CHAPTER 5

Systemic Toxicity

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Introduction

Human skin is exposed to a plethora of chemicals from birth to death. Following percutaneous absorption, a chemical and/or its metabolites may cause toxicity in another organ distant from the point of entry. Although not generally appreciated, some chemicals are more toxic, at least in animals, when applied topically rather than orally. Further, many compounds are absorbed to a greater degree from the skin than the gastrointestinal (GI) tract, and whole-body exposure can produce systemic absorption of grams of material. This chapter focuses on the limited epidemiologic material available, depending largely on case reports. Many drugs for topical use are capable of producing systemic side effects whose occurrence and severity depends largely on factors that affect the absorption of topically applied drugs.

Factors Affecting Percutaneous Absorption

Integrity of the Barrier

The stratum corneum layer of the epidermis is a major barrier to percutaneous absorption. Anything that alters the structure or function of the stratum corneum will affect epidermal absorption. The integrity of this barrier is reduced by any inflammatory process of the skin, such as any form of dermatitis or psoriasis, which may result in increased percutaneous absorption. Similarly, removal of the stratum corneum by stripping or damage by alkalis, acids, etc. will increase absorption.

The Physicochemical Properties of the Substance

Absorption is affected by the relative water/lipid solubility of the drug and the relative solubility of the drug in its vehicle compared with its solubility in the stratum corneum. In order for a chemical to penetrate through the skin into the systemic circulation, it requires both a degree of lipophilicity (to facilitate its entry into the stratum corneum) and hydrophilicity (to aid its passage through the viable epidermis and dermis). Other factors, such as molecular weight, molecular volume and melting point, will also be important determinants.

Occlusion

The penetration of some topicals may be increased by up to a factor of ten or more by the use of an occlusive covering. This can be due to increased water retention in the stratum corneum, increased blood flow, increased temperature, and increased surface area after prolonged occlusion (skin wrinkling). Occlusion also prevents accidental wiping off or evaporation (for volatile compounds), hence maintaining a higher dose on the skin surface.

Vehicle Containing the Drug

The greater the affinity of a vehicle for the drug it contains, the less the percutaneous absorption of the drug. Physical properties of vehicles, especially the degree of occlusion they produce, affect percutaneous absorption, as discussed above (greases). Structural or chemical damage to the barrier layer can be caused by the vehicle used; vehicles, such as dimethyl sulfoxide, cause greatly increased percutaneous absorption. In general, a higher concentration of the drug in its vehicle enhances penetration. Enhanced solubility produces greater thermodynamic activity, yielding greater flux. Extensive documentation on factors affecting penetration is found in Bronaugh and Maibach (1990, 1991) and Smith and Maibach (1995).

Site of Application

Regional differences in permeability of skin largely depend on the thickness of the intact stratum corneum (Wester and Maibach 1989). According to the findings of a study by Feldmann and Maibach (1967), the highest total absorption of hydrocortisone is that from the scrotum, followed (in decreasing order) by absorption from the forehead, scalp, back, forearms, palms and plantar surfaces.
Age

The greatest toxicological response to topical administration has been seen in the infant. The preterm infant does not have intact barrier function and hence is more susceptible to systemic toxicity from topically applied drugs (Nachman and Esterly 1971; Greaves et al. 1975). A normal full-term infant probably has a fully developed stratum corneum with complete barrier function (Rasmussen 1979). However, topical application of the same amount of a compound to both adults and newborns reveals greater systemic availability in the newborn (Wester et al. 1977). This is because the ratio of surface area to body weight in the newborn is three times that in the adult. Therefore, given an equal area of application of a drug on to the skins of newborns and adults, the proportion absorbed per kilogram of body weight is much higher in the infant. Barrett and Rutter (1994) and Maibach and Boisits (1982) provide extensive documentation on this issue. Although counterintuitive, absorption of some compounds decreases in the aged (Roskos et al. 1989). Later, Roskos and Maibach (1992) reported that, in older subjects, absorption was decreased for steroids but unchanged for other, more hydrophilic compounds. They suggested that this was due to the decreased concentration of surface lipids in older subjects.

Temperature

Generally, increased skin temperature enhances penetration rate (Jetzer et al. 1988). This may be due to the increased blood flow associated with increased skin temperature or an increase in skin hydration (Danon et al. 1986; Siddiqui 1989).

Metabolism

It has been well documented that the skin is capable of metabolizing a wide range of xenobiotics and has a full complement of phase-I and phase-II enzymes. The specific activities found in the skin are relatively low when compared to their equivalent hepatic forms. However, when the total volume of the skin is taken into account, then it is apparent that the skin is an efficient drug-metabolising organ. Recent information on skin metabolism is found in Hotchkiss (1995).

Systemic Side-Effects Caused by Topically Applied Drugs and Cosmetics

Topically applied drugs and cosmetics can cause allergic or irritant contact dermatitis. However, this type of side effect, usually limited to the skin, is outside the scope of this chapter. The reader is referred to the textbooks of Fisher (1986) and Rycroft (1995) for references to contact dermatitis. Systemic side effects from topically applied chemicals can sometimes result from either a toxic (irritant) reaction or a hypersensitivity reaction. The latter can be an anaphylactic type of reaction, which is the extreme manifestation of contact urticaria syndrome (Amin et al. 1996). Many topical drugs and cosmetics have reportedly caused anaphylactic reactions. While anaphylactic reactions to topical medications are uncommon, their potentially serious nature warrants attention. However, reports of toxic (as distinct from allergic) reactions to applied drugs and cosmetics are more numerous and include many medicaments that have been safely used for many years but which can be toxic under special circumstances.

The following is a list, in alphabetical order, of the chemicals to be reviewed, followed by a detailed discussion of each chemical.

1. Agrochemicals
2. Anti-acne creams
3. Antibiotics
   - Chloromycetin
   - Clindamycin
   - Gentamycin
   - Neomycin
4. Antihistamines
   - Diphenylpyraline hydrochloride
   - Promethazine
   - Doxepin
5. Antimicrobials
   - Boric acid
   - Castellani's paint
   - Hexachlorophene
   - Homosulfanilamide
   - Iodine; povidone–iodine
   - Phenol
   - Resorcinol
   - Silver sulfadiazine
   - Trichlorocarbanilide
6. Aromatic amines
7. Arsenic
8. Carmustine
9. Camphor
10. Coal tar
11. Cosmetic agents
12. Crude oil
13. Diethyltoluamide (DEET)
14. Dimethyl sulfoxide (DMSO)
15. Dinitrochlorobenzene (DNCB)
16. Ethanol
17. Fumaric acid monoethyl ester
18. Insecticides