Opioid transdermal delivery system: a useful method for pain management in children

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Abstract: Transdermal delivery system (TDDS) is a non-invasive and less expensive method for drug delivery. Despite its feasibility, only a restricted group of drugs can be delivered by TDDS, because of the little permeability of skin. Moreover, TDDS is limited to lipophilic drugs with small molecular masses and it is not indicated for peptides, macromolecules and hydrophilic drugs. Among opioids, fentanyl and buprenorphine are suitable for transdermal administration only for chronic pain management (not for acute pain). However, opioid TDDS still remains off-label for chronic pain management in children. In this review, we describe the main features of the adhesive TDDS and the main characteristics of pediatric skin and the differences from the adult one. Moreover, we focus on fentanyl and buprenorphine patches and their non-invasive mechanism of action, and on the main aspects that make them suitable for pain management among the pediatric population.

Keywords: Buprenorphine; children; fentanyl; opioid; transdermal

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Introduction

Over the millennia skin has been used mostly for the application of medications with a local topical effect (i.e., creams, ointments, gels, pastes, poultices). The use of adhesive skin patches for drug delivery has been systematically studied only since the last century. The scopolamine patch for motion sickness was the first adhesive transdermal delivery system (TDDS) approved by the Food and Drug Administration in 1979. TDDS became a widely recognized delivery drug method only in 1991, when nicotine patches were introduced in order to stop smoking.

TDDS has an insignificant first-pass effect through the liver which can prematurely metabolize drugs delivered by the oral route. Besides, compared with hypodermic injections, TDDS is painless, it doesn't produce dangerous medical waste and it reduces the risk of disease transmission by needle reuse. In addition, TDDS is non-invasive and it is generally less expensive than other methods of drug delivery, providing drug release for up to one week. Moreover, it can be self-administered, improving patients' compliance (1).

However, application of TDDS is limited by the low permeability of skin. Only a restricted number of drugs are suitable for TDDS since they must have molecular masses only up to a few hundred Daltons, octanol-water partition coefficients that should favor lipids and doses of milligrams per day or less. Transdermal route is not suitable for delivering hydrophilic drugs, peptides and macromolecules. Active transdermal delivery can overcome some of the limitations of passive patches based on the diffusion through the concentration gradient (2).

Children skin physiology

Human skin counts several functions, such as photo-protection, thermoregulation, hormonal synthesis, sensory perception, immune and barrier functions. Barrier function is crucial for drug absorption (3,4).

In relation to barrier function and transdermal absorption, pediatric skin is divided into two large groups: preterm neonates' skin, which has a thinner and dysfunctional epidermal barrier, and children skin, that is functionally almost identical to the adult one.

In preterm infants, the immature stratum corneum (SC) provides a defective barrier and results in a significantly elevated transepidermal water loss (TEWL), that is correlated with a large inward percutaneous penetration of chemicals. On the contrary, the SC of term neonates having an TEWL similar to adult skin, results in an efficacious barrier (5).

Although TEWL is almost the same in adults and full-term infants, other characteristics of skin function can change after birth. Infant skin physiology is different from the adult due to properties as skin and SC thickness, skin surface pH, hydration, desquamation and corneocyte size. Nevertheless, none of the factors mentioned above is unquestionably associated with the percutaneous absorption of chemicals as TEWL (6).

Furthermore, the cutaneous blood flow is another relevant element for skin barrier function (4). In preterm infant dermal microcirculation adaptation can take longer, even though it has not been exactly explained how that may alter skin absorption. Ambient temperature, relative humidity and nutrition may modify skin blood flow. TEWL is controlled by SC structure and composition of intercellular lipids, which also are important in regulating the rate and extent of skin absorption trough this barrier (7).

For other delivery approaches (i.e., iontophoresis) sweat glands and hair follicles are significant permeation pathways, but the relevance of skin annexes on barrier function is less known (8).

Opioid TDDS

TDDSs provide some advantages for opioids administration, especially in the pediatric population. In fact, they avoid blood peaks, allowing steady and continuous drug delivery and reducing inconvenient side-effects (such as vomiting, nausea, sedation and respiratory depression). Patient compliance is visibly improved, due to the reduced number of daily administrations (72 hourly or weekly). For the treatment of cancer patients with chronic pain fentanyl and buprenorphine patches are commonly used, but they are unsuitable for acute pain treatment, because of their pharmacokinetics (9).

Fentanyl TDDS

Fentanyl is an ideal drug for transdermal delivery since is soluble both in fat and water, and has a low molecular weight and high potency. Fentanyl patches are licensed for treatment of patients older than two years that have developed tolerance to opioids used for moderate to severe persistent chronic pain. The British National Formulary for children does not recommend their adoption, but it suggests that they can be used to treat severe chronic pain in "non-currently treated" 16–18 years old patients. For analgesia in children with moderate to severe cancer pain, intravenous fentanyl as background infusion plus patient-controlled analgesia is safe and efficacious (10).

Transdermal patches provide a convenient alternative in younger children, when controlled anesthesia is not suitable. They are also useful in younger children that may be unable to retain oral and sublingual formulations and to swallow them, which results in substantial variation in drug blood levels, also due to a marked first pass effect (11-13).

Because of the incidence of respiratory depression observed in postoperative adult population, fentanyl patches are not administered for the management of post-operative pediatric pain (14). Children with chronic pain already exposed to opioid therapy benefit from fentanyl TDDS which is well-tolerated and it seems to be associated with improved scores on the patients' quality of life assesses by the Play Performance Scale and the Child Health Questionnaire (15).

Fentanyl TDDS is also used for palliative care in children with dysphagia and for reducing morphine side-effects (16). Passive patches cannot provide acute pain control, because percutaneous absorption is invariably slow. Ionsys (Manufacturer: Penn Pharmaceutical Services Ltd 23–24 Tafarnaubach Industrial Estate; Tredegar, Gwent, South Wales, NP22 3AA, United Kingdom. Medicinal product no longer authorized), the ionophoretic system, was developed to skip this limitation, although it was not recommended for patients under 18 years of age (17).

There are several transdermal devices for the administration of fentanyl (*Table 1*). The most utilized fentanyl patch is Duragesic, (Janssen Pharmaceuticals, Inc. 1000 U.S. Route 202 South Raritan, NJ 08869, USA) which

Table 1 Fentanyl TDDS brand names, doses and manufacturers

Brand	Doses (mcg/h)
Duragesic[†]	12, 25, 50, 75, 100
Fencino[¥]	12, 25, 50, 75, 100
Fentalis reservoir[α]	25, 50, 75, 100
Matrifen[β]	12, 25, 50, 75, 100
Mezolar[α]	12, 25, 37.5, 50, 75, 100
Mylafent[γ]	12, 25, 50, 75, 100
Osmanil[‡]	25, 50, 75, 100
Tilofyl[α]	25, 50, 75, 100
Victanyl[§]	12, 25, 50, 75, 100
Yemex[α]	12, 25, 50, 75, 100

[†], Janssen Pharmaceuticals, Inc. 1000 U.S. Route 202 South Raritan, NJ 08869, USA. [¥], Luye Pharma AG, Am Windfeld 35, Miesbach D-83714, Germany. [α], Hexal AG, Industriestrasse 25, 83601 Holzkirchen, Germany. [β], Takeda Pharma A/S, Dybendal Alle 10, DK-2630 Taastrup, Denmark; Takeda GmbH, Robert-Bosch-Strasse 8, D-78224 Singen, Germany. [γ], Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom. [‡], Acino AG, Am Windfeld 35, 83714 Miesbach, Germany. [§], Actavis Group PTC ehf Reykjavikurvegur 76-78 IS-220 Hafnarfjordur, Iceland.

consists of a four-layer laminate on a protective liner. The backing layer includes a clear polyester/ethylene film and is heat sealed around the perimeter of the rate-controlling membrane. A fentanyl base dissolved in ethanol and gelled with hydroxyethyl cellulose forms the drug reservoir. The rate by which fentanyl is released to the skin surface from the TDDS is determined by the rate-controlling membrane, an ethylene-vinyl acetate copolymer film. The adhesive layer allows the drug to pass freely and determines the adherence and the release of the starting loading dose of drug to the skin. At the time of production fentanyl base is embedded exclusively inside the drug reservoir. Following manufacture, fentanyl migrates from the reservoir, passes the rate-controlling membrane, until its concentration in the adhesive layer is balanced with the concentration in the reservoir. Fentanyl loading dose is included in the adhesive layer. After the equilibration period, the drug reservoir contains fentanyl at saturation. At the time the patch is attached to the skin, the drug moves from the adhesive to the adhesive/skin interface and later penetrates into the skin and hence into the systemic circulation. A fentanyl delivery of 7.2 mg is obtained with a 100 mcg/h patch applied for the planned 3 days. The reservoir patch is an important improvement of the transdermal formulation because is designed to contain 28% of residual fentanyl, while the initial loading dose contains 10 mg of the drug. This special feature prevents the possibility of removing fentanyl from the reservoir and its potential abuse (18).

There are five different strengths of patch available from 12 to 100 mcg/h. The lowest available patch strength is 12.5 mcg/h, which is designated as 12 mcg/h to distinguish it from an eventual 125 mcg/h dosage. Dose may be also increased by the application of multiple patches. Children aged 16 years and above follow adult dosage, whereas a table with recommended Duragesic doses for pediatric patients based upon daily oral morphine dose has been provided for children aged 2–16 years (19).

The pharmacokinetics of transdermal fentanyl in the pediatric population is similar to published adult values (20). Paut *et al.* found that the elimination half-life was 14.5 hours, suggesting that during the application period a skin reservoir of the drug is accumulated (11). After transdermal administration, a wide range of plasma concentrations are observed, because fentanyl pharmacokinetics are very variable, but at least the hepatic first-pass effect and its variability are avoided. Transdermal fentanyl was effective and accepted in patients 2 to 18 years old, for whom treatment with opioids was necessary to treat cancer pain or other severe conditions. The median dose administered at 15 days was 1.9 mcg/kg/h, this was increased to 3.2 mcg/kg/h required for patients with terminal cancer to control rapidly raising pain. Patients who finished 15 days of treatment were grouped in two clusters, with age under and above 10 years respectively. There was no statistical difference of patch strength at start or at 15 days between the two groups. Although, the fentanyl dose, calculated by weight (mcg/h/kg), was higher in younger children (median 1.6 mcg/h/kg) than in older ones (0.7 mcg/h/kg) at start and also at 15 days (median 5.4 and 1.4 mcg/h/kg respectively in the younger and older patients). Children younger than 10 years needed more dose increments (16). In their pharmacokinetic study about transdermal fentanyl, Collins *et al.* showed that pediatric patients had a higher plasma clearance and a larger volume of distribution of fentanyl compared to adults (20). Moreover, in neonates and infants a higher weight-normalized volume of distribution of fentanyl has been reported: in term neonates the volume of distribution is 5.9 L/kg and during infancy it diminishes with age to 4.5 L/kg, in childhood to 3.1 L/kg and in adults to 1.6 L/kg (21).

Two kind of side effects are associated to the use of transdermal fentanyl. The first one is severe and common and it depends on the drug itself. It includes vomiting, nausea and constipation. Although patients that receive transdermal fentanyl present less commonly constipation than those treated with sustained-release oral morphine as shown by data from open and randomized trials. In the United States premarketing trials, the most severe adverse event reported was hypoventilation, the incidence being of approximately 2%. The second kind of side effect depends on the device itself and is due to the mentioned adhesion problems, that can be addressed by application of medical tape. Local pain when removed (if excessively adherent) and application site reactions (such as erythema, papules, itching and edema) may be often observed (14,16,21-23).

Before applying the patch, it is essential to avoid the use of soaps, heat sources, lotions, oils and alcohol-based formulations at the skin site, which needs to be clean and dry. The patch should be placed in the upper body (chest, back or upper arm) in a non-hairy skin region (19).

Local blood supply does not modify fentanyl distribution, although an increase of absorption rate of about 30% can be caused by an elevation of body temperature up to 40 ℃ (23).

Buprenorphine TDDS

Buprenorphine is a synthetic lipophilic opioid, it delivers 30–50 times more analgesia than morphine. Buprenorphine exerts its actions primarily by binding to the three opioid receptors, with partial agonism at μ, inverse agonism at κ and the lowest binding at delta which debatably produces agonism or antagonism. The partial agonism at μ-opioid receptor (MOR) induces analgesia and limited euphoria, while the blockade at κ lowers dysphoria (24-26).

The effect of buprenorphine on delta receptors has not been fully elucidated. MOR signaling induced by buprenorphine demonstrates high potency to activate MOR-Gi/o protein signaling determining analgesia, but not β-arrestin-2 recruitment or receptor internalization, both actions are more associated with opioid effect (27).

What still remains a mystery is how buprenorphine's unique pharmacology contributes to its physiological effects. Potential clues to what underlies these properties are its long and stable receptor occupancy and its ability to chaperone additional MORs to the cell surface (28).

These properties all contribute to make buprenorphine suitable for use in acute pain management as well as in maintenance therapy to treat opioid addiction as it yields a prolonged therapeutic effect, with slower tolerance onset and low opioid dependency. Buprenorphine is used to treat moderate to severe pain with equivalent pain relief as compared with morphine, hydromorphone, oxycodone, fentanyl and methadone. Furthermore, buprenorphine was also efficient to reduce chronic and neuropathic pain in many human studies (29-31).

Due to these strong analgesic properties of buprenorphine, several pharmaceutical companies are currently developing different ways of administration or innovative formulations, including transdermal patches, subdermal implant, mucoadhesive buccal film and sublingual or injectable formulations (32).

A recent review encourages the use of transdermal buprenorphine to treat chronic pain. As indicated in the label information, in the pediatric population safety and efficacy of buprenorphine patches have not been established (33,34).

Although treatment with buprenorphine has been revised in pediatrics, data on buprenorphine transdermal delivery derives only from case reports on treatment pain. The patch with the lower rate of drug delivered should be utilized for the pediatric population (33).

Butrans (Bard Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambrige CB40GW, United Kingdom; Mundipharma DC B.V., Leusderend 16, 3832 RC Leusden, The Netherlands), one of the many transdermal devices for the administration of buprenorphine (*Table 2*), was used to treat pain in four children (aged 3–10 years) with chronic pseudo-obstruction syndrome pain. Good pain control was obtained with the use of 5–10 mcg/h patches combined, for breakthrough pain, with fentanyl nasal spray or sublingual buprenorphine. In children, local skin reactions ranging from mild pruritus to erythema, were the most frequent side effects (in 3 of 4 patients), which showed a good response to topical steroid spray. To prevent skin reaction, it is recommended to use a new site for the patch at each replacement and to avoid the previous site for up to 4 weeks. In one patient, the time Butrans patch was applied was reduced from the normal 7 to 4 days (35).

Ruggiero *et al.* in their single-arm, nonrandomized trial evaluated the efficacy and side-effects of buprenorphine TDDS in pediatric patients with cancer pain (36). Buprenorphine patches were applied every 72 hours to the back, chest or upper arm, in 16 pediatric patients (aged 2–17 years) with cancer related pain treated with

Table 2 Buprenorphine TDDS brand names, doses and manufacturers

Brand	Doses (mcg/h)
Bupeaze[λ]	35, 52.5, 70
Buplast[f]	35, 52.5, 70
Bupramyl[f]	5, 10, 20
Butec[τ]	5, 10, 20
Butrans[τ]	5, 10, 20
Carlosafine[χ]	35, 52.5, 70
Panitaz[ψ,λ]	5, 10, 20
Prenotrix[‡]	35, 52.5, 70
Reletrans[α]	5, 10, 15, 20
Relevtec[α]	35, 52.5, 70
Sevodyne[χ]	5, 10, 20
Transtec[ω]	35, 52.5, 70

[λ], Betapharm Arzneimittel GmbH, Kobelweg 95, Augsburg, 86156, Germany.[f], Gerard Laboratories, Unit 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland. [τ], Bard Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB40GW, United Kingdom; Mundipharma DC B.V., Leusderend 16, 3832 RC Leusden, The Netherlands. [χ], Tesa Labtec GmbH Heykenaukamp 10, 21147 Hamburg, Germany. [ψ], Dr Reddy's Laboratories Ltd., 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, United Kingdom. [‡], Acino AG, Am Windfeld 35, 83714 Miesbach, Germany. [α], Hexal AG, Industriestrasse 25, 83601 Holzkirchen, Germany. [ω], Grunenthal GmbH Zieglerstrasse 6 Aachen D-52078.

previous non-opioid therapies. The starting dose of buprenorphine TDDS was 8.75, 17.5, and 35 mcg/h for children with weight inferior to 15 kg, between 15 and 30 kg, and superior to 30 kg respectively. The dose rate was increased to a maximum of 140 mcg/h. To obtain the smallest doses, 35 mcg/h patch was cut into 2 or 4 pieces to achieve 1/2 or 1/4 of dose delivery respectively. Every child started on buprenorphine patches showed good pain control with very few administrations of rescue drugs for breakthrough pain. Pain promptly resolved; 4 days from start of treatment pain score was considerably better, and a gradual further reduction was reported in particular during the first 14 days. Throughout the period of the study pain was well controlled, thus, in the pediatric population buprenorphine TDDS seems to be a valuable treatment for moderate to severe cancer pain.

Conclusions

Due to their pharmacological characteristics, fentanyl and buprenorphine are suitable for transdermal administration. Even though skin physiology is similar in term neonates, children and adults, opioid TDDSs remain off-label for chronic pain management in children.

In fact, the main researches on fentanyl and buprenorphine transdermal patches are related to adults, and there are only few studies that investigate their use in the pediatric population.

We hope that new studies with a large number of patients will increase the knowledge about safety and efficacy of this drug delivery system, allowing its use for pain management in the pediatric population.

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