

REVIEW ARTICLE

Pharmacology and Toxicology of Infant Skin

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Cutaneous metabolism and pharmacology have been the focus of increased scientific inquiry in the past 2 decades. However, in the past few years, attention has been focused specifically on the effects of topically applied drugs in infants as different qualitatively or quantitatively from their effects in adults.

Prior to 1972, it was known that brain damage occurred in animals with prolonged blood levels of 1 $\mu\text{g}/\text{ml}$ hexachlorophene, and that washing newborn babies with a standard 3% hexachlorophene liquid soap for 3-5 days resulted in significant blood levels of the compound. However, this knowledge was not disseminated widely enough to prevent the tragic deaths of infants after the use of baby powder contaminated with 6.6% hexachlorophene [1]. This incident highlighted the need for increased understanding of drug effects not only from the viewpoint of the skin as a target organ, but also of percutaneous penetration and resultant blood levels; the affinity of other body tissues for drugs and their metabolites; metabolites which may result from the effect of the skin itself acting on the drug; and the infant's much greater ratio of surface area to body weight, allowing the infant to percutaneously absorb proportionately greater quantities of topical medication than an adult. Although tissue distribution of most drugs has not been studied in infants, it is known that such distribution often depends on age. For example, in infants and children with a given plasma level, of drugs such as barbiturates, morphine and tetracycline, the brain tissue level may exceed that of the adult. Thus, drugs and chemicals that penetrate infant skin may produce effects different than those penetrating adult skin.

NEONATAL PHARMACOLOGY AND DEVELOPMENT OF ORGAN SYSTEMS

Cutaneous permeability of preterm infants is greater than in adult skin. Once absorbed, a given drug may be more toxic for a neonate than for an adult. Factors such as drug absorption, protein binding, metabolism, distribution and excretion may be altered because several organ systems such as the hepatic, renal and central nervous systems are not structurally and functionally fully developed. Morselli [2] includes the following physiologic distinctions that exist between the neonate and the adult: (a) Lower blood pressure and variable blood flow patterns; (b) Brain and liver make up a greater proportion of body weight; (c) Changes in drug excretion due to incomplete development of kidney giving different pH proportions of urine and blood; (d) Body compartments are of different (relative and absolute) proportions; (e) Total body water is larger and the ratio of extra/intra-cellular water is considerably elevated; (f) Adipose tissue is less.

The neonate shows decreased plasma protein binding which leads to drug toxicity at lower doses. Also, albumin is qualitatively different and has less binding potential which increases the likelihood of drug displacement and toxicity at lower doses. Drug metabolism is altered because of immature metabolic pathways in the liver. Drugs requiring metabolism for detoxification and deactivation may show longer half-lives in neonates. Usually, the deficient metabolic pathways in the neonate are the oxidative and reductive systems while hydrolytic reactions may show relatively little difference between the newborn and the adult with some drugs. Depending on the drug, conjugative and other synthetic pathways may show small or large differences between neonates and adults in the metabolism of drugs [3].

Drugs requiring renal excretion may show a similar prolongation of half-life in the neonate because of immature renal function. At birth, glomerular filtration rate in full-term infants is half that of an adult and only reaches adult levels at 1 yr of age. Tubular function is even more greatly reduced, and less than maximal ability to concentrate urine in preterm infants often leads to metabolic acidosis.

An infant must undergo considerable neurological development. In proportion to total body weight, the infant's brain weight represents a larger share than in the adult. Myelination starts in the second trimester and is completed slowly during infancy. At least 2 factors may be important in increasing infantile brain susceptibility to drug-induced seizures: The blood-brain barrier is more permeable in newborns than in adults and preterm infants are more susceptible to seizure activity because of low carbonic anhydrase levels.

Body Surface Area

Several physiologic processes such as cardiac output, blood volume, glomerular filtration and organ development closely correlate with body surface area. As a human grows in volume, so does the surface area but at a much slower rate. Adults have relatively small surface area while infants have relatively large surface areas. This serves to maximize the dose of a topical drug in the newborn. The infant surface area is greater than would be expected from weight alone. Proportions of newborn to adult with respect to weight, surface area and length are respectively 1:21, 1:9 and 1:3.3 [4].

Drugs are often dosed according to body surface area in pediatrics and in all ages with various chemotherapy protocols. This principle of dosing is not clinically used to any great extent in the dosing of topical medications for infants. Perhaps dosing based on body surface is appropriate for some medications but all rules for dosing fail for preterm and neonatal infants. The established dosing rules based on body surface area become useful in older infants. Studies with salicylic acid show that a proportionately larger systemic dose is delivered in infants than in adults with topical applications of the same product. It is postulated that this is due to differences in body surface area, i.e., body weight ratios, but differences in cutaneous and other organ system kinetics probably play a role.

Growth Rate

The postnatal growth of preterm infants resembles the growth rate of fetuses of the same size rather than that of full-term infants of the same postnatal age.

PHARMACOLOGY OF INFANT SKIN

Since the ability of the skin to accept, transfer and metabolize drugs is clearly related to its structural and biochemical development, a rapid review of these processes appears to be in order.

Epidermis

The human embryo of 2-4 weeks is covered by the single layered periderm which resembles amniotic epithelium and permits exchange of nutrients and other substances between the fetus and amniotic fluid. The stratum germinativum, developing in the 4-week embryo, gives rise to the epidermis and its appendages. At 3 mo of fetal life, the epidermis is 2-4 cell layers thick and by the 5th month, keratohyalin granules appear within epidermal cells. By the 6th mo, functioning melanocytes are present within the basal layer. At birth, the stratum corneum is fully developed in mammalian species, including man, and its ultrastructure is virtually indistinguishable from that of an adult.

Percutaneous penetration is affected by multiple factors including the physical properties of the penetrant and the vehicle, skin hydration and temperature, and epidermal and dermal metabolism. The main barrier to penetration is the stratum corneum. Adult human studies indicate that regional body variations in skin penetration result from differences in the thickness of the stratum corneum and to a slighter degree, differences in amount of epidermal appendages.

Infant epidermis is less thick than adult epidermis [5] and it is assumed that the stratum corneum is proportionately also thinner. However, we know little about the barrier function differences as they relate to stratum corneum thickness in infants and less about the barrier qualities of the newborn keratin as opposed to that of the adult. Pediatricians have long used the newborn's skin appearance as a criterion for assessing prematurity or postmaturity, as well as disease states such as the Gray syndrome or diabetes mellitus.

Most evidence regarding differences in percutaneous absorption between newborn and adult skin comes from studies in preterm infants. Skin permeability in preterm infants was evaluated with topically applied phenylephrine [6]. Infants 28 to 34 weeks of gestational age had a rapid blanching response lasting from 30 min to 8 hr. Infants 35 to 37 weeks in most instances failed to exhibit blanching. This suggested that preterm infants have immature epidermal barrier function.

While there is increased water content in normal full-term infant epidermis, some factors predispose to transepidermal water loss (TWL) in *immature* infants. These include thinner stratum corneum, increased water content and increased permeability. However, healthy term newborns have lower TWL's than adults. This could be due to a more efficient barrier in term newborns or due to the influence of eccrine gland activity on TWL in adults [7]. Again, skin microphotographs show that a newborn infant has a much thicker stratum corneum than an 1-mo-old infant and that this covering is shed within the first few days of life [5].

Biosynthesis and percutaneous absorption of a wide variety of lipids takes place in infant skin. Abdominal skin from young adults can synthesize a number of different lipids in proportions similar to that occurring in infant foreskin, but older adult abdominal skin is less active. Differences in lipid synthesis may also exist at various body sites as well as in different age groups [8].

Cyclic nucleotide metabolic studies are variable, but there may be some differences between adult and newborn or preterm infant skin. Subtle differences were detected between the cyclic

AMP-dependent protein kinases of neonatal human skin and adult human skin but no prominent distinguishing features were noticeable [9]. Newborn mouse epidermis contains adenylate cyclase responsive to β -adrenergic stimulation, but is relatively insensitive to isoproterenol stimulation. Cyclic AMP levels are rapidly elevated following injection of isoproterenol or epinephrine and the elevations can be blocked by propranolol. Mitotic rate in epidermis is essentially the same in infants as in young adults.

Appendages

The trans-appendageal route probably accounts for a relatively small amount of drug absorption both in adults and infants. There has been neither a qualitative or quantitative difference demonstrated in drug absorption in different age groups.

Hair development starts in humans during the third fetal month and most follicles are formed before birth. The earliest hair (lanugo) is fine, soft, unmedullated, poorly pigmented and distributed widely. In the newborn, the hair growth phases are synchronized with about 80% of hairs in the telogen phase. A temporary alopecia may occur during dyssynchronization of growth.

Eccrine glands are anatomically completely formed by the 5th fetal month. Apocrine glands are well developed at the 7th-8th fetal month, producing a milky-white fluid containing water, lipids, protein, reducing sugars, ferric iron and ammonia. Sebaceous glands start differentiating at about 13-15 weeks of fetal life and almost begin to produce sebum. Their growth and activity up to and immediately after birth is governed, in part, by maternal androgen and endogenous steroid production. The shedding of sebaceous gland cells into amniotic fluid late in gestation forms the basis of the Nile blue sulfate stain test of fetal maturity [10]. The sebaceous cells stain orange or brown while epidermal fetal squames stain blue. Cytological count of 10% fat-laden cells occur at 36 weeks while a 20% count occurs at 40 weeks of pregnancy.

Dermis

At birth, the dermis is about 2-4 mm thick. There is little evidence to suggest age differences in the uptake of drugs into the dermis, but the release of drugs out of the dermis may differ because of the differences in water binding qualities and the differences in ground substances in the dermis. The dermis of the human embryo starts as an undifferentiated cellular myxomatous tissue in which fibrils first appear between 2 and 4 mo of age. Collagen and elastic fibers are found between 20 to 40 weeks of life. Elastic tissue continues to increase postnatally and to contain less lysine than does fetal tissue. The ground substance is mainly composed of the mucopolysaccharides, hyaluronic acid, chondroitin sulfate B (dermatan sulfate) and water. Neonatal skin is often edematous because of dermal loosely bound water and sodium excess, most of which is lost within a few days.

Subcutaneous Fat Tissue

Subcutaneous fat first appears in the 14th week of fetal life and accumulates mainly in the last trimester of pregnancy. The preterm infant has a poorly developed fat supply, a relatively large surface area and a small body mass. All of these factors are disadvantages in trying to maintain body temperature. Brown adipose tissue, which is practically absent in the adult, is found in specific anatomical areas of the newborn infant, e.g., in the interscapular region, at the base of the neck and in the posterior abdominal wall. This tissue performs a central role in postnatal regulation of body temperature. A newborn infant regulates body temperature not by shivering but by increased oxidation of fatty acids within the adipose tissue. Therefore, the effect of cold is depletion of brown adipose tissue with slight influence on white adipose tissue. It is unknown how adipose

tissue change affects topically applied drugs and percutaneous absorption in infants, but several lipid soluble drugs such as DDT and lindane, are stored in white adipose tissue in adults.

DERMATOTOXICOLOGY AND INFANT SKIN

Several commonly used drugs and chemicals have been reported as the cause of percutaneous toxicity in infants. In many of these reported cases, the preterm infant appears to be at greatest risk because of incomplete epidermal barrier to penetration of toxic drugs and chemicals. There are many reports of less commonly encountered drugs and percutaneous toxicity in infants which are not included in this review.

Phenol, Resorcinol and Castellani's Paint

Phenol and phenolic derivatives have been frequently reported as causes of percutaneous toxicity. An outbreak of percutaneous poisoning with epidemiological follow-up occurred in 1967 with a laundry product containing pentachlorophenol. Twenty newborn infants developed symptoms of profuse, generalized diaphoresis, fever, tachycardia, tachypnea, hepatomegaly and acidosis. Nine infants became severely ill and 2 babies died. High concentrations of the chemical were found in nursery linens which provided a source for percutaneous absorption evidenced by toxic serum and tissue levels [11]. Several infant deaths due to topical application of resorcinol have been reported. Methemoglobinemia, cyanosis, hemolytic anemia, drowsiness, shallow respiration and hemoglobinuria are also problems which have followed topical resorcinol application in infants [12].

Boric Acid

Historically boric acid proved to be a significant toxic hazard to infants because it was commonly applied in talcum powders, ointments or solutions in 5-10% concentrations to inflamed and occluded areas of diaper dermatitis. Several infant fatalities have been reported from percutaneous boric acid toxicity and it should no longer be used on infant skin [13].

Salicylic Acid

In 1946, Weiss and Lever reviewed percutaneous salicylate intoxication and found reports of 13 fatal cases, 10 of which were children under 3 yr of age [14]. Symptoms were those of salicylism.

Epinephrine

Epinephrine (1:1000, 0.1 ml) was applied locally to a hemorrhaging circumcision area instead of the usual 1:100,000. The child was 2 days old. The patient soon showed tachycardia of 220/min, local pallor of the penis and base of the shaft as well as perioral acrocyanosis. The case illustrated the local and systemic complications of absorbed epinephrine specially in the newborn infant [15].

Corticosteroids

Systemic effects from percutaneous absorption of topically applied corticosteroids in infants are frequently reported in the literature and appear to exhibit greater toxicity if the steroid is fluorinated with significant glucocorticoid potency and the infant is preterm, low birth-weight, and has severe inflammation or extensive denuded areas of skin.

Infants with active atopic dermatitis were treated for 15 days with uniform quantities of topical 0.1% betamethasone valerate ointment in one group and 1% hydrocortisone ointment in a subsequent group [16]. Polyethylene occlusion was used in both groups. Adrenocortical function was decreased on the second posttreatment day in 75% of infants using fluorinated steroid versus no evidence of suppression in the hydrocortisone group. Thus, with topical fluorinated steroids, chronic suppression of adrenal axis function and impairment of growth is probably a

significant risk factor evidenced in infants. Unlike the infant groups, adult groups were also studied and axis function recovered rapidly when treatment was stopped.

Greater than one-third of the applied dose is systemically absorbed in infants with active atopic dermatitis. Topical hydrocortisone-induced suppression of the hypothalamic-pituitary-adrenal-axis in infants is minimal and rapidly reversible. A more prolonged suppression may be seen with topical fluorinated steroids and side effects similar to those seen with systemic administration of corticosteroids are possible [17].

Estrogens

In infants of both sexes, pseudoprecocious puberty has resulted from application of topical estrogen ointments for 2-18 mo periods with 2-10 daily applications [18]. There has been intense pigmentation of mammillary areolae, the linea alba and genitals with mammary enlargement and growth of pubic hair. Female infants have developed vaginal discharge and bleeding.

Hexachlorophene

Chlorinated hydrocarbons are neurotoxic chemicals (cytotoxic to nerve cells) producing characteristic signs of CNS toxicity if given acutely in a sufficient high dose. Factors contributing to hexachlorophene toxicity in infants include a greater number of exposures to the drug, increased concentration of the drug, absence of adequate rinsing, presence of large areas of abraded skin, hepatic, biliary or renal disease and low birth weight. UV-lights (bili-lites) help to dechlorinate (detoxify) the hexachlorophene and exert a protective effect. General suggestions for use of hexachlorophene include: limit exposure to 1-2 baths, do not use in infants under 1200 gm or under 35 weeks of age or where large areas of abraded skin or hepatic, biliary or renal disease are present and follow with immediate and thorough rinsing [19]. Histopathology of the CNS in infants with hexachlorophene intoxication has shown vacuolar encephalopathy with brain stem reticular formation [20].

Lindane

Lindane is another chlorinated hydrocarbon and neurotoxic agent. A 4-mo-old premature infant had a single application of lindane over the entire body for 24 hr with subsequent washing. Neurological testing 2 days later showed marked mental motor retardation. Serum level of lindane 20 hr after the bath showed a level of 0.1 mg/ml (normal <0.001 µg/ml). This level is 10-fold higher than that previously reported in children and was seen with the then standard recommendation of only one application for 24 hr [21]. CNS toxicity due to prolonged application of lindane has also been seen in older children. The increased serum levels in infants corresponds to the increased blood and brain levels seen in newborn versus adult guinea pigs after topical application of 1% lindane lotion [22].

Chlorhexidine

Low serum levels of the antimicrobial skin cleanser, chlorhexidine, without apparent clinical effect, were detected in newborn infants with intact skin who were bathed in a standard manner [23]. Pre-term babies had more readily detectable serum levels than full-term infants.

DISCUSSION

There is much to be learned about percutaneous penetration and the resultant dermatopharmacology and dermatotoxicology of infant skin. Although full-term infant skin may provide a functioning barrier to absorption similar to adults, it appears that the preterm infant is at much greater risk of suffering toxicity from topically applied drugs and chemicals. Furthermore, little is known about differences in dermal clearance of drug absorbed through the epidermis of full-term infants and adults, differences which ultimately could represent a variable

determining cutaneous toxicity as important as the stratum corneum barrier.

Cutaneous metabolic and detoxification pathways have not been determined for most drugs. It is known, however, that some topically applied drugs are metabolized in the skin producing metabolites different from those the same drug would produce by a different route of administration. Although several systems are not fully established in newborns, it remains unknown whether variations exist in cutaneous metabolism and detoxification between preterm infants, full-term infants and adults.

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