CASE STUDIES IN TOXICOLOGY

Series Editor: Lewis S. Nelson, MD

A Compounded Problem

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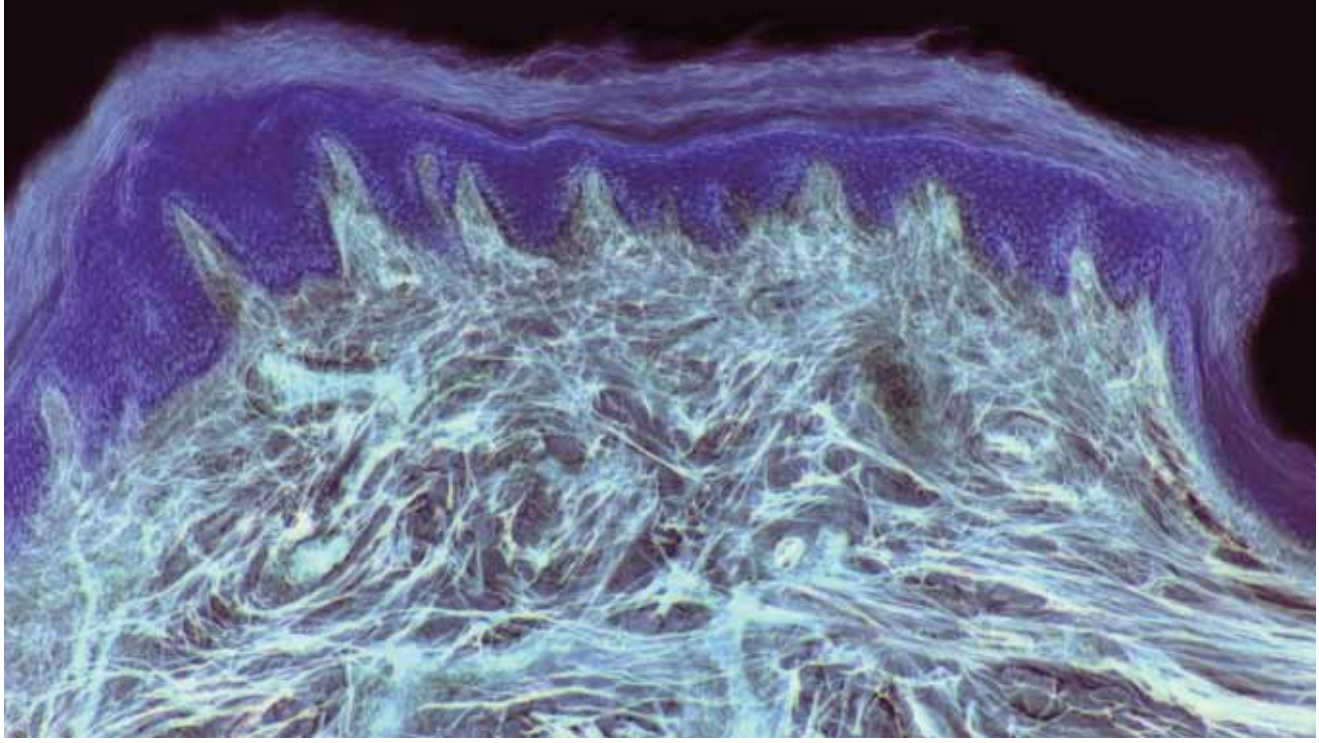
What unique risks does exposure to adult transdermal medications pose to children? This question is examined in tandem with a discussion of compounding, and the efficacy, tolerability, and application properties of topical medications.



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Colored light micrograph of human skin layers. The top layer is the stratum corneum (flaky, blue), the living epidermal layer is directly below (stratum germinativum, dark blue), and the lowest layer shown is the dermis (pale blue).

An 18-month-old boy is brought to the emergency department (ED) by his mother for having "a really red face, and acting crazy." In the ED, the patient's skin appears flushed and he is picking at the air. Vital signs at presentation are as follows: blood pressure, 95/65 mm Hg; pulse, 175 beats/min; respiratory rate, 24 breaths/min; oxygen saturation, 99% on room air; temperature, 98.9°F. His physical examination is significant for an awake and alert, altered child with a combination of agitation and delirium. His face is flushed, his pupils are 6 mm and reactive, and he has decreased bowel sounds and a palpable bladder. The skin is warm and dry. Laboratory tests, including a basic metabolic panel and creatinine kinase, are normal, and an electrocardiogram shows sinus tachycardia.

Upon questioning, the mother indicates that the child

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Table.
Topical Medications Intended for Local or Systemic Effects

Drug Name	Class	Availability
Local		
Diphenhydramine -Topical	Dermatologic/anti-itch	Non-Rx
Hydrocortisone -Topical	Corticosteroid	Non-Rx/Rx
Methylsalicylate/menthol -Topical	Analgesic	Non-Rx
Retinoids -Topical	Dermatologic/anti-acne	Non-Rx/Rx
Systemic		
Clonidine - Patch	Antihypertensive	Rx
Fentanyl - Patch	Opioid analgesic	Rx
Nicotine - Patch	Smoking cessation aid	Non-Rx
Scopolamine - Patch	Antiemetic/motion sickness	Rx

Note: Under certain conditions, both local and systemic topical preparations can lead to systemic toxicity.
Non-Rx = nonprescription; Rx = prescription.

takes no medications, but recently had been suffering from a diarrhea-associated diaper rash. The mother states that she applied her husband's "special cream" to the rash; the cream is mailed to her husband from a compounding pharmacy, and he uses it for the treatment of "chronic nerve pain." In the ED, the patient has a Foley catheter placed and receives several doses of benzodiazepines, reducing both heart rate and agitation.

Why is dermal drug delivery appealing?

Topically applied medications, particularly transdermal drug formulations, are very popular and increasingly available. Topical medications can have both local effects and systemic bioavailability, resulting in effects remote from the application site. This latter feature, in addition to the unique pharmacokinetics associated with this route of administration, makes transdermal preparations a useful means of administering medications for chronic medical conditions, such as pain and hypertension. Transdermal preparations are appealing due to their ease of use, the long-lasting and relatively stable blood concentrations they produce, and their ability to offer a discrete treatment option.

Skin functions as a barrier that helps the body retain water and resist microorganisms and noxious chemicals. The skin is composed of three main layers: the epidermis, the dermis, and subcutaneous tissues. The outermost layer of the epidermis, the *stratum corneum*, provides almost all the skin's protective properties. The stratum corneum is made up of keratin-filled skin cell remnants and fibrous proteins that overlap in layers. Properly formulated, however, a medication can penetrate the stratum corneum to gain access to the deeper skin layers, and subsequently the systemic circulation. Most drug absorption is transcellular, involving solute movement through the cells.[1] The magnitude of diffusion will depend both on the integrity of the skin and the physicochemical properties of the applied drug. Drugs with low molecular weight (< 800 daltons) and with solubility in both lipid (epidermis) and water (dermis) layers of the skin are optimal.[1] The properties of lipophilicity and hydrophilicity are used to establish the octanol/water partition coefficient of a drug, which is a measure of the difference in solubility of a compound in the two phases. This coefficient represents the ratio of the solubility of a compound in octanol (hydrophobic and nonpolar solvent) and wa-

ter (a hydrophilic and polar solvent). Hydrophilic drugs (low octanol/water partition coefficients) are unable to penetrate the keratinaceous layer of the skin, while lipophilic drugs, with high octanol/water partition coefficients, readily dissolve in the superficial skin lipids but cannot subsequently enter the water-based subcutaneous tissues. Drugs with either extremely high or low coefficients are not ideal candidates for transdermal delivery.

What are some types of transdermal (topical and systemic) medication delivery systems, and what characteristics do they have?

The efficacy, tolerability, and application properties of a topical medication are often related to the base, or vehicle, in which the active drug is delivered. Bases are a mixture of components with various properties that affect transdermal absorption, most notably, polarity, hydrophilicity, and lipophilicity. Interactions between the base, skin, and drug will influence the effect of the preparation and release of the drug.[2]

Lotions are often liquid suspensions, or a powder in a water-in-oil mixture. They possess low viscosity and most often have low oil content. Gelling agents are sometimes added to enhance viscosity just enough so that lotions can be readily applied. Lotions have low drug penetration properties.[2] Benzoyl peroxide, used to treat acne, is often used as a lotion, although it is also available as a cream, gel, and wash.

Creams are multiphase preparations consisting of a lipophilic phase and an aqueous phase (emulsion). Creams are usually oil-in-water emulsions. In either case, the water content is usually between 31% and 80%. Creams have moderate oil content and drug penetration properties.[2] Zinc oxide, used to treat diaper rash, often is used as a cream, although it is also available as an ointment, gel, powder, and pad.

➤➤Fast Track

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Ointments are semisolid preparations in which solids or liquids may be dispersed. Ointments can be water-in-oil emulsions, with water content less than 25%. Some typical bases for ointments include petrolatum, paraffins, vegetable oils, and animal fat. Due to their high oil content, ointments are usually associated with high drug penetration properties.[2] Hydrocortisone is available as an ointment, as are methylsalicylate/menthol topical preparations.

Gels are semisolid preparations consisting of a solid component, which forms a matrix, and a liquid component that exists within the solid matrix. The liquid phase is usually water or alcohol and often contains additives like propylene glycol, glycerol, or sorbitol.[2] Gels have high oil content and high drug penetration properties. Progesterone intravaginal gel, used in assisted reproductive technology methods or for secondary amenorrhea, is an example of a drug that comes in a gel formulation.

Patches represent a complex approach to the prolonged administration of transdermal medications, but they utilize many of the same principles detailed above. Patches typically contain an occlusive backing, a reservoir of drug, a microporous membrane, and an adhesive.[1]

Why are children at greater risk than adults for developing systemic toxicity?

Topical medications, when systemically absorbed, can result in unwanted and unintended effects. In children, the application of an adult patch, which delivers an adult dose, is associated with a high risk for toxicity. Several other factors present in young children make them vulnerable to systemic toxicity from topical medications.

Size. Absorption depends on the amount of skin surface area exposed to a topical drug. The area of absorptive surface is the same in a child and an adult, but there is usually a substantial weight difference between them; as a result, a child will absorb a relatively higher dose than an adult.[1]

Nature of the epidermis. If the epidermal barrier is diseased or damaged, percutaneous absorption may be greatly increased.[1] Furthermore, percutaneous penetration can be affected by skin hydration, temperature, and occlusive bandages or clothing.[3] Patches capitalize on the improved absorption in hydrated skin by acting as a locally occlusive dressing. Children's skin is naturally more hydrated than adults. For example, in 1885 an outbreak

of cyanosis in newborn infants at the Marylebone Workhouse in London was linked to aniline dye used to stamp an image on the children's diapers. The dye was being absorbed from freshly stamped diapers, leading to methemoglobinemia; this phenomenon has occurred several times since.[4]

Maturity of the epidermis. Preterm infants, particularly those with gestational age less than 28 weeks, have a poorly developed stratum corneum. Topically applied agents can be readily absorbed in these patients, with potential for dangerous consequences. For example, hexachlorophene, a chlorinated hydrocarbon used as an antiseptic, proved neurotoxic when applied to children with an immature epidermis, leading to vacuolar encephalopathy and spongiform myelinopathy.[5] Term infants and children have barrier properties similar to an adult's. Preterm infants have rapid maturation of their stratum corneum, and will develop a full protective barrier within 2 to 3 weeks of age.[1]

What are compounding pharmacies?

Pharmaceutical compounding is the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription.[6] According to the International Academy of Compounding Pharmacists (IACP), there are 56,000 community-based pharmacies in the United States. Some 7,500 compounding pharmacies specialize in what the IACP calls "advanced compounding services," which compound medications and preparations outside the scope of traditional pharmacies. Approximately 3,000 of these pharmacies make sterile products.[7] However, most community and hospital pharmacies compound only in a limited fashion (eg, IV admixtures). The US Food and Drug Administration (FDA) holds that compounding is both ethical and legal, as long as a licensed practitioner has prescribed the compounded medication for a specific patient.[6,8] Although the FDA has oversight capabilities, most regulation and inspection of compounding pharmacies falls to state pharmacy boards, and the rules vary by state.[6,8]

Compounding pharmacies recently gained notoriety after the Centers for Disease Control and Prevention (CDC) and the FDA recommended that health care professionals cease use of and remove from their pharmaceutical inventory any product produced by the New England Compounding Center (NECC).[9] A multistate investigation, conducted in part by the CDC and FDA, found multiple cases of *Aspergillus* meningitis among patients who received an epidural steroid injection produced by NECC. The investigation so far has identified more than 510 cases, including 36 deaths across 19 states.[10] Furthermore, the investigation also found fungal infections associated with injections in peripheral joint spaces. Deficiencies have been found in the compounding center's clean room, which is a space designed to maintain low levels of contamination.[10-12]

Case Conclusion

In this case, the patient's father had a prescription for a compounded cream that contained 50 mg of imipramine (amount of dosage dispensed per pump), a tricyclic antidepressant with antimuscarinic properties. The child was admitted to the pediatric intensive care unit and was discharged the following day with no sequelae. **EM**

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