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Effective use of transdermal drug delivery in children☆

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ABSTRACT

Transdermal administration offers a non-invasive and convenient method for paediatric drug delivery. The competent skin barrier function in term infants and older children limits both water loss and the percutaneous entry of chemicals including drugs; but the smaller doses required by children eases the attainment of therapeutic concentrations. Transdermal patches used in paediatrics include fentanyl, buprenorphine, clonidine, scopolamine, methylphenidate, oestrogens, nicotine and tulobuterol. Some patches have paediatric labelling supported by clinical trials whereas others are used unlicensed. Innovative drug delivery methods, such as microneedles and sonophoresis are being tested for their safety and efficacy; needleless injectors are primarily used to administer growth hormone; and two iontophoretic devices were approved for paediatrics. In contrast, the immature and rapidly evolving skin barrier function in premature neonates represents a significant formulation challenge. Unfortunately, this population group suffers from an absence of approved transdermal formulations, a shortcoming exacerbated by the significant risk of excessive drug exposure via the incompletely formed skin barrier.

Contents

1. Introduction . . . 0
2. The development of skin barrier function . . . 0
3. Skin absorption: potential for toxicity and for transdermal drug delivery in paediatrics . . . 0
3.1. In vitro and in vivo skin drug absorption studies . . . 0
3.2. Unwanted skin absorption and potential for toxicity . . . 0
3.3. Models for paediatric skin absorption . . . 0
4. Paediatric use of transdermal therapeutic systems (TTS) . . . 0
4.1. Scopolamine (hyoscine) . . . 0
4.2. Fentanyl . . . 0
4.3. Clonidine . . . 0
4.4. Methylphenidate . . . 0
4.5. Buprenorphine . . . 0
4.6. Tulobuterol . . . 0
4.7. Oestrogen therapy . . . 0
4.8. Nicotine . . . 0
4.9. Other actives . . . 0
5. Innovative methods for paediatric transdermal drug delivery . . . 0
6. Conclusions . . . 0
References . . . 0

1. Introduction

The topical and transdermal routes of administration offer some clear and specific advantages for drug delivery. Topical delivery allows targeting of the drug to the local area minimising systemic exposure; topical formulations usually contain anti-inflammatory, anti-histaminic,

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antifungal, antiseptic, and analgesic drugs incorporated into creams, ointments, gels, sprays and, less frequently, patches. Transdermal drug delivery (TDD), the object of this review, aims to provide effective systemic concentrations for central, rather than, local effect and is applicable to different therapeutic areas. TDD offers a non-invasive approach to avoid the first-pass effect, and can sustain plasma levels within the therapeutic window for extended periods. Transdermal patches are usually well accepted, easy to apply and represent a valuable alternative when oral administration is difficult (e.g., patient cannot swallow, or is in a coma) or may result in erratic absorption (nausea, vomiting, etc.) [1]. While these advantages are of general interest for the paediatric population, neonates and preterm infants would benefit particularly from a non-invasive route of drug administration and an alternative to oral and intravenous delivery [2]. Unfortunately, the effective barrier properties of the skin mean that TDD is not suitable for all drugs and only those with appropriate physicochemical, pharmacokinetic and pharmacodynamics properties are candidates for delivery across the skin [1,3]. All drugs available in commercial, passive patches are highly potent, have molecular weights less than 500 Da, and log P (P = octanol/water partition coefficient) values typically between 3 and 5 [3]. While newer delivery methods such as iontophoresis, needleless injectors and microneedles expand the range of drugs administrable, by easing the constraints related to drug polarity, charge and size, the doses deliverable across the skin remain small. Conveniently, because younger children require smaller doses than adults, it is conceivable that some drugs could be delivered transdermally for paediatric but not for adult use.

Human skin is responsible for several functions including photoprotection, thermoregulation, hormonal synthesis, sensory perception, and immune and barrier functions [4,5]. Among these, barrier function is the most relevant to drug absorption and not surprisingly, many enhancement techniques have been examined to overcome this challenge [1,6]. Nevertheless, it is important that the normal functioning of this organ is not disrupted severely because of its key role in survival. The majority of techniques developed to enhance skin transport have been tested in adult human skin or in animal models [1,6]. A key question, therefore, is the extent to which "paediatric skin" is represented by these models and whether the knowledge obtained from these models can be transferred and exploited for the benefit of the paediatric population. Importantly, while the latter represents a heterogeneous group of individuals; from the standpoint of the skin barrier function and transdermal absorption, it divides (to all intents and purposes) in two large parts: (1) all children, including neonates born at full-term, whose skin is functionally indistinguishable from adult skin, and (2) preterm neonates who have a thinner and dysfunctional epidermal barrier.

A premature neonate born at ~25 weeks gestational age (GA) with very low weight (<0.75 kg) has a very fragile skin which can easily tear; infants born at 30–31 weeks GA and weighing 0.75–1.25 kg have a more resilient, although still immature, skin; finally, the skin of infants born from ~36 weeks GA (1.2–2.0 kg) will be almost as tough and functional as that of full-term new-borns [4]. Premature neonates are obviously the most challenging group concerning transdermal drug administration. Despite significant progress, the relationship between skin absorption, GA and post-natal age (PNA) in this population is insufficiently characterized, making it difficult, if not impossible, to modify drug input in response to not only the rapidly evolving skin barrier function but also to the drug dose requirements (which also increase with PNA); in addition the situation is likely to be further complicated by other underlying developmental and disease issues. Information about the criteria for formulation selection is also missing; for example, whether a patch adhesive is suitable for fragile premature skin, or the potential risk associated with the unexpectedly high absorption of an excipient. While the remarkable immaturity and poor barrier function of preterm infant skin is universally recognized, there has been debate about the point at which the skin of term infants gains adult functionality. The next section summarizes the key issues and deals more specifically with the development of the skin barrier function.

Importantly, while permeation across the stratum corneum (SC) or outermost layer of the skin, constitutes the rate-limiting step for the skin absorption for most chemicals, the overall absorption process can be modified by other factors not related to the skin barrier maturation (including occlusion, thickness of applied formulation, area of application versus body surface area); furthermore, drug response and toxicity are also determined by pharmacokinetics and pharmacodynamics which change within the paediatric population and may be quite different from those in adults. To illustrate this point, the skin represents ~13% of the body weight of a pre-term infant but only 3% of that of an adult [7]; the area and site of application of a transdermal patch may have a dramatic impact, therefore, on the safety and efficacy of a treatment in neonates [2,8].

2. The development of skin barrier function

The differences between infant and adult skin physiology, as well as the development of skin functionality, including the effects of GA and PNA on transepidermal water loss (TEWL), skin surface pH, skin hydration, skin electrical properties, skin structure and roughness and natural moisturizing factor (NMF) abundance, have been recently and extensively reviewed [5,7,9,10].

The development of skin structure from the embryo until birth was comprehensively reviewed by Hardman et al., [10]. Briefly, at 4–5 wk GA the ectoderm of the embryo is covered by the periderm; epidermal stratification starts around 8 wk GA, and the development of skin appendages around 12 wk GA [4,5]. The periderm acts as the interface between the amniotic fluid and the developing epidermis prior to SC formation; later the periderm sheds to become part of the vernix caseosa at 15–20 wk GA. The effects of GA and PNA on the histological development of the epidermis were reported in 169 (24–40 wk GA) infants aged from a few hours to 1 year old [11]. The thickness and number of epidermal cell layers, the degree of undulation of the dermo-epidermal junction, and the SC thickness increased clearly with GA in children who had died within 7 days of birth; both the SC and the dermo-epidermal undulations were barely perceptible until 34 wk GA. It was suggested later that, while functional maturation of the SC starts around the 24th week of gestation, a well-defined SC is not visible before 34 wk GA. Indeed, SC formation has been observed at 22 wk GA in the epidermis of the head/scalp and in palmar/plantar skin and, at 25 wk, over the rest of the body [12]. According to some, a functional skin barrier appears regionally, with the inter-follicular barrier forming at 20–21 wk GA on the head and at 23–24 wk GA on the abdomen. The barrier appears to develop between 20 and 24 wk GA in a patterned manner, starting at specific initiation sites but also around emerging hair follicles. The link between epidermal differentiation and skin permeability during foetal development was characterized for 55, 75, 84, and 96 d GA and 115 d (full-term) swine foetuses [13]; the permeability to arecoline decreased significantly for the 96 d GA group corresponding to the visual appearance of the SC and the partially keratinized epidermis. Notably, the permeability of ionized arecoline across skin from 96 d GA and older foetuses was significantly less than that of the unionized species, an observation consistent with the development of a lipid barrier.

It is now generally accepted that the inward percutaneous penetration of chemicals is correlated to the transepidermal water loss (TEWL) [14]. Further, the link appears to be maintained throughout the human-life span. The topical absorption of hydrocortisone in a group of 3 children and 6 adults (3 to 52 years) with widespread dermatitis produced a significant correlation between TEWL and the post-application plasma levels of cortisol irrespective of age [15]. It is therefore not surprising, that TEWL has been extensively used both to characterize the degree of skin barrier function and maturity and to predict chemical absorption.

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