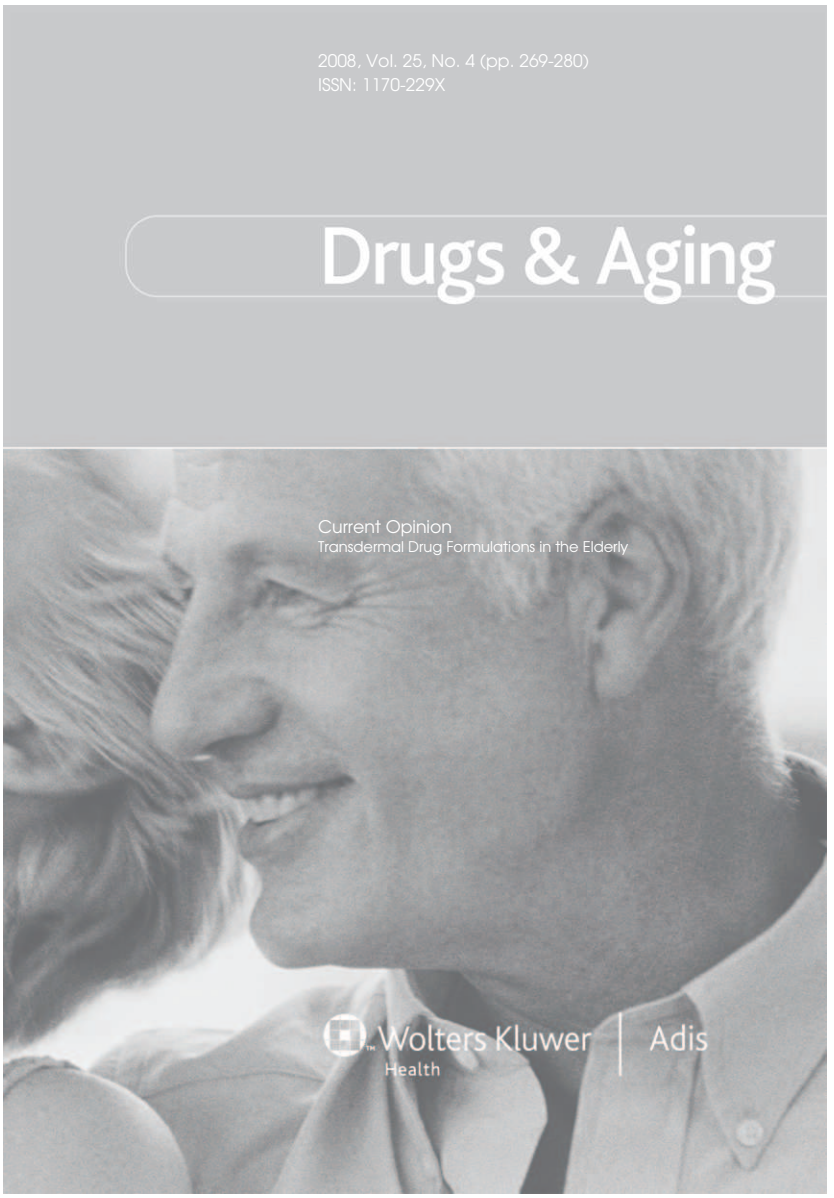

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Use of Transdermal Drug Formulations in the Elderly

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Abstract

Transdermal drug delivery systems are pharmaceutical forms designed to administer a drug through the skin to obtain a systemic effect. They ensure a constant rate of drug administration and a prolonged action. Several different types of transdermal delivery devices are available on the market. They are either matrix or reservoir systems and their main current uses are to treat neurological disorders, pain and coronary artery disease, and as hormone replacement therapy.

Transdermal drug administration has a number of advantages compared with the oral route: it avoids gastrointestinal absorption and hepatic first-pass metabolism, minimizes adverse effects arising from peak plasma drug concentrations and improves patient compliance. Compared with the parenteral route, transdermal administration entails no risk of infection. For elderly people, who are often polymedicated, transdermal drug delivery can be a good alternative route of administration.

Transdermal absorption depends on passive diffusion through the different layers of the skin. As skin undergoes many structural and functional changes with increasing age, it would be useful to know whether these alterations affect the transdermal diffusion of drugs. Studies have shown that age-related changes in hydration and lipidic structure result in an increased barrier function of the stratum corneum only for relatively hydrophilic compounds. In practice, no significant differences in absorption of drugs from transdermal delivery systems have been demonstrated between young and old individuals. The need for dose adaptation in elderly patients using transdermal drug delivery systems is therefore not related to differences in skin absorption but rather to age-related cardiovascular, cerebral, hepatic and/or renal compromise, and to ensuing geriatric pharmacokinetic and pharmacodynamic changes.

Oral administration of drugs has various limits such as sensitivity to gastrointestinal absorption, hepatic first-pass metabolism or compliance problems related to multiple daily doses. Therefore, other routes of administration have been investigated. Transdermal administration is an interesting alternative route for drugs requiring a long-lasting action with low plasma concentration, and for drugs with low therapeutic indices.

Transdermal formulations of several drugs taken by elderly patients are now being developed. Since age effects are so manifest in the skin's appearance,

reviewing how age-related skin changes influence the diffusion of drugs through the skin of elderly patients is of interest. In this article we describe the effects of age on skin structure and function and their influence on transdermal diffusion of drugs administered by transdermal delivery devices. We also discuss the advantages and disadvantages of transdermal administration in elderly patients and the different classes of drugs administered by this route.

1. Transdermal Diffusion

The skin comprises two layers: the epidermis and the dermis. The epidermis, which is avascular, is composed of a multilamellar structure that represents different stages of cellular differentiation. The outer layer of the epidermis is the stratum corneum. The dermis contains capillaries, sebaceous and sweat glands, hair follicles and nerves. The highly vascularized dermis supports apocrine and eccrine sweat glands as well as hair follicles, which pass through pores in the epidermis to reach the skin surface.

1.1 Principles of Passive Diffusion through the Skin

The natural function of the skin is to protect the body from the external world, preventing penetration of exogenous substances and loss of physiologically essential substances such as water. However, it is known that many products can pass through the skin barrier. This depends on the structure and physicochemical properties of the molecule and on certain properties of the skin itself.

Permeation of drugs includes diffusion through the intact epidermis and accessorily through the skin appendages (hair follicles or sweat glands) to capillaries and finally to the general circulation.[1] Diffusion is a passive process whereby molecules move towards equilibrium in response to a concentration gradient. Diffusion can be described by Fick's first law of diffusion (equation 1):

$$J = (D \times K/L) \times \Delta C \quad \text{(Eq. 1)}$$

where J = flow, D = diffusion constant of the molecule, K = partition coefficient, L = thickness of the membranes that are to be crossed (stratum corneum, membrane of the transdermal delivery system, etc.) and ΔC = concentration gradient between the two compartments.[2]

The stratum corneum is the principal obstacle to percutaneous penetration and provides the rate-limiting or slowest step in the penetration process.[3] The barrier role of the stratum corneum is due to the specific content, composition and arrangement of the intercellular lipid matrix and the lipid envelope surrounding the cells of the stratum corneum lipids.[1] Because of the structure of the stratum corneum, diffusion across it is not homogeneous, and the results of Fick's equation provide only an approximate prediction of the diffusion.

Diffusion through the epidermis occurs either through the intercellular lipids (between the cells) or through the cells (transcellular route). The intercellular lipid matrix is now recognized as the major determinant of percutaneous transport rate.[3,4] Transdermal permeation of drugs requires a low molecular weight (<1000 g/mol) and an adequate solubility in oil and water (high lipophilicity).[5,6] A drug that is soluble in the lipophilic layer as well as in the more aqueous structures, and at the same time has a small molecular size, has the greatest permeability through the skin barrier. These requirements have limited the number of products commercially available for transdermal or dermal delivery.

The influence of subcutaneous tissue on percutaneous absorption can be considered negligible, although it may act as a potential drug depot.[3] For example, a drug that is highly lipophilic will easily cross the stratum corneum but its diffusion across the hydrophilic layers below will be slower. This process is called the reservoir effect.[5]

In summary, penetration through the skin depends on many factors, including the time-scale of permeation (steady-state vs transient diffusion); the physicochemical properties of the penetrating substance (acid dissociation constant [pKa], molecular size, stability, binding affinity, solubility and partition coefficient); the integrity, thickness and com-

ponents of the skin; cutaneous metabolism; the site, area and duration of application; and, finally, on the vehicle, the properties of the transdermal device, and the creation of a local depot at the site of application.[3,7]

1.2 Strategies for Increasing Drug Diffusion through the Skin

There are several strategies for increasing skin permeation of a drug: (i) increase drug diffusivity in the skin; (ii) increase drug solubility in the skin; or (iii) increase the degree of saturation of the drug in the formulation.[1,3]

Various strategies have emerged over recent years to optimize delivery, and these can be categorized into passive and active procedures. Passive methods optimize formulation or drug-carrying vehicles to increase skin permeability (penetration enhancers, supersaturated systems, prodrugs or metabolic approaches, liposomes or other vehicles). However, the amount of drug that can be delivered using these methods remains limited because the barrier properties of the skin are not fundamentally changed. Active methods have been shown to be generally superior but they remain seldom used nowadays in clinical practice. These active modalities entail physical or mechanical methods of enhancing delivery, using electrical techniques (iontophoresis, electroporation), mechanical processes (abrasion, ablation by suction perforation with microneedles, skin stretching) and other energy-related methods such as ultrasound, laser radiation, radiofrequency or magnetophoresis.[6,8] At present, active procedures are not routinely used to enhance the efficacy of transdermal delivery systems, and a detailed explanation of these techniques is beyond the scope of this article. However, they remain interesting alternatives for future research in transdermal pharmacology.

2. Aging and Skin Changes

Aging alters the skin in several ways, which in turn affect percutaneous absorption of drugs. Both intrinsic or chronological skin aging and extrinsic or sun-exposed skin aging modify cutaneous structures. Exposure to the sun appears to account for a major portion of the observed skin changes that occur with aging. In non-exposed skin, there seems to be little overall effect of chronological aging other than a decline in elastin content that contributes to decreased skin elasticity with aging.[9] In general, the mechanisms are not dramatically different, but sun-exposed aging is an amplification of chronological aging.[10]

2.1 Epidermis

Because the appearance and number of horny cells in the stratum corneum do not appear to change, this layer retains its thickness;[9,11] however, an age-associated decrease in epidermal turnover rate has been shown.[10,12] Irregular pigmentation of aged skin reflects a decrease in the number of melanocytes,[10,13] but the qualitative and quantitative aspects of keratinization do not appear to change with age.[11,14]

In the basal layer of the epidermis, cells have displayed variations in size, shape and colour.[11] Microscopic examination of aged skin reveals a thinner epidermis than that in younger individuals. The epidermal thinning results from flattening of the interface between the dermis and epidermis.[9-11,14]

Modifications in the hydration level of stratum corneum with increasing age have been noted and aged skin is often dry. Amino acids in aged skin differ from those in younger adults, with an increase of hydrophobicity. As amino acids are believed to play a key role in stratum corneum water binding, this could partially explain the dryness of aged skin.[15] Glycosaminoglycans (GAGs) are widely distributed in the different skin layers and bind water. Skin hydration is related to dermal GAGs, especially hyaluronic acid. In aged skin, the amount and localization of GAGs are modified, which seems to prevent binding of water.[16]

Levels of lipids that form multilamellar sheets within the intercellular spaces in the stratum corneum apparently decrease because of a slow replacement of neutral lipids with age.[11,17,18] Changes in lipidic composition of the skin are also explained by

the reduced activity of sebaceous glands in aged skin.[19]

2.2 Dermis

Collagen is the predominant component of the human dermis, representing approximately 70–80% of the dry weight of the skin. It is responsible for the skin's tensile strength. A noticeable change in aged skin is an apparent increase in the density of the collagen network, because of a decrease in the ground substance that normally forms spaces between collagen fibres.[11,20] Paradoxically, this change could make the skin stiffer, but clinical observation shows that the skin becomes more distended.[9] In chronologically aged skin, a decrease in rate of collagen synthesis, collagen solubility, and thickness of collagen fibre bundles may also be seen.[21]

The elastic fibre network, which occupies approximately 2–4% of the dermis volume, shows definite changes associated with aging. Through different mechanisms, photoaging and intrinsic aging ultimately result in a deficiency of functional, structurally intact elastic fibres, which contributes to decreased skin elasticity.[9,20]

Little difference in local blood flow in the skin has been shown between older and younger people,[22,23] and the overall results of studies make a clear conclusion difficult, although it appears possible that increased age may be associated with decreased cutaneous perfusion, especially in photo-exposed areas.[14]

The thickness of the dermis and epidermis demonstrate similar variations. Both thin with age on some body sites (back or upper arm) but remain constant on others (buttock, shoulder or dorsal forearm).[24,25] At present, the clinical implications of these observations are unclear.

2.3 Appendages

Age-related changes in the density, colour and distribution of hairs are obvious. The total number of hair follicles is reduced and the remaining hair is often smaller in diameter and slower growing.[12]

A reduction in the absolute number of eccrine sweat glands or in their functional capacity has been shown in aged skin. Reduced sebaceous gland activity results in a decrease in the amount of skin surface lipids.[17,19,26]

3. Influence of Age on Percutaneous Absorption

Drug permeation can vary among individuals and with the site of administration.[5,27] Furthermore, inter- and intraindividual variability increases with increasing age. Accordingly, there are significant variations in cutaneous thickness between individuals and between sites in the same individual.[14]

In vivo and *in vitro* studies have been conducted to measure the percutaneous absorption of drugs in aged subjects.[12,28] Changes in skin appendages do not appear to affect drug permeation significantly because of their minor role in drug permeation through the skin. Flattening of the dermo-epidermal junction and a possible reduction in capillary numbers lead to reduced resorption capability.[12,14,28]

In aged skin, the stratum corneum is dryer. Hydration of the horny layer alters the environment of the skin and, as a result, may affect percutaneous absorption. It is known that one of the crucial steps in percutaneous absorption is the partitioning of drug into the lipids of the stratum corneum. This essential process is sensitive to the type and amount of skin lipids, and the reduction in lipid content in aged skin implies a diminished dissolution medium for chemicals that are administered on the surface. Furthermore, reduced hydration would again imply that the environment of aged skin is less attractive to hydrophilic products. Conversely, lowered lipid and water content may not affect dissolution into the stratum corneum of highly lipophilic molecules.[28]

In summary, age-related changes in hydration and lipids result in increased barrier function of the stratum corneum only for relatively hydrophilic compounds. Highly lipid-soluble chemicals may still be able to dissolve readily into the stratum corneum even when the available lipid medium is reduced.[28]

In practice, no significant differences in absorption of drugs from transdermal delivery systems have been demonstrated between young and old individuals. The need for dose adjustment is therefore not related to differences in skin absorption but rather to the usual geriatric pharmacokinetic changes. Kinetic changes associated with advanced age will be determining factors to consider with transdermal administration, just as for other routes of administration. Depending on the therapeutic index of the drug, titrating the proper dosage may be more difficult with a patch formulation, but once a stable dosage has been determined, switching to a patch is relatively straightforward.

4. Description of Transdermal Delivery Systems

A transdermal drug delivery system is a pharmaceutical formulation designed to administer a drug through the skin to obtain a systemic effect. It ensures a constant rate of drug administration and a prolonged action. In its simplest form, the single-dose pharmacokinetic profile for transdermal delivery consists of three distinct periods: (i) the time until serum concentrations are achieved (lag time); (ii) the steady-state phase with constant plasma concentrations; and (iii) a declining phase after the patch is removed or when it is empty. This last phase has a characteristic duration of continued drug presence that often reflects a skin depot of the drug.[7,29]

Current transdermal drug delivery systems consist of an impervious external layer, a compartment containing the drug, and an adhesive layer with a removable protective support that needs to be withdrawn before use.

The rate of diffusion of a drug from a transdermal delivery system is influenced by a number of factors, such as the characteristics of the skin, the properties and concentrations of the drug, the surface and properties of the patch and the duration of administration. Diffusion of the drug might be limited by the skin, by the polymer of the monolithic system or by the rate-controlling membrane.

Technically, transdermal drug delivery systems may be categorized into two types, monolithic (matrix) and membrane-controlled (reservoir) systems. Monolithic systems incorporate a drug into a polymeric layer that controls its release. Membrane-controlled systems are designed to contain a drug reservoir and a rate-release-controlling membrane (figure 1).[30]

Several types of monolithic (matrix) system are possible:

1. Simple matrix: the drug reservoir is formed by dispersing or dissolving the drug in a polymer layer, which controls drug delivery.
2. Drug-in-adhesive system: the drug is dispersed in an adhesive polymer matrix, which controls drug delivery. This system has the advantage of being thin and flexible.
3. Multilayer matrix: a concentration gradient is created by superposition of layers with various drug concentrations.

The capacity of diffusion of the drug between the polymeric chains controls its release. Generally, release does not follow linear kinetics, except if a gradient of concentration is created within the matrix (multilayer systems). Matrix systems are modified-release patches and the skin itself is the limiting factor for penetration of the drug.[31]

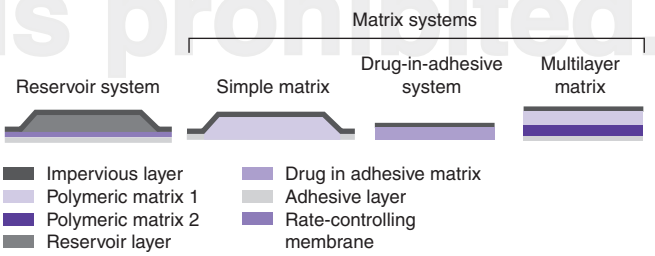

Fig. 1. Different types of transdermal delivery systems.

In membrane-controlled (reservoir) systems, the drug reservoir is embedded between an impervious layer and an adhesive membrane. The drug in the reservoir compartment can be in the form of a solution, suspension or gel, or dispersed in a solid polymer matrix.[12] Release of drug is controlled by a rate-controlling membrane. Drug release follows zero-order kinetics, which means that the drug is continually released at a constant rate.

5. Advantages and Disadvantages of Transdermal Delivery Systems

5.1 Advantages

Transdermal delivery of a drug eliminates variables that sometimes hinder gastrointestinal absorption. These factors include changes in pH as the molecule moves from an acid pH in the stomach to a basic pH in the gut, the rate and extent of gastric emptying, transit times, the presence of and interaction with food, and intestinal motilities.[28] Moreover, transdermal drug delivery systems avoid the 'first-pass' phenomenon by which the liver can metabolize the drug before it passes into the systemic circulation. Possible deactivation of the drug by digestive and liver enzymes is also avoided. Although the skin itself possesses some metabolic capability,[3] studies have shown that, compared with the oral route, fewer metabolites are formed.[32]

Transdermal administration is particularly interesting when a constant drug effect is desired. The fact that the delivery rate is well controlled can also minimize adverse effects associated with peak plasma drug concentrations and thus decrease the risk of overdosage. Area under the plasma concentration-time curves of transdermal delivery systems are favourable with respect to adverse effects, as their profiles are usually lower than those for oral or intravenous administration. Therapeutic drug concentrations are therefore reached more gradually and the patch can be removed as soon as an adverse reaction is detected. Systemic adverse effects might also be reduced. In contrast to perfusion, transdermal drug delivery systems minimize discomfort and do not carry the risk of infections associated with catheters. The transdermal route of administration also improves patient compliance.[27] A substantial majority of patients prefer transdermal to oral therapy, and adherence to treatment is greater because of the ease of use of transdermal systems, even in old patients.[33] Another advantage of transdermal delivery devices is the simple and direct termination of drug administration that can be achieved at any time by removing the patch.[28] However, delivery can sometimes continue through the stratum corneum after removal of the transdermal device. This is a consequence of the long response times of horny layer membranes, which could act as a drug reservoir.[3,28]

5.2 Disadvantages

There are few adverse effects specific to topical administration of drugs via transdermal delivery systems. The most frequent adverse effect is skin sensitivity and skin irritation by patches. This can be a major problem for aged people who have sensitive and fragile skin. The risk is minimized by varying the site of application of the patch.[34,35] Another disadvantage specific to transdermal drug delivery systems is associated with the reservoir effect of the skin. Adapting drug dosages can be difficult because drug diffusion continues after patch removal.[5]

As with other drug formulations, the cost-benefit ratio of a treatment delivered via a patch is a matter of concern. Because such formulations are often new and complex, their cost can be higher than that of oral formulations. However, generic brands of transdermal delivery devices do tend to reach the market, which may bring patch prices down.

5.3 Advantages and Disadvantages in Elderly Patients

There are number of advantages associated with delivering drugs to older patients using transdermal devices (table I).

Geriatric patients take many concomitant drugs because of their frequent polymorbidity. Reducing the number of medications to be taken can be achieved by prescribing prolonged-action drugs administered by any route, including transdermal de-

Table I. Advantages and disadvantages of transdermal drug delivery systems in elderly patients

Advantages	Disadvantages
Independent of gastrointestinal absorption	Skin irritation
No hepatic first-pass metabolism	Limited number of drugs marketed
Long-lasting action	Reservoir effect of horny layer of skin
Peak plasma concentrations slowly reached	Handling difficulties for arthritic patients
Good compliance	Risk of forgetting by cognitively impaired patients
Alternative route in case of polypharmacy	
Alternative route in case of dysphagia	
No risk of infection	
No need for venous access	

vices. This may improve patient compliance, an essential element of successful pharmacotherapy. Elderly patients also often suffer from dysphagia, which can make swallowing tablets difficult. In this setting, transdermal administration of drugs is an efficient alternative. Older patients also tend to have decreased venous access. Thus, when parenteral therapy is not feasible, patches are a convenient alternative.

Transdermal drug delivery in the aged does not solve the difficulties elderly arthritic patients have with handling medications: removing the adhesive film on patches can be as difficult as extracting a pill from a jar or blister pack.[12] It also does not totally resolve compliance problems related to cognitive decline and memory loss. Some patients forget they are wearing a patch and have trouble remembering when to change their transdermal medication.

Finally, although transdermal drug delivery systems present many advantages, only a limited number of drugs are marketed in this form.

6. Clinical Applications of Transdermal Drug Formulations

Many transdermal drugs are already being used in aged patients (table II) or are under evaluation (table III). Several of these are discussed in this section.

6.1 Neurological Disorders

6.1.1 Parkinson's Disease

In Parkinson's disease, it is recognized that pulsatile stimulation of dopamine receptors may be an important mechanism in the generation of the motor fluctuations that often develop and compromise the effectiveness of long-term levodopa administration.[36] Unfortunately, levodopa and many dopamine receptor agonists are not sufficiently soluble to be administered via the transdermal route. Nevertheless, it has been shown that transdermal administration of lisuride or apomorphine reduces motor fluctuations and duration of 'off' periods. Apomorphine, which has a short half-life and a high first-pass metabolism, has shown a good penetration profile after transdermal iontophoretic administration and pretreatment with percutaneous enhancer.[37] Lisuride patch application was reported to improve motor function in eight patients with Parkinson's disease.[38]

Recently, rotigotine patches were launched onto the market. Rotigotine is a non-ergoline dopamine $D_3/D_2/D_1$ receptor agonist administered via a continuous-dosing transdermal patch formulation applied once a day. Use of this patch has been shown to improve motor function in early-stage disease and

Table II. Main transdermal drugs available on the market for elderly patients

Molecule	Indication
Rotigotine	Parkinson's disease
Selegiline	Major depressive disorder
Fentanyl	Chronic pain
Buprenorphine	Chronic pain
Estrogens	Postmenopausal therapy
Progesterone	Postmenopausal therapy
Glyceryl trinitrate (nitroglycerin)	Angina pectoris, left ventricular heart failure
Oxybutynin	Overactive bladder

Table III. Drugs under evaluation for transdermal administration for elderly patients

Molecule	Indication
Apomorphine	Parkinson's disease
Lisuride	Parkinson's disease
Physostigmine	Alzheimer's disease
Tacrine	Alzheimer's disease
Rivastigmine	Alzheimer's disease
Nicotine	Alzheimer's disease
Estradiol	Dementia
Testosterone	Andropause syndromes
Insulin	Diabetes mellitus

to be an effective adjuvant therapy to levodopa in advanced Parkinson's disease.[39-43] Its use in treating restless leg syndrome is also under evaluation. The short-term adverse events of rotigotine patches appear to be similar to those of other dopamine receptor agonists (nausea, somnolence), with mild-to-moderate application site reactions being common (affecting 44% of rotigotine patch-treated patients vs 12% of placebo recipients in a recent study).[41]

Rotigotine patches may be especially helpful in the treatment of patients with swallowing difficulties or poor compliance.

6.1.2 Dementia

Behavioural and cognitive problems in neurodegenerative diseases interfere with therapeutic compliance. Increased numbers of daily doses have also been found to decrease compliance in elderly patients. Use of transdermal formulations could alleviate memory-related non-adherence.

Clinical studies have been conducted to evaluate whether anticholinesterase drugs such as physostigmine, tacrine and rivastigmine can be administered by the transdermal route.[44] Physostigmine appears to be safe, but the results of studies are not conclusive and more data are needed to prove that the transcutaneous formulation is effective in Alzheimer's disease.[45,46] Tacrine, which has high first-pass metabolism, a relatively short elimination half-life and a potential dose-dependent hepatotoxicity, is a good candidate for transdermal administration. A promising tacrine transdermal delivery system has been developed using an ion-exchange fibre and iontophoresis.[47] A rivastigmine patch formulation appears safe and to be as efficacious as higher doses of the drug in capsule form, while displaying a better tolerability profile.[48]

Studies investigating the effectiveness of the alkaloid nicotine (which is already available as a transdermal system for smoking cessation) in the management of behavioural problems in patients with Alzheimer's disease have also been conducted. Preliminary reports did not provide homogeneous results and the number of patients studied was not sufficient to allow conclusions to be drawn about the efficacy of this therapy.[49,50]

Estradiol, which has shown a variety of neurotrophic and neuroprotective properties, has been evaluated in transdermal systems. To date, however, efficacy for estradiol in alleviating several dementia symptoms has not been clearly proven.[51,52]

6.1.3 Depression

The monoamine oxidase (MAO) inhibitor selegiline is currently used as oral therapy in low dosages for the treatment of Parkinson's disease. At such doses, selegiline is selective for MAO-B. At the high oral dosages needed to treat depression, selegiline inhibits both MAO-B and MAO-A, resulting in hypertensive adverse effects when tyramine-rich food is ingested.[53] In 2006, a once-a-day patch of selegiline was approved by the US FDA for treatment of major depressive disorder. This patch has been shown to be efficacious and well tolerated, with the only adverse effects being application-site reactions.[54,55] Use of the selegiline transdermal system allows targeted inhibition of the MAO-A and MAO-B isoenzymes with minimal effects on MAO-A in the gastrointestinal and hepatic systems. Tyramine dietary restrictions are no longer necessary when using the 6 mg/24 h selegiline patch.[56,57]

6.2 Pain

Sustained-release formulations have become a major therapeutic option for the treatment of chronic pain. Transdermal application of opioids is a comfortable and easy method for providing continuous analgesia to patients with chronic pain. The most widely used formulation is the transdermal thera-

peutic system containing fentanyl. Several studies have shown that patients are more satisfied with transdermal fentanyl compared with sustained-release oral forms of morphine.[58-61] The convenient once-every-72 hours dosage regimen and more favourable adverse effect profile make fentanyl patches a good alternative to oral opioids. However, opioid intoxication following transdermal administration of fentanyl has been reported.[62,63]

In practice, very elderly sick patients requiring opioids will often be prescribed very low initial doses of morphine (e.g. 6 × 2.5 mg/day orally). The dosage is then increased rapidly according to the effect on pain and whether unwanted adverse effects appear. For example, the lower dosages of buprenorphine patches (35 μg/h in Europe) correspond approximately to oral morphine 30–60 mg/day.[64] It may therefore be unsafe to start opioid treatment in sick elderly patients using the current doses of most patches.

Transdermal buprenorphine is also used successfully in the management of moderate-to-severe chronic and neuropathic pain.[65-67] It is generally well tolerated, with systemic adverse events typical of other opioid treatments.

Fentanyl and buprenorphine transdermal therapeutic systems are suitable for patients with stable pain, because of the slow onset of analgesic effect and elimination of the drug.

6.3 Hormones

Trends in postmenopausal hormonal therapy appear to be favouring non-oral delivery routes for both estrogen and progestogen in postmenopausal women, and many hormonal patches are already being used in this indication.[68] Continuation of long-term hormonal replacement therapy into old age is a subject of debate, with only some experts recommending continued hormonal replacement therapy for prevention of osteoporosis.[69] If maintenance of hormonal replacement therapy is prescribed, selection of the route of administration would be a matter of preference and cost rather than efficacy.

Several other delivery systems, including vaginal gels and rings or intrauterine systems, are either available or under development.[70] These are meant to provide systemic effects rather than local effects only. Studies are also underway to evaluate the efficacy of testosterone administration by the transdermal route to treat andropause syndromes in aging men.[71,72]

Diabetes mellitus is a very common disease in the elderly. Transdermal insulin administration could be an interesting alternative to avoid subcutaneous injections.[73] Ultrasound, liposomal or iontophoretic methods have been studied to enhance insulin diffusion through the skin, but none of these strategies has been completely successful to date.[74,75]

6.4 Cardiovascular Diseases

Organic nitrates are a standard therapy widely used in the management of coronary artery disease. Transdermal glyceryl trinitrate (nitroglycerin) patches are an effective anti-ischaemic medication and are frequently used for the treatment of myocardial infarction. The therapeutic value of organic nitrates is limited by the rapid development of tolerance to their haemodynamic and clinical effects.[76,77] The only widely accepted method for preventing tolerance is to provide an overnight interval with no nitrate exposure during each 24-hour period.[78,79] Transdermal delivery of organic nitrates is an appealing route of administration for prophylaxis and long-term treatment of coronary artery disease compared with the oral route, which requires multiple administrations per day.

6.5 Urogenital Disorders

Oxybutynin is an antagonist of muscarinic receptors on the detrusor muscle of the bladder. It has anticholinergic and spasmolytic effects.[80] Transdermal administration of oxybutynin has been shown to be as effective as oral treatment, while minimizing the anticholinergic adverse effects.[81,82] The patch must be changed twice a week.

7. Transdermal Delivery Formulations in Practice

Transdermal drug delivery systems must be applied on a clean, dry and hairless skin. Wounded or burnt skin must be avoided because of the risk of increased drug absorption. For the same reason, exogenous sources of heat, such as a hot-water bottle, must not be applied to the transdermal device.[83] Alternating the sites of application helps to prevent primary skin irritation. The drug-release properties of transdermal systems are independent of the site of application.[29]

When lower doses of the drug need to be administered, matrix patches can be cut or folded without damaging their drug-release properties because the drug is in a solid form within the matrix. Conversely, reservoir systems cannot be cut. Leakage of reservoir contents can occur if the reservoir is not kept intact, and exposure to light and air may affect the drug.[84] As a general rule, cutting patches should not be encouraged, because the exact dosage cannot be guaranteed. Most manufacturers recommend against cutting patches.

Transdermal delivery systems are waterproof and do not need to be removed before bathing or showering. If a patch is removed or falls off, however, it must not be reused.

The impervious membrane of some transdermal devices contains aluminium. It is recommended that patients remove patches before undergoing magnetic resonance imaging or receiving an external electrical shock because of the risk of burns or formation of an electrical arc.[85]

8. Conclusion

While only a limited number of drugs are currently available for administration by transdermal delivery devices, studies of new molecules for the transdermal route and new technologies for skin penetration enhancers are promising. Transdermal delivery of drugs improves patient adherence because it reduces the discomfort associated with multiple administration of drugs and eliminates problems with swallowing oral preparations. The risk of systemic adverse effects or hepatic first-pass effects can be significantly reduced, and the need for repeated administration to obtain constant therapeutic plasma concentrations can be avoided. There are also no significant alterations in transdermal diffusion of drugs through mature skin with present-day transdermal delivery systems. Thus, the need for dose modification in elderly patients is not related to differences in skin absorption but rather to the usual geriatric pharmacokinetic changes. Taken together, these considerations suggest that the elderly are a group of patients who can derive large benefits from transdermal delivery of drugs.

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References

1. Moser K, Kriwet K, Naik A, et al. Passive skin penetration enhancement and its quantification in vitro. Eur J Pharm Biopharm 2001; 52: 103-12
2. Aiache JM, Devissaguet JP, Guyot-Hermann AM. Galenica 2: biopharmacie. Paris: Technique et Documentation, 1978
3. Ranade VV. Drug delivery systems 6: transdermal drug delivery. J Clin Pharmacol 1991; 31: 401-18
4. Potts RO, Guy RH. Predicting skin permeability. Pharm Res 1992; 9: 663-9
5. Rikke HL, Nielsen F, Sorensen JA, et al. Dermal penetration of fentanyl: inter- and intraindividual variations. Pharmacol Toxicol 2003; 93: 244-8
6. Brown MB, Martin GP, Jones SA, et al. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv 2006; 13: 175-87
7. Buri P, Puisieux F, Doelker E, et al. Formes pharmaceutiques nouvelles. Paris: Technique et Documentation, 1985
8. Meidan VM, Michniak BB. Emerging technologies in transdermal therapeutics. Am J Ther 2004; 11: 312-6
9. Thomas DR. Age-related changes in wound healing. Drugs Aging 2001; 18: 607-20
10. Aubert JP, Crickx B. La peau du sujet âgé. Rev Pratic 2003; 17: 1209-12
11. Lavker RM. Structural alterations in exposed and unexposed aged skin. J Invest Dermatol 1979; 73: 59-66
12. Roskos KV, Maibach HI. Percutaneous absorption and age: implications for therapy. Drugs Aging 1992; 2: 432-49
13. Gilchrest BA, Blog FB, Szabo G. Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol 1979; 73: 141-3
14. Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (I): blood flow, pH, thickness, and ultrasound echogenicity. Skin Res Technol 2005; 11: 221-35
15. Jacobson TM, Yuksel KU, Geesin JC, et al. Effects of aging and xerosis on the amino acid composition of human skin. J Invest Dermatol 1990; 95: 296-300

16. Bernstein EF, Underhill CB, Hahn PJ, et al. Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. Br J Dermatol 1996; 135: 255-62
17. Saint Leger D, Francois AM, Leveque JL, et al. Age-associated changes in stratum corneum lipids and their relation to dryness. Dermatologica 1988; 177: 159-64
18. Makrantonaki E, Zouboulis CC. Characteristics and pathomechanisms of endogenously aged skin. Dermatology 2007; 214: 352-60
19. Pochi PE, Strauss JS, Downing DT. Age related changes in sebaceous gland activity. J Invest Dermatol 1979; 73: 108-11
20. Waller JM, Maibach HI. Age and skin structure and function – a quantitative approach (II): protein, glycosaminoglycan, water, and lipid content and structure. Skin Res Technol 2006; 12: 145-54
21. Uitto J. Connective tissue biochemistry of the aging dermis: age-associated alterations in collagen and elastin. Clin Geriatr Med 1989; 5: 127-47
22. Kelly RI, Pearse R, Bull RH, et al. The effects of aging on the cutaneous microvasculature. J Am Acad Dermatol 1995; 33: 749-56
23. Roskos KV, Bircher AJ, Maibach HI, et al. Pharmacodynamic measurements of methyl nicotinate percutaneous absorption: the effect of aging on microcirculation. Br J Dermatol 1990; 122: 165-71
24. Sandby-Moller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites: relationship to age, gender, pigmentation, blood content, skin type and smoking habits. Acta Derm Venereol 2003; 83: 410-3
25. Branchet MC, Boisnic S, Frances C, et al. Skin thickness changes in normal aging skin. Gerontology 1990; 36: 28-35
26. Yamamoto A, Serizawa S, Ito M, et al. Effect of aging on sebaceous gland activity and on the fatty acid composition of wax esters. J Invest Dermatol 1987; 89: 507-12
27. Grond S, Radbruch L, Lehmann KA. Clinical pharmacokinetics of transdermal opioids. Clin Pharmacokinet 2000; 38: 59-89
28. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. J Pharmacokinet Biopharm 1989; 17: 617-30
29. Berner B, John VA. Pharmacokinetic characterisation of transdermal delivery systems. Clin Pharmacokinet 1994; 26: 121-34
30. Ansel HC, Popovich NG. Pharmaceutical dosage forms and drug delivery systems. Philadelphia (PA): Lea and Febiger, 1990
31. Wasilewski-Rasca AF, Vogt-Ferrier NV. CAPP-INFO -systèmes transdermiques (ou patchs): structure-utilisation-aspects pratiques [online]. Available from URL: http://www.hcuge.ch/Pharmacie/infomedic/cappinfo/cappinfo18.pdf [Accessed 2007 May 7]
32. Beckett AH, Gorrod JW, Taylor DC. Comparison of oral and percutaneous routes in man for the systemic administration of ephedrines. J Pharm Pharmacol 1972; 24: 65-70
33. Burris JF, Papademetriou V, Wallin JD, et al. Therapeutic adherence in the elderly: transdermal clonidine compared to oral verapamil for hypertension. Am J Med 1991; 91: 22S-8S
34. Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. Drug Saf 1994; 10: 151-9
35. Murphy M, Carmichael AJ. Transdermal drug delivery systems and skin sensitivity reactions: incidence and management. Am J Clin Dermatol 2000; 1: 361-8
36. Pfeiffer RF. Potential of transdermal drug delivery in Parkinson's disease. Drugs Aging 2002; 19: 561-70
37. Li GL, Vries JJ, van Steeg TJ, et al. Transdermal iontophoretic delivery of apomorphine in patients improved by surfactant formulation pre-treatment. J Control Release 2005; 101: 199-208
38. Woitalla D, Muller T, Benz S, et al. Transdermal lisuride delivery in the treatment of Parkinson's disease. J Neural Transm 2004; 68 Suppl.: 89-95
39. MacMahon DG. Use of apomorphine in clinical practice. Adv Neurol 1999; 80: 529-33
40. Guldenpfennig WM, Poole KH, Sommerville KW, et al. Safety, tolerability, and efficacy of continuous transdermal dopaminergic stimulation with rotigotine patch in early-stage idiopathic Parkinson disease. Clin Neuropharmacol 2005; 28: 106-10
41. Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of rotigotine in early Parkinson disease. Neurology 2007; 68: 272-6
42. LeWitt PA, Lyons KE, Pahwa R, et al. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER study. Neurology 2007; 68: 1262-7
43. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007; 6: 513-20
44. Priano L, Gasco MR, Mauro A, et al. Transdermal treatment options for neurological disorders: impact on the elderly. Drugs Aging 2006; 23: 357-75
45. Moller HJ, Hampel H, Hegerl U, et al. Double-blind, randomized, placebo-controlled clinical trial on the efficacy and tolerability of a physostigmine patch in patients with senile dementia of the Alzheimer type. Pharmacopsychiatr 1999; 32: 99-106
46. Levy A, Brandeis R, Treves TA, et al. Transdermal physostigmine in the treatment of Alzheimer's disease. Alzheimer Dis Assoc Disord 1994; 8: 15-21
47. Kankkunen T, Sulkava R, Vuorio M, et al. Transdermal iontophoresis of tacrine in vivo. Pharm Res 2002; 19: 704-7
48. Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease: rivastigmine patch versus capsule. Int J Geriatr Psychiatry 2007; 22: 456-67
49. Wilson AL, Langley LK, Monley J, et al. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav 1995; 51: 509-11
50. Snaedal J, Johannesson T, Jonsson JE, et al. The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. Dementia 1996; 7: 47-52
51. Henderson VW, Paganini-Hill A, Emanuel CK, et al. Estrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol 1994; 51: 896-900
52. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. Neurology 1998; 50: 996-1002
53. Transdermal selegiline. Med Lett Drugs Ther 2006; 1235: 41-2
54. Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. J Clin Psychopharmacol 2006; 26: 579-86
55. Robinson DS, Amsterdam JD. The selegiline transdermal system in major depressive disorder: a systematic review of safety and tolerability. J Affect Disord 2008; 105: 15-23
56. Pae CU, Lim HK, Han C, et al. Selegiline transdermal system: current awareness and promise. Prog Neuropsychopharmacol Biol Psychiatr 2007; 31: 1153-63

57. Frampton JE, Plosker GL. Selegiline transdermal system in the treatment of major depressive disorder. Drugs 2007; 67: 257-65
58. Muijsers RB, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 2001; 61: 2289-307
59. Payne R. Factors influencing quality of life in cancer patients: the role of transdermal fentanyl in the management of pain. Semin Oncol 1998; 25: 47-53
60. Payne R, Mathias SD, Pasta DJ, et al. Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. J Clin Oncol 1998; 16: 1588-93
61. Kornick CA, Santiago-Palma J, Moryl N, et al. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. Drug Saf 2003; 26: 951-73
62. Klockgether-Radke AP, Gaus P, Neumann P. Opioid intoxication following transdermal administration of fentanyl. Anaesthesist 2002; 51: 269-71
63. Klockgether-Radke A, Hildebrandt J. Opioid intoxication: inappropriate administration of transdermal fentanyl. Anaesthesist 1997; 46: 428-9
64. Compendium Suisse des médicaments. Basel: Documed, 2007 [online]. Available from URL: http://www.kompendium.ch [Accessed 2007 May 9]
65. Sittl R. Transdermal buprenorphine in cancer pain and palliative care. Palliat Med 2006; 20: 25-30
66. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2004; 26: 1808-20
67. Evans HC, Easthope SE. Transdermal buprenorphine. Drugs 2003; 63: 1999-2012
68. Girdler SS, Hinderliter AL, Wells EC, et al. Transdermal versus oral estrogen therapy in postmenopausal smokers: hemodynamic and endothelial effects. Obstet Gynecol 2004; 103: 169-80
69. Dören M, Samsioe G. Prevention of postmenopausal osteoporosis with oestrogen replacement therapy and associated compounds: update on clinical trials since 1995. Hum Reprod Update 2000; 6: 419-26
70. Sitruk-Ware R. Routes of delivery for progesterone and progestins. Maturitas 2007; 57: 77-80
71. Lund BC, Bever-Stille KA, Perry PJ. Testosterone and andropause: the feasibility of testosterone replacement therapy in elderly men. Pharmacotherapy 1999; 19: 951-6
72. Beer TM, Bland LB, Bussiere JR, et al. Testosterone loss and estradiol administration modify memory in men. J Urol 2006; 175: 130-5
73. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. Diabetes Metab 2003; 20: 886-98
74. King MJ, Badea I, Solomon J, et al. Transdermal delivery of insulin from a novel biphasic lipid system in diabetic rats. Diabetes Technol Ther 2002; 4: 479-88
75. Lee S, Snyder B, Newnham RE, et al. Noninvasive ultrasonic transdermal insulin delivery in rabbits using the light-weight cymbal array. Diabetes Technol Ther 2004; 6: 808-15
76. Longobardi G, Ferrara N, Abete P, et al. Efficacy of transdermal nitroglycerin patches evaluated by dipyridamole-induced myocardial ischemia in patients with coronary artery disease: comparison between continuous and intermittent schedule. Cardiovasc Drugs Ther 2002; 16: 535-42
77. Kiraly C, Kiss A, Timar S, et al. Effects of long-term transdermal nitrate treatment on left ventricular function in patients following myocardial infarction. Clin Cardiol 2003; 26: 120-6
78. Klemsdal TO, Gjesdal K. Intermittent or continuous transdermal nitroglycerin: still an issue, or is the case closed? Cardiovasc Drugs Ther 1996; 10: 5-10
79. Parker JO, Amies MH, Hawkinson RW, et al. Intermittent transdermal nitroglycerin therapy in angina pectoris: clinically effective without tolerance or rebound. Minitran Efficacy Study Group. Circulation 1995; 91: 1368-74
80. Bang LM, Easthope SE, Perry CM. Transdermal oxybutynin for overactive bladder. Drugs Aging 2003; 20: 857-64
81. Dmochowski RR, Nitti V, Staskin D, et al. Transdermal oxybutynin in the treatment of adults with overactive bladder: combined results of two randomized clinical trials. World J Urol 2005; 23: 263-70
82. Dmochowski RR, Starkman JS, Davila GW. Transdermal drug delivery treatment for overactive bladder. Int Braz J Urol 2006; 32: 513-20
83. Wasilewski-Rasca AF, Bonnabry P. Systèmes thérapeutiques transdermiques: aspects pratiques chez le patient âgé. Med Hyg 2004; 62: 2320-5
84. Lee AH, Anderson PO. Giving partial doses of transdermal patches. Am J Health Syst Pharm 1997; 54: 1759-60
85. Dispositifs transdermiques contenant de l'aluminium: risques de brûlures [editorial]. Rev Prescrire 2007; 27: 191-2

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