REVIEW

Optimizing delivery of therapeutics: percutaneous technologies

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Abstract

The purpose **of this communications is to 1) demonstrate the potential of percutaneous drug-delivery on the example of female reproductive steroids, 2) point out the differences between transdermal and conventional drug dosing, and 3) outline new technologies and innovations that are looming on the horizon, specifically in the area of pain control.**

Transdermal delivery systems are of two basic types. The first ones employ principles of *passive* diffusion, and they are used for hormonal replacement therapy (HRT) and contraception. Patches for HRT, designed to release estradiol (E_2) only, require a simultaneous dosing with oral progestogens. Patches employing both E_2 and a progestogen release the combination either continuously or sequentially. In the latter method, estrogen-only patches are applied for 14 days, followed by a 14-day application of patches releasing both hormones. Both methods successfully cope with symptoms and signs of menopause, including bone loss.

Contraceptive **transdermal patches deliver ethinylestradiol in combination with the progestogen norelgestromin. This system provides high contraceptive protection with predictable withdrawal bleeding and without major adverse events and weight changes.**

Hormones delivered by the skin avoid first-pass liver metabolism. Other advantages include rapid onset and termination of action, self—administration, and attainment of therapeutic hormone levels with low daily doses. A disadvantage is the variable intra- and inter-individual percutaneous absorption. In some patients, patches can cause skin irritation.

Active **systems deliver therapeutics across intact skin non-invasively by means of an electric potential (*electrotransport*). A system consisting of tooth-like titanium *microprojections* that penetrate only the keratinized epidermis facilitates painless and needle-free transport of complex molecules to the capillaries of the dermis. Other devices use *low frequency ultrasound.* These systems enable precise dosage, delivery of large molecules, such as growth hormone and vaccines, and dosing of analgesics „on demand". Novel transdermal technologies are profoundly changing the current methods of pain management. *(Fig. 6, Ref. 47.)***

Key words: percutaneous technologies, pregnancy, obstetrics, gynaecology, drug delivery.

The second part of the last century witnessed a dramatic proliferation of medicinal compounds. At the same time, it became apparent that many modern drugs cannot realize their full therapeutic potential when administered by conventional methods — by the digestive tract or by injections. New drug delivery techniques have been sought to be better suited to fulfill the elementary principles of pharmacology, namely, to achieve therapeutic effects with a minimal dose and without major adverse events, as well as convenient and painless drug administration. *Transdermal drug deliery systems* have emerged from this search as viable alternatives to conventional methods. Their rapid spread in many disciplines of medicine warrants a review that would be of interest to specialists and general practitioners alike.

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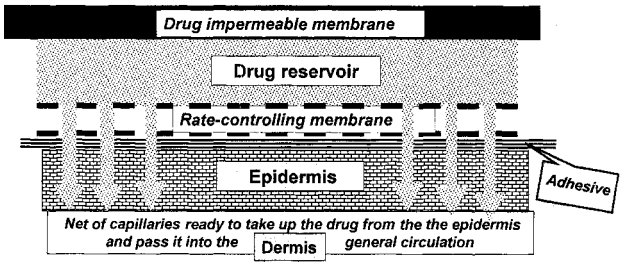

Fig. 1. Schematic presentation of passive transdermal patch, which release the drug from a drug reservoir through a system of membranes. Developed were also matrix-based patches that integrate the drug, the release-controlling membrane, and the adhesive backing into one layer — the matrix.

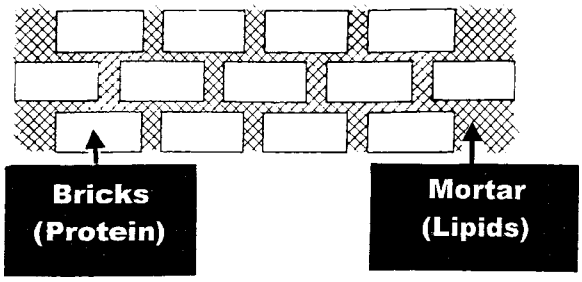

Fig. 2. brick and mortar structure of the stratum corneum of the human skin. The "mortar" consists of hydrophobic substances. To facilitate the transport of the drug through the skin, permeation enhancers are sometimes used. They dissolve the intercellular lipoid substances without damaging the cell membranes and make the skin accessible to water soluble compounds.

and innovations that are looming on the horizon, specifically in the area of pain control.

Traditionally, skin has been regarded as a barrier protecting the body from outside influences proof that skin has a systemic function and can absorb substances from the environment and pass them into general circulation was Gerlach's discovery of percutaneous breathing (1). During the great wars of the 20th century, workers in ammunition factories exposed to nitrates experiences headaches (due to vasodilation) at the start of each working week. Headaches rapidly abated as workers acquired tolerance to nitrates; however, they reappeared after each weekend. The workers soon discovered that placing a small amount of nitrate in a headband over the weekend prevented the repetition of headaches. This measure can be considered as the first rational, if primitive, transdermal drug application. It also was noted that workers with nitrates experienced fever attacks of angina pectoris, and nitroglycerin ointment was introduced for the management of angina in 1954 ((2, 3).

Modern transdermal systems started to evolve during the 1970s and 1980s. Among the first were transdermal patches with scopolamine and nitroglycerin (Alza Corporation, Mountain View, California) (4).

Estradiol (E_2) was the first reproductive steroid clinically used in a transdermal system (5, 6). Today, several transdermal systems containing natural estrogens and synthetic progestogens have been established for hormonal replacement therapy (RHT), while transdermal systems for hormonal contraception became available only recently (7).

The transdermal systems

Transdermal systems are built either on principles of *passive* diffusion across the skin barrier, or they transport therapeutic agents *actively* by electrically assisted technologies.

Passive transdermal systems are of two types. The first one release the drug from a *reservoir* through a *rate-controlling membrane.* An outer drug-impermeable plastic laminate prevents escape of the drug and evaporation of fluids from the area it covers and protects the patch from outside influences. An adhesive layer attaches the patch to the skin and prevents its dislocation even if the skin stretches, shrinks, or moves during physical activities (Fig. 1).

The second type are *matrix-based* patches that integrate the drug, the membrane that controls its release, and the adhesive backing into one layer — the matrix.

The area of contact with the skin determines the total amount of the delivered drug. An adequately steep gradient between drug concentrations in the reservoir and the skin secures an effective diffusion. In the architecture of the patch, functions of individual components must be coordinated, so that the resulting drug diffusion would maintain the drug concentration in the blood at a level that provides the desired therapeutic benefit (8).

The most difficult obstacle for entrance of a drug into the body is the epidermis with is keratinized layer, which is only 10—25 μm in diameter. Barrier properties of epidermis are given by its „brick and mortar" structure in which the bricks are the individual cells, and the mortar are the substances filling the intercellular space (Fig. 2).

Once the drug has crossed the epidermis, its molecules can pass into the net of capillaries of the dermis and enter the general circulation. During this route, the molecules bind to receptors of the various tissue components. Only after all receptors had been saturated, the drug flow can be constant enough to maintain the steady state concentration of the drug in the circulation. The time to achieve the constant flow varies with each drug. For estrogens and progestogens, it is 8 to 24 hours.

Two other functions of the skin should be mentioned. An array of enzymes in the skin facilitates biotransformation reactions similar to those in the liver. However, concentrations of these enzymes are low. Although the skin can oxidize, reduce, glucuronize, and sulphate, various hormonal steroids, they reach the general circulation mostly intact. Irritation and sensitization reactions of the human skin provide a warning system for entrance of xenobiotics and limit the time for which a patch can be attached to the skin.

Transdermal drug delivery systems

Female reproductive steroids are an excellent case in the study of transdermal drug delivery systems. They are widely used for an extended period of time. With the current low oral dosage of estrogens, compliance problems can lessen their efficacy. Steroid molecules are suitable to be administered through the skin because of their relatively small size.

Female reproductive hormones delivered by transdermal systems are designated for 1) HRT, and 2) contraception.

Hormonal replacement therapy

Systems for HRT are of two types, delivering either E_2 only, or a combination of E_2 and a progestogen (Fig. 3).

Women with preserved uteri, when using E_2-only patches, have to add oral progestogens for a minimum of 10 days in order to prevent hyperstimulation of the endometrium. Regular withdrawal bleeding occurs in over 70 % of cycles (9, 10). Women with intact uteri should use the system in a cyclic fashion, usually for three weeks followed by an one-week pause. Women who had a hysterectomy can use patches continuously and without an added progestogen. Treatment with E_2-only patches should be initiated with a system delivering the lowest amounts of E_2. Dosing can be upregulated until the clinical symptoms are under control.

Combination patches employ the natural estrogen E_2 with the synthetic progestogen norethindrone acetate. Patches for *combined continuous* treatment release both hormones simultaneously and continuously. In *sequential* regimens, patches releasing E_2 only are applied for two weeks, followed by a two-week application of patches releasing both E_2 and norethindrone acetate. Patches releasing E_2 0.05 mg/day combined with norethindrone acetate 0.25 mg/day achieve beneficial therapeutic effects without excessive stimulation of the endometrium. The *combined continuous* treatment has been associated with 20 % complete amenorrhea, spotting occured in 11 %, and 70 % women reported irregular bleeding; however, the total number of bleeding days only 24 per year. Most patients (60 to 70 %) receiving the *combined sequential* regimen reported withdrawal bleeding that followed the termination of the progestogen phase of the progestogen phase of the treatment. Only about 7—10 % patients experienced amenorrhea or spotting (10).

Patches for HRT have to be changed every 3–4, some only every 7 days. They can be applied to the skin of the upper arm, lower abdomen, buttocks, upper torso, but not to the breasts. When changing patches, a different location should be chosen to avoid skin irritation.

Differences between oral and transdermal hormonal replacement therapy

Comparative pharmacokinetics and pharmacodynamics of E_2 have addressed this problem. After *oral* dosing E_2 is absorbed from the digestive tract and rapidly converted by the liver into

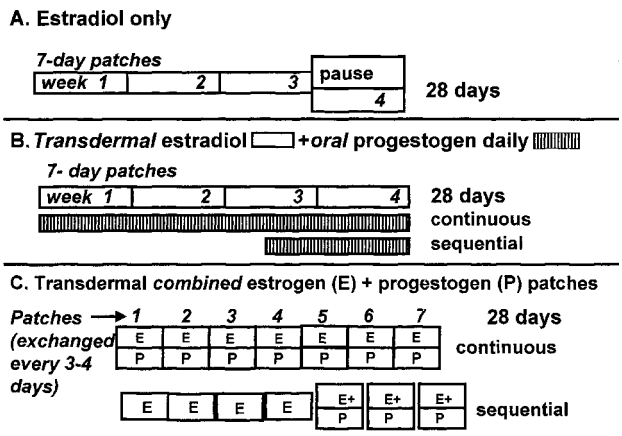

Fig. 3. Transdermal systems for hormonal replacement therapy. E — estradiol, P — progestogen.

estrone and its conjugates. Under physiological conditions, the ratio of the circulating E_2/estrone is around 1, while after oral dosing of E_2, the estrone levels are four to six times higher than those of E_2. Moreover, oral E_2 dosing results in unphysiological daily highs and troughs of circulating E_2 and estrone (Fig. 4) (11).

In contrast, skin metabolizes E_2 only minimally, and E_2 released from a patch enters the systemic circulation directly and mostly intact. Bypassing the liver metabolism, transdermal administration achieves therapeutic concentrations with smaller daily doses of E_2 than oral therapy does. After application of the patch, circulating levels of E_2 increase gradually, and within 12 to 24 hours achieve values consistent with the early follicular phase of normal menstrual cycle (~50 pg/ml). As long as the patches are regularly exchanged, circulating E_2 avoids fluctuations typical for oral administration, and the E_2/estrone ratio is maintained around 1. After removal of the patch, circulating levels of E_2 and estrone return to baseline within 24 hours. This rapid elimination of E_2 is clinically important with respect to adverse events.

Pharmacokinetic differences between transdermal and oral routes of estrogen administration translate into *pharmacodynamic* differences. Several studies addressed this issue and an excellent discussion by Crook has recently been published (12–15).

Oral dosing exposes the liver to an unphysiological „bolus" of estrogens with consequent stimulation of the liver tissue to produce sex hormone-, thyroxine-, and cortisol-binding globulins. Oral estrogens are also associated with an increase of circulating renin substrate and a decrease of anti-thrombin III activity. In contrast, transdermal E_2 is not associated with increased levels of circulating hormone-binding globulins and does not affect renin substrate (16–18). In this context, intriguing are clinical studies showing a reduction in mean ambulatory BP with transdermal E_2, while oral treatment had no effect on BP (21, 22). These observations await confirmation (19, 20).

Transdermal E_2 does not affect *lipid metabolism*; however, combined estrogen-progestogen therapy does alter the lipid pro-

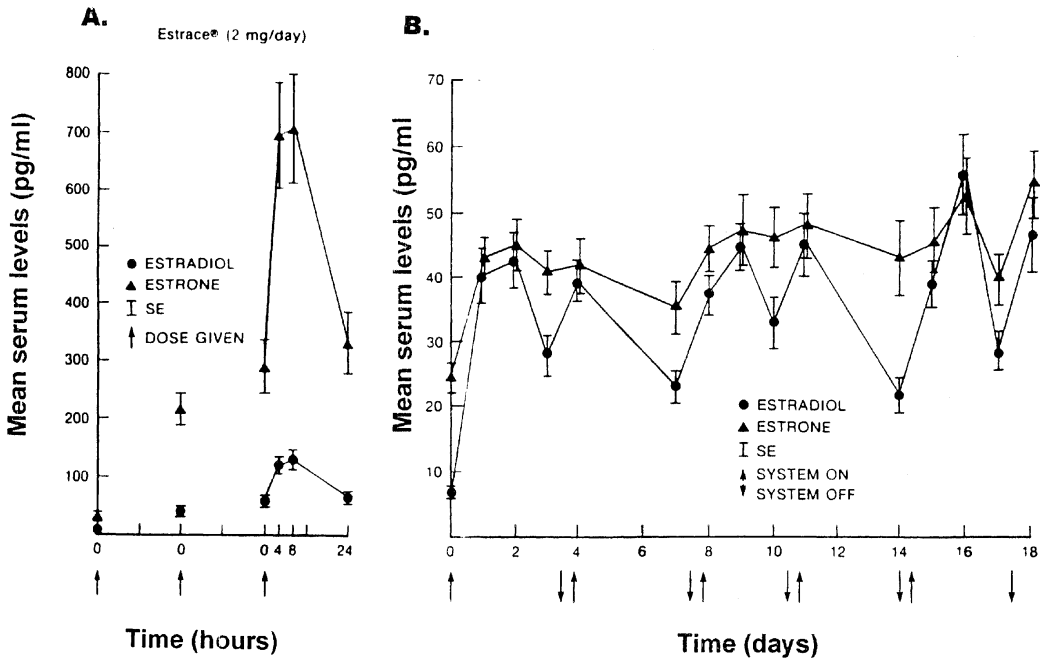

Fig. 4. Pharmacokinetics of estradiol given (A) orally and by (B) transdermal patches. Note the difference in scales for estrone and estradiol serum concentration in the two graphs.

file. A double-blind clinical trial compared the effects of patches releasing E_2 (0.05 mg) + norethindrone acetate (0.25 mg/day) with oral Premarin (0.0625 mg/day) combined with dl-norgestrel (0.15 mg/day) for 12 days/months, for 6 months. Transdermal HRT showed a significant decrease of triglycerides, while in the oral HRT group, triglycerides remained unchanged or showed an increase. Total cholesterol, as well as HDL and LDL cholesterol significantly declined in both treatment groups (12, 21).

Glucuronidation is another measure of estrogen effect on the liver since the process is almost exclusively accomplished in the liver. Plasma levels of estrone-3-glucuronide – a marker of glucuronidation – do not increase after percutaneous E_2, while a 3-fold rise of this metabolite occurs after ingestion of E_2-valerate, an estrogen used for HRT in Europe (16).

HRT affects profoundly biochemical markers of bone metabolism and prevents bone loss even in patients suffering from rheumatoid arthritis who use glucocorticoids-compounds well known to diminish bone density (22, 23). Noteworthy is an intriguing case of a man with *congenital aromatase deficiency*. Such men synthesize normal amounts of testosterone; however, due to the lack of aromatase, steroidogenic tissues can not convert androgens into estrogens. A significant loss of bone density ensues. In the described case, a patch releasing daily 0.025 mg of E_2 restored normal bone density (24).

Therapeutic effects and safety of transdermal HRT

Therapeutic effects of transdermal HRT are equivalent to oral HRT. Female steroids given transdermally relieve unplaeasant sensations associated with *vulvar and vaginal atrophy*, such as vaginal dryness and itching.

With respect to *vasomotor symptoms*, double-blind randomized clinical trials (34) have singled out the combination of E_2 0.05 mg/day, with norethindrone acetate, 0.25 mg/day, as the optimal schedule. Beginning since the second week of treatment, the frequency and severity of vasomotor symptoms, including sweating, significantly deceased. At the end of 12 weeks, the daily mean number of hot flashes from 11 to 1.4. Transdermal estrogens also suppress the pituitary output of both FSH and LH (6, 17, 25).

The *prevention of postmenopausal bone loss* was examined in studies emploiyng trandermal E_2 0.05 mg/day, 3 weeks/month, combined with the oral progestogen medroxyprogesterone acetate, 5—10 mg/day, for 10 to 15 days per month. A long-term follow-up, for 18 and 24 months, has shown a significant increase of bone mineral density (up to >5 %), while the untreated control group experienced a significant loss of bone mineral density (up to >4 %). HRT was also associated with a significant reduction of biochemical markers of bone turnover, such as serum osteocalcin and urinary calcium/creatinine ratio (26—32).

Clinical laboratory tests of patients receiving transdermal HRT did not disclose any meaningful deviations from the range of normal values. With respect to *adverse events,* patients with patches frequently reported skin irritation, but discontinuations for this side effect has been low.

Contraception

The most recently developed contraceptive patch releases *ethinylestradiol* combined with the progestogen *norelgestromin.* Ethinylestradiol has been employed since it is the most widely used estrogen in oral contraceptives, and an substantial body of safety data has been accumulated. Rationally, the developers decided to use norelgestromin, the active metabolite of norgestimate, which has been a component of several oral contraceptive schedules. Norelgestromin is a highly potent progestogen with minimal metabolic impact (33).

The patch delivers 20 μg of ethinylestradiol and 0.15 mg of norelgestromin daily and has to be changed only once a week. The sites of application are similar to those used for HRT. Women can bathe and swim while wearing the patch, but should not apply oils and/or cosmetics around or on the patch. It is recommended to use the patches for three consecutive weeks followed by a one-week patch-free period.

Pharmacokinetics, safety, contraceptive efficacy, and metabolic effects associated with the use of the contraceptive patch have been thoroughly studied.

Within 48 hours after application of the contraceptive patch, ethinylestradiol and norelgestromin achieve *steady state* concentrations of about 50 pg/ml and 1 ng/ml, respectively. These hormonal levels are maintained as long as the patches are used. After removal of the patch, the mean elimination $T_{1/2}$ for EE is 21 hours, and for norelgestromin, it is 32 hours.

The *efficacy and safety* of the ethinylestradiol/norelgestromin contraceptive system has been established in three independent pivotal registration studies encompassing an experience of 3,319 women during 22,160 cycles of use. The pooled data show an overall Pearl Index of 0.88 (34).

Contraceptive efficacy has been analyzed in more detail in a randomized study comparing the described transdermal contraception with an oral contraception (Triphasil, consisting of graded doses of ethinylestradiol and norgestrel; Weyth-Ayerest Laboratories, Radnor, Pennsylvania, USA). A total of 812 women used contraceptive patch, while 605 women received oral contraceptives. A total of 5 and 7 pregnancies occurred in the patch and in the oral contraceptive group, respectively. The overall Pearl Index (i.e. not corrected for patient failure) was numerically lower for the patch group than for the oral contraceptive group, 1.2 vs. 2.18, (not statistically significant).

Withdrawal bleeding occurred at the expected time with both compared contraceptive regimens. During the first contraceptive cycle, breakthrough bleeding occurred in 3.7 % and 4.2 % of women using the patch and oral contraception, respectively. During the 13th cycle, women on the transdermal regimen reported no breakthrough bleeding, while 2.3 % women on oral contraception reported it. With respect to *adverse events,* women of both groups reported those typical for hormonal contraception. As expected, about 20 % women receiving the patch experienced irritation at the site of application; however, only a fraction of these women discontinued the treatment (2.5 %). The overall incidence of breast discomfort was higher in the patch group than in the oral contraception group, but the difference was statistically significant only during the first two contraceptive cycles; however, discontinuation rate between the two groups for breast discomfort was statistically not significant. Transdermal contraceptive hormones did not induce marked weight changes.

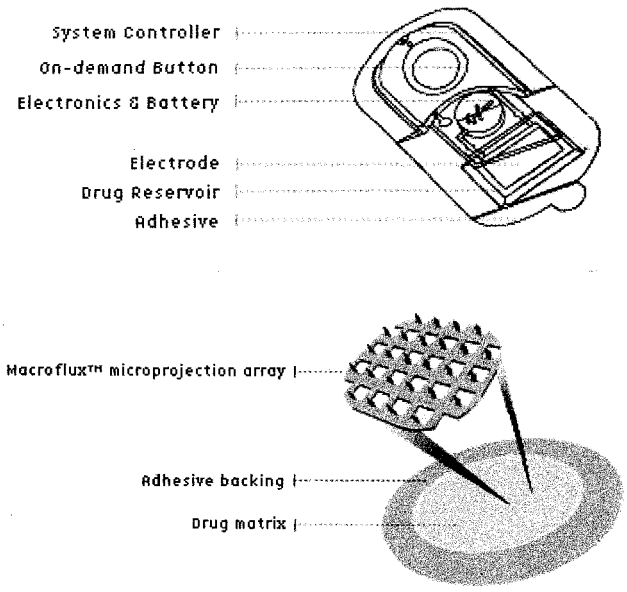

Fig. 5. (A) Active transport of delivering medicinal substances through the skin by means of electrical current. This E-TRANS technology (Alza Corp., Mountain View, CA, USA) can be programmed for continuous, patterned, on-demand, or feedback-controlled drug delivery. (B) The microprojection patch includes a small titanium disk with microscopic titanium tooth-like projections. They penetrate adequately the keratinized cells of the skin to create microchannels for passage of large molecules, but not deeply enough to cause pain. (Macroflux™, Alza Corp., Mountain View, CA, USA).

The compliance of women with the prescribed contraceptive regimen was significantly higher in the contraceptive patch group than in the oral contraception group (88.2 % vs. 77.7 %, $p<0.001$).

A separate study of close to 140 participants compared *lipid profiles* of contraceptive patch wearers to women who were assigned to placebo patches. Compared to placebo, total cholesterol, HDL cholesterol, and total triglycerides increased significantly in the contraceptive patch group. The increase of HDL was entirely due to an increase of the HDL_3 — a subfraction instrumental for removal of cholesterol from the circulation to be ultimately excreted by the liver. The LDL-cholesterol remained uninfluenced by the transdermally administered hormones, but the LDL/HDL ratio was significantly lower. It should be noted, however, that the end values of total cholesterol, HDL-cholesterol, and total triglycerides did not reveal any significant changes from baseline (35—39).

New developments

The most significant progress in the technology of transdermal drug delivery involves electrotransport — the use of electric

potential to move charged therapeutic molecules across the skin. These systems provide „tailored" drug delivery according to the patient's need. Traditionally, electrotransport systems for drug delivery have been table-top devices connected via cables to the drug units. Innovations in electric circuitry and battery technology have enabled the development of small, patch-size systems for percutaneous delivery of medicinal agents including high weight and complex molecules, such as peptides and proteins (40) (Fig. 5).

Modern electrotransport systems are important for *pain management*. Since the permeation rate of drug in electrotransport systems is proportional to the applied current, the dose of the delivered drug can be easily manipulated by controlling current. thus, both rapid onset of delivery and intermittent, pulsatile, and on-demand patient-controlled dosing can be achieved (41).

Figure 6 shows that electrotransport maintains circulating levels of the analgesic Fentanyl equally effectively as does intravenous administration. Clinicians, familiar with the management of acute and chronic pain, as well as pain suffering patients, appreciate the simplicity and ease of use of transdermal electrotransport as compared to intravenous dosing (42, 43).

Other innovative transdermal technologies include the *microprojection patch* and the use of *low-frequency therapeutic ultrasound*. Both technologies offer a needle-free transdermal drug delivery of large-molecular-weight compounds, principally proteins (insulin), certain peptidic hormones, such as growth hormone, and vaccines.

The *microprojection* patch includes a small titanium disk with microscopic titanium teeth-like projections. They penetrate, without causing pain, just the 10 to 25 μm thin layer of keratinized dead cells of the epidermis. In this way, they create „holes" — microchannels through which medicinal molecules proceed to deeper layers of the epidermis and into the extensive vascular network of the dermis, and ultimately into the general circulation (44, 45).

Since 1995, it has been known that *low-frequency ultrasound* increases significantly skin's permeability. This technology allows effective transmission of therapeutic agents of complex structure, many up to 100 times the molecular weight of E_2 (46, 47).

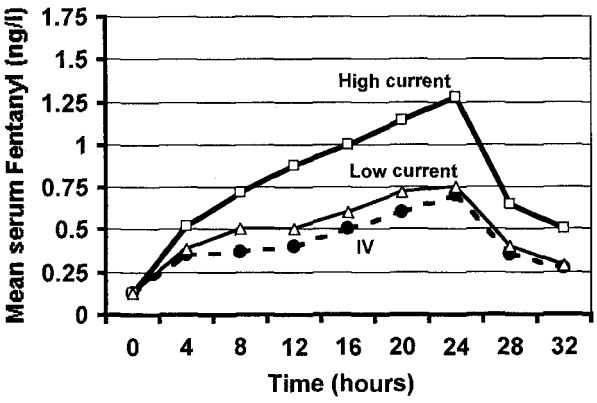

Fig. 6. Circulating levels of a potent opioid analgesic — Fentanyl, administered every hour for 24 hours by intravenous line and by electrotransport technology. The blood levels of the analgesic depend on the activated electrical current.

Conclusions

Transdermal delivery is an important expansion of the means by which medicinal substances are administered to the human body. Initially developed on principles of passive diffusion, transdermal delivery systems have been suitable for administration of female hormonal steroids and are widely used in HRT, and most recently, in hormonal contraception.

Certain advantages compared to oral dosing should be pointed out. Female hormonal steroids delivered transdermally are not subject to gastrointestinal enzymatic activity; therefore the administered amounts can be lower. Transdermal hormone application avoids first-pass metabolism, principally deactivation and metabolic transformation in the liver. Compared to the bolus oral dose, the transdermal hormone application impacts the liver to a minimal degree and can be considered more physiological.

Transdermal administration of female reproductive steroids has also advantages over their intramuscular administration. Intramuscular contraception with depot preparations of medroxyprogesterone acetate and norethindrone enanthate is associated with unphysiologically high circulating levels of the injected steroid, mainly in the first weeks after dosing. In contrast, transdermal dosing can be titrated, so that the circulating concentrations of administered natural hormones remain within the physiological range, and concentrations of synthetic steroids are limited to levels necessary to exercise their desired function, such as suppression of ovulation.

Passive transdermal hormonal systems can be self-administered, and a single application can extend the effective therapy for up to 7 days. This is important for hormones with short half-lives, such as E_2. Transdermal application of E_2 prolongs its therapeutic effects and avoids the necessity of daily oral administration. Another advantage is that in emergencies, the patch medications can be easily identified and the effects of the drug can be rapidly terminated.

With the passive systems, the variable intra- and interindividual percutaneous absorption could be a disadvantage. The amount of the drug in a patch is limited; therefore, the time for which the patch can be effective is variable. Some estrogen patches can be affixed for 7 days, while others must be exchanged every 3 to 4 days.

The long-term clinical consequences of transdermal use of female steroids have not yet been fully assessed. It would require large-scale and long-term clinical trials to evaluate the clinical significance of the lack of interactions with the liver and other metabolic differences of the transdermal vs. the oral route of hormonal dosing.

A substantial enrichment of transdermal methods have been the *active* systems, based upon electrotransport. These systems

can deliver medicinal substances of complex molecules, such as the growth hormone and vaccines. The amount of the delivered substances can be precisely determined and tailored to the individual's needs. In this respect, the *microprojection patch* and the use of *low-frequency ultrasound* have brought innovations that compete with intravenous dosing. Some opinion leaders maintain that progress in transdermal technologies may turn the intravenous route obsolete. Novel transdermal technologies are profoundly changing the current methods of pain management.

It is important to realize that ultrasonically permeabilized skin may be used not only for drug delivery, but also for extraction of analytes (47). Therefore, it is not outside the realm of possibility to develop systems with built-in feedback mechanisms that would interact between the drug concentration in the circulation or tissue and an electronic transdermal delivery system. Changes in concentration of the drug would modify its release. Stretching the imagination further, one could envision a regulatory interplay between endogenous substances, such as hormones, and the administered therapeutic agent.

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