moulded into a disc of a controlled thickness and applied onto an occlusive baseplate in a compartment fabricated from a drug-impermeable plasting backing. The adhesive is applied only along the circumference to form an adhesive rim around the medicated disc.

The microreservoir type system

This type of system consists of a suspension of the drug solids in an aqueous solution of water-soluble liquid polymer. This drug suspension is dispersed homogeneously in a lipophilic polymer to form numerous microscopic spheres of drug reservoir. This dispersion is thermodynamically unstable and is stabilized by cross-linking the polymer chains *in situ*. The medicated polymer disc is then covered by an occlusive baseplate and surrounded by an adhesive rim.

Other systems are under investigation, especially Poroplastic® membranes. These patches have the appearance of adhesive bandage and are made of ultramicroporous membranes of cellulose triacetate. The drug is contained within the microporous membrane [7].

The adhesive is one of the most critical components of TDS, as it should be highly permeable, non-irritant and adhesive by simple pressure onto the skin. So far, silicone medical adhesive and polyisobutylene/mineral oil have been utilized. The adhesive properties of the system, as well as the skin absorption, can also be modified by various parameters affecting the skin. For example, environmental factors such as temperature and humidity can affect permeation and adhesion, the thickness of the skin may differ slightly at different sites, and absorption is easier through the thinnest areas. Cosmetics and the use of oily creams will obviously affect adhesion. Occlusion of the system enhances local hydration and hence increases penetration [7].

STEROIDS FOR TRANSDERMAL DELIVERY FOR CONTRACEPTION

To date, the delivering of contraceptives through the skin has involved steroid agents already used in oral contraception, e.g. estrogens and progestins. In order to select an appropriate candidate for transdermal drug delivery, several criteria should be met:

—the drug must be potent, requiring a low daily dose of milligrams or less, allowing for a small surface area of TDS;
—drugs subject to extensive hepatic first-pass metabolism after oral intake such as sex steroids would benefit from the TDS route;
—the drug should not be irritant or allergenic, as an occlusive TDS obviously may itself induce a mild irritation, and sensitization in rare instances;
—the drug should not be subject to cutaneous metabolism within the epidermis;
—the occurrence of tolerance should be monitored as the constant delivery of the drug may in some cases elicit desensitization.

Both 17β-estradiol and progesterone can be readily absorbed through the skin when dissolved in an appropriate solvent. However, progesterone (P) itself is subject to a cutaneous metabolism through the 5α-reductase enzyme and is inactivated into 5α-dihydroprogesterone [8]. Also high doses are required to elicit the desired progestational effect and therefore other progestins are better candidates for contraceptive devices such as levonorgestrel (L-NG) [1, 2] or 19-norprogesterone derivatives such as ST 1435 [9, 10].

Estradiol absorption

Estradiol (E_2) is the most appropriate steroid for transdermal delivery and when applied to human skin in an appropriate enhancer, it rapidly penetrates the epidermis and the dermis via the pathway above-described. About 10% of the total dose applied topically is actually absorbed [3, 11].

In the reservoir systems available for HRT since the mid-1980's as Estraderm® rate-controlled systems, 25, 50 or 100 μg/day can be delivered over a period of 3–4 days through a small surface area of 5, 10 or 20 cm^2 and have been shown to achieve plasma levels of about 25, 40 and 75 pg/ml respectively [12].

Although these levels are adequate for HRT, the doses required to inhibit the luteinizing hormone (LH) ovulatory peak would be far higher, giving the risk of endometrial hyperstimulation if given unopposed.

Watson *et al.* [13] in a very small number of women (10) have shown that ovulation can be suppressed with a dose of 200 μg/day of E_2 given transdermally for three consecutive cycles. They monitored the follicles diameter with ultrasonography and did not detect any follicle exceeding 10 mm in diameter and progesterone levels assessed every other day remained constantly below 2 nmol/l. It is obvious that concomitant use of progestins would be necessary to avoid endometrial stimulation, enhance the inhibition of the LH peak and allow for lower levels of E_2 coadministration. This has been achieved by Chien *et al.* [1] with a combination of about 40 μg/day of E_2 and 30 μg/day of L-NG.

L-NG skin absorption

L-NG is one of the most potent progestins derived from 19-nortestosterone and when administered orally can suppress ovulation at doses as low as 75 μg/day [14]. When delivered parenterally through implants [15] or vaginal rings [16] daily doses as low as 30–50 μg or 20 μg, respectively, were found to be effective [15–17].

Friend [2] has tested two enhancers for L-NG and has found that ethyl acetate (EtAc) was 7–8 times more potent than ethanol (EtOH) in enhancing the rate of penetration of L-NG through mouse skin. He obtained a flux through human cadaver skin of 0.20–0.25 μg/cm^2/h when the vehicle used was EtAc which results in a TDS of 5 cm^2 to deliver 25–30 μg L-NG/day.

Chien *et al.* [1] have used TDS of the micro drug reservoir-type delivering both E_2 and L-NG at daily dosages of 38.4 ± 7.5 and 28.8 ± 7.2 μg/10 cm^2/day respectively, and showed ovulation suppression in a small number of women.

Upon completion of a 1 month pretreatment cycle, 12 women received either one or two TDS per week for 3 consecutive weeks starting on day 5 of the treatment cycle. They received a placebo patch in the fourth week. In this study the results indicated that each subject received a daily dose of 27.6 ± 2.3 μg/day when one patch only was applied on the abdominal site and 57.7 ± 3.4 μg/day when two patches were used. This led to fairly constant levels of L-NG during the first 2 weeks of therapy reaching 84.7 ± 8.3 pg/ml or 133.7 ± 13.1 pg/ml respectively [18].

The contraceptive efficacy demonstrated with such low plasma levels of L-NG is surprising as it was

previously shown in Norplant users that plasma levels of about 300 pg/ml were necessary to suppress ovulation [15].

Absorption and efficacy of ST 1435

ST 1435 (16-methylene-17-α-acetoxy-19-nor-4-pregnene-3,20-dione) is a synthetic progestin derived from 19-norprogesterone. Although ineffective when given orally, it is able to inhibit ovulation in women when given in subdermal implants at doses leading to plasma concentrations above 50 pg/ml [9]. Given its structure and its potency at very low doses, its ability to cross the skin was explored using suspension of micronized ST 1435 crystals in acetylated lanolin [9]. The suspension was delivered percutaneously over the periumbilical area at doses of 1 or 2 mg/day in normal female volunteers. Applications were administered every other day and plasma samples were taken twice daily for hormone evaluation. The highest progesterone values in these women having documented ovulations in the pretreatment cycle were below 3 ng/ml indicating ovulation suppression mainly with the 2 mg/day dosage.

In another study, Laurikka-Routti *et al.* [10] using a hydroalcoholic gel as the vehicle for topical application of ST-1435 have shown that a 0.8 mg dose of the progestin administered once daily was able to suppress ovulation in nine women followed up for three consecutive cycles. In both studies [9, 10], plasma levels of E_2 were maintained in the follicular range and plasma values of P indicated ovulation suppression. During treatment with 2 mg/day, E_2 serum levels were in the range of 73–240 pg/ml and P levels below 3 ng/ml. ST 1435 serum levels were measured and were maintained above 100 pg/ml. In another study from Haukkamaa *et al.* [19] ST 1435 was measured in plasma and saliva over 7 days of therapy with repeated dose of 2.3 mg daily in an hydroalcoholic gel. High excretion of the progestin was detected in the saliva 2 h after application and peak serum levels reached 232 pmol/l at 24 h. Interindividual variations were observed in these women volunteers.

From the data mentioned above it appeared that plasma levels comprised between 50 and 100 pg/ml would be sufficient to consistently suppress ovulation [9]. Croxatto and Zepeda [9] indicated, however, that in 17 of the 21 cycles studied in their initial experiments, 17 cycles reflected irregular bleeding patterns. The number of bleeding days was prolonged compared to previous regular menses observed in the control cycles and intermenstrual spotting was observed in eleven cycles. Similar findings have been reported with other methods of continuous delivery of low doses of progestin agents [15].

Absorption of norethisterone acetate (NETA)

Derivatives from 19-nortestosterone, such as NETA, have been shown to penetrate the skin at doses of 250 μg/day delivered together with 50 μg/day of E_2 from TDS applied twice weekly for correction of menopausal symptoms [20]. This system is not intended for contraception purposes. As L-NG has been shown to be 10-fold more potent than norethisterone [14] it is likely that a dose of about 300 μg/day of NETA would be effective to achieve ovulation suppression. However, with vaginal delivery of E_2 and NETA, doses of 700 μg/day of NETA associated with 150 μg/day of E_2 were necessary to achieve about 90% ovulation inhibition [21]. Therefore transdermal systems of a very large surface area would be required to deliver NETA in the appropriate doses for contraception.

In order to achieve ovulation suppression with steroids administered transdermally, only very potent progestins appear to be the ideal candidates and especially L-NG and derivatives of 19-norprogesterone which have shown high progestational and high antigonadotropic potencies [9, 14].

CONCLUSION

An ideal contraceptive delivery system should provide a high efficacy in fertility control, minimum side-effects, an increased ease of administration, an improved patient compliance as well as the possibility to rapidly terminate therapy in case of side-effects. The TDS appear to be good candidates to answer these needs and their development would bring a real breakthrough in the field of woman's health.

When TDS is proposed to women for contraceptive purposes, such systems should be perfectly adhesive, well-tolerated locally and should achieve nearly 100% efficacy. These targets are very challenging but the potential advantages of such a method are so high, given its simplicity and very low toxicity potential, that it deserves further evaluation.

The results obtained in the preliminary studies described above appear highly promising and further large studies with long-term follow-up are required to confirm the efficacy, tolerability and safety of such contraceptive systems.

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