Clinical Pharmacology of Skin Disease

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General Editor's Foreword

The skin is an unique organ. It protects us by its relative impermeability to most substances in our environment; it may reflect what is happening in other organs and it can, when diseased itself, make human beings miserable. Since human beings first walked the Earth, they have anointed their skin with oils, slathered it with potions and creams, painted it with dyes and washed it with soap. Most recently we have even used it to deliver drugs to the systemic circulation.

A great deal is now known about the physiology of normal skin and the mechanisms underlying the pathophysiology of disorders of the skin as well as the basis of the rational treatment of these disorders. David Bickers and his colleagues, in this monograph, provide the reader with this type of information in a clear, concise manner. Physicians in any type of practice can profit from the information contained herein.

Daniel L. Azarnoff, M.D.

Preface

The application of fundamental principles of pharmacology to the skin has been a slow process relative to that of most other organs. The reasons for this are not completely clear but undoubtedly relate to the peculiar structural characteristics of the skin which render it relatively impermeable to most topically applied drugs and make it a tissue that is difficult to work with in the laboratory. Furthermore, there is little clear knowledge regarding movement of systemically administered drugs into the skin.

The purpose of this book is to summarize insofar as possible the pharmacologic properties of the major agents that are used in the treatment of dermatologic disorders. It is not meant to be an exhaustive review but rather to provide the reader with pertinent information regarding the more commonly used agents. No effort has been made to discuss every drug used by the practicing dermatologist. Rather an arbitrary selection has been made that encompasses the major categories of agents. Each chapter is divided into sections that discuss history, chemical class, metabolism and kinetics, clinical use and side-effects. An effort has been made to provide a generous list of references for the interested reader. In the appendix, highlights of most of the drugs discussed in the text are provided as a quick reference source.

It is our hope that this book may stimulate new ideas and new investigations in the field of dermatopharmacology, an area with many unsolved problems in which new insights could lead to novel approaches to the management of patients who suffer from diseases of the skin as well as to new techniques for the percutaneous administration of drugs for systemic diseases.

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Introduction to Dermatopharmacology

GENERAL CONCEPTS

The treatment of diseases that affect the skin is necessarily specialized because of certain unique attributes pertinent to the structure and function of this tissue, which is a major interface between the body and its environment. Dermatologic therapy centers around the use of a broad spectrum of pharmacologic agents, many of which can be administered topically and/or systemically. Furthermore, physical modalities such as ultraviolet radiation either alone or in combination with drugs are highly effective in managing selected diseases of the skin.

The method of administration of drugs used for treating diseases affecting the skin may produce quite different effects. Such differences are undoubtedly due in part to variations in the rates of uptake, distribution, metabolism, and excretion of drugs when administered by topical or parenteral routes. Because of the effectiveness of the stratum corneum as a barrier to penetration of the epidermis, the topical application of many drugs is a grossly inefficient method for introducing drugs into the body. Yet this method of application is quite an efficient means of placing large concentrations of drug directly at the site of diseased cutaneous tissue for therapeutic purposes.

Furthermore, it is also clear that the impermeability of the skin provides a relatively high therapeutic index for many topically applied drugs used in dermatologic thereapy. Thus classic dose–response curves cannot be assumed for topical therapy. Indeed a drug applied to skin, although producing high

concentrations of the chemical on the cutaneous surface, will have little or no pharmacologic effect in the skin or elsewhere in the body unless it is capable of reaching the lower layers of the epidermis and the dermis. The skin is certainly not unique in this regard. For example, the ability of the blood–brain barrier to modify the accessibility of drugs to specific receptors in the central nervous system is well known. This principle is illustrated by the cytotoxic drug methotrexate and the antimycotic agent amphotericin B, both of which must be administered intrathecally in order to attain therapeutic levels in the central nervous system (1,2).

The distribution of topically applied drugs in cutaneous tissue is influenced considerably by the properties of the vehicle. Thus drugs that are in solution in a vehicle are more readily absorbed and distributed into the skin than are drugs in suspension (3). The entire field of vehicles is an exceedingly complex one. For example, it is now becoming clear that substances such as petrolatum, which were previously thought to be pharmacologically inert, may be capable of modulating prostaglandin synthesis in the skin (4).

Another important determinant of the effectiveness of a drug in skin is its rate of metabolism. It is well known that the liver is the major organ in the body in which the biotransformation of drugs and other exogenous chemicals occurs. However, it is now known that extrahepatic tissues also possess similar cytochrome P-450 dependent enzyme systems capable of metabolizing drugs (5). The skin, particularly the epidermis and its related organelles including sebaceous glands and hair follicles, can metabolize certain drugs and environmental chemicals, and such metabolic activity could prove an important determinant of the pharmacologic activity of these agents in the skin. For example, cutaneous tissue can metabolize certain types of environmentally encountered chemical carcinogens in two major ways, either by converting them into inert metabolites (detoxification) or by converting such chemicals into highly reactive metabolic species that can bind to cellular macromolecules, thereby initiating toxic responses, such as carcinogenesis (6). These variable metabolic pathways could also apply to drugs used therapeutically in the skin.

Skin is one of the largest organs of the body and is uniquely structured for its role as a major interface between the body and its environment. Cutaneous tissue is remarkably tough and resistant to chemical and physical agents, yet is quite pliable, permitting considerable freedom of movement. It is also a highly impermeable membrane that is capable of both passive and active "barrier" functions. It is passive only in the sense that the outer, keratinizing epidermal layer is impervious to many natural and synthetic chemical agents as well as physical agents present in the environment. It is active, in that there is gathering evidence indicating that multiple enzyme systems are important for the normal differentiation of the keratinocyte as well as the

aforementioned P450-dependent monooxygenase that may be capable of metabolizing topically applied drugs and chemicals (7).

Certain specialized anatomic features of the skin may alter the usual movement of certain drugs across this barrier. The conventional concept of movement of systemically administered drugs from the dermal vasculature and then by diffusion into the epidermis may not always apply. For example, the systemically administered antifungal agent, griseofulvin, may actually reach the epidermal surface by transport through the sweat with subsequent back-diffusion into the stratum corneum (8). This action may prove true of other drugs as well.

There are a number of solvents such as dimethylsulfoxide which are capable of increasing the permeability of the skin to selected compounds. Topical agents that would otherwise not be absorbed percutaneously may penetrate the skin when incorporated into specialized vehicles. There are now a number of pharmacologic preparations of nitroglycerin for angina pectoris and scopolamine for motion sickness that are administered by application to the skin with subsequent penetration through the epidermis into the dermal vasculature. This approach provides a reservoir of drug at the cutaneous surface that permits continuous maintenance of a therapeutically effective plasma concentration of drug (9). It is quite likely that this route of administration will be increasingly exploited in the future.

Awareness of the pharmacologic properties of the drugs used in treating dermatologic disease is essential for a rational approach to management of such patients. The skin's response to pathologic stimuli produces changes that seem to call forth the need to use contradictory therapeutic methods ("when it's wet, dry it, and when it's dry, wet it"). Empirical methods of treatment have historically been widely used in dermatology and are likely to remain a significant component of the therapeutic armamentarium of the dermatologist; until such time as better information is available regarding the pathophysiology of dermatologic disease, this will necessarily be the case.

A good example of this dilemma is illustrated by a unique cutaneous symptom, pruritus. This symptom is experienced primarily in the skin and can be defined as a sensation that stimulates the desire to scratch. This is hardly a meaningful definition in terms of biochemical changes or neurophysiologic events. It is known that the sensation of itching is transmitted through the C fibers of the peripheral nervous system. Unfortunately, there is little undertanding of the chemical mediators of this most distressing cutaneous symptom, although recent studies indicate that the neurotransmitter, substance P, may play an important role (10). Therapeutic approaches to treating pruritus illustrate some of the challenging aspects of dermatologic therapy. Because no specific treatment for pruritus itself is available, it is necessary either to sedate the patient so that the sensation becomes subliminal or to

substitute a more tolerable symptom in its place (i.e., heat or cold) by the use of topical agents such as menthol, phenol, or camphor.

Because symptoms of cutaneous diseases often differ dramatically from those involving other organs, dermatologic therapy may require the use of specialized approaches quite different from those used to treat diseases of other organs. Furthermore, since the skin and mucous membranes are the only parts of the body to which medicaments are directly applied, different considerations in the therapy of diseases involving these sites must be kept in mind. For example, diphenhydramine is a potent antihistamine when administered systemically; however, the drug also has direct anesthetic properties when in contact with mucosal surfaces and is often of value in treating painful conditions of the mucosa such as aphthous ulcers.

PERCUTANEOUS ABSORPTION

The major determinant of drug efficacy in the skin is the ability of the agent to penetrate cutaneous tissue. Human skin consists of two major compartments: the relatively thin outer compartment known as the epidermis and the relatively thick inner compartment known as the dermis.

The epidermis is a stratified squamous epithelium composed of a replicating basal cell layer, several layers of cells known as keratinocytes (100 μm thick), which ultimately differentiate into the keratin-rich stratum corneum (10 μm thick). The stratum corneum is a thin but compact acellular membrane forming the surface layer of the epidermis. It functions as the major barrier to the percutaneous absorption of topically applied drugs. Several lines of experimental data support the concept that the stratum corneum is the major epidermal barrier (11): (*1*) Stripping away the stratum corneum by repeated application of cellophane adhesive tape greatly enhances the percutaneous absorption of topically applied drugs; (*2*) experimentally isolated stratum corneum is almost as impermeable as whole skin; and (*3*) dead skin used in *in vitro* experiments has permeability characteristics analogous to those of living skin indicating that viable epidermis is not essential to barrier function.

The structural features of the stratum corneum important for barrier function include the following:

1. It is a compact layer of greatly compressed keratinocytes (5–25 cells).
2. Each cell has a thick membrane resistant to dilute acids and bases, to proteases, and to many keratolytic agents.
3. Each cell contains alpha-keratin filaments 6–8 nm in diameter rep-

resenting about one-half its mass. The fibrous proteins are embedded in an amorphous matrix rich in disulfide bonds. This intracellular fibrous and nonfibrous protein mass is resistant to many chemicals but is destroyed by keratolytics and strong acids and bases. In addition to these structural elements, stratum corneum cells contain lipids and water-soluble materials that permit hydration.

4. The intercellular spaces are filled with lipids of lamellar structure released during keratinization by membrane coating granules (Odland bodies). It is currently thought that the diffusion of aqueous solutes is controlled by these lipid-rich structures.

Percutaneous absorption can be broken down into a series of steps or processes. First, molecules of a drug or chemical must adsorb to the surface of the stratum corneum. Second, the molecules must diffuse through the stratum corneum. Third, they must reach the viable epidermis. Finally, they must move through the viable epidermis into the upper dermis, where they penetrate the vascular compartment and are transferred through the circulation to other areas. Diffusion through the stratum corneum is the rate-limiting step in this sequence, since the remaining processes generally occur quite rapidly.

To begin to understand the factors that determine percutaneous absorption it will be necessary to define several terms, which can be expressed by the following equation:

$$J = K_p \cdot C$$

where

$$K_p = \frac{D \times k_1}{e}$$

$$J = \frac{D \times k_1}{e} \cdot C$$

where J = amount of drug absorbed per unit time and area
K_p = permeability constant
C = difference in concentration above and below the membrane (C_1 and C_2 respectively; C_2 is generally negligible)
D = diffusion constant of the drug in the stratum corneum

k_1 = partition coefficient of the drug between stratum corneum and the vehicle
e = thickness of the stratum corneum

From this equation, several generalizations can be made: (1) the extent of percutaneous absorption will be directly proportional to the diffusion constant of the drug in the stratum corneum, to the partition coefficient between drug and vehicle, and to the amount of drug applied to the skin; and (2) the extent of percutaneous absorption will be inversely proportional to the thickness of the stratum corneum.

Diffusion constant: This is a measurement of the rate of transport of a drug through the stratum corneum. It is inversely proportional to both molecular size and to the viscosity of the cells. The extremely high viscosity of the stratum corneum renders the diffusion constant of most substances quite low (on the order of 10^{-9} cm^2 sec^{-1} for alcohols and 10^{-12}–10^{-13}, cm^2 sec^{-1} for steroids). In contrast, viable keratinocytes have diffusion constants closer to 10^{-6} cm^2 sec^{-1}.

Partition coefficient: Because the stratum corneum behaves in many ways like a lipophilic membrane, drugs with a relatively high lipid : water partition coefficient have relatively high permeability constants. Thus when k_1 is high, the drug moves rapidly into the stratum corneum from the surface and is therefore adjacent to the viable keratinocytes of the epidermis from which the drug can move rapidly across intercellular spaces and through the epidermis. Slight water solubility is also necessary for percutaneous absorption. Drugs that are purely lipid soluble or largely water soluble are absorbed rather poorly.

Percutaneous absorption is also greatly influenced by a number of other factors including age, race, degree of hairiness, body region, and degree of hydration of the stratum corneum. The state of hydration of the stratum corneum plays a major role in determining the rate of percutaneous absorption. In general, it can be stated that hydration increases the rate of absorption of all substances that can permeate the skin, particularly water-soluble compounds. Furthermore, it is known that elevated ambient temperatures and relative humidity both enhance the toxic effects of chemicals in occupational settings. In general, diseased skin is more susceptible to water loss and is more permeable to topically applied drugs.

At any given time, the hydration of the stratum corneum is dependent

on three factors: (*1*) the rate at which water moves into the stratum corneum from the underlying viable keratinocytes, (*2*) the rate at which water moves from the stratum corneum into the environment by evaporation, and (*3*) the capacity of the stratum corneum to retain moisture.

The movement of water through the skin (either from outside to inside or vice versa) is purely a passive process. The diffusional resistance of the stratum corneum is 1000 times that of the viable epidermis.

Hydration of the stratum corneum also enhances the percutaneous absorption of many compounds, including salicylic acid and corticosteroids (12). In general, increased hydration and ambient temperature are capable of enhancing absorption as much as 5–10-fold. These *in vitro* observations have been confirmed by *in vivo* studies using occlusive films of thin plastic. The increase in humidity and temperature at the skin surface greatly enhances percutaneous absorption of the pharmacologically active compound (13).

In addition to penetrating directly through the stratum corneum, drugs may also be capable of short-circuiting by way of sebaceous follicles or the sweat apparatus. Immediately after topical application of a drug, there is rapid movement through these shunts. The surface area of hair follicles represents 0.1–0.5 percent of the area of the epidermis and the diffusion constant through the epidermis is 100–10,000 times less than the diffusion constant through the hair follicles. In general, the flux by the two routes rapidly becomes constant, so that each participates in absorption. The lag time for percutaneous absorption will therefore be determined by the diffusion constant of the agent, that is, the greater the diffusion constant, the less the lag time.

One important consequence of the relative impermeability of the stratum corneum is known as the reservoir effect. Certain drugs, particularly the glucocorticosteroids, which are slowly released from the stratum corneum may exert pharmacologic effects for prolonged periods (14).

Percutaneous absorption can also be altered by the solubility characteristics of the vehicle. Thus drugs that have a relatively high stratum corneum/vehicle partition coefficient will generally have greater percutaneous absorption (15). Hydration of the stratum corneum with vehicles such as petrolatum will increase percutaneous absorption of drugs. Emulsions of both oil in water (O/W) and water in oil (W/O) alter percutaneous absorption. It seems that the permeability constant is primarily dependent on the partition coefficient between the stratum corneum and the continuous phase of the emulsion.

The pattern of absorption and distribution of many topically applied drugs remains ill defined. Nevertheless, it is clear that drugs can penetrate through the barrier of the avascular epidermis as described above into the dermis and then move into the rich vascular supply of the dermis from which they can be carried into the general circulation. Specific receptors or targets for drug action in the skin remain to be identified. However, it is now known that gluco-

corticoid receptors analogous to those previously identified in other tissues are present in human epidermal and dermal cytosol (16). These receptors may prove of great importance in understanding corticosteroid action in the skin.

It is now well appreciated that active metabolism of drugs occurs in the skin. Not only drugs, but chemical carcinogens and steroid hormones as well, are metabolized by skin enzymes. This metabolism may play an important role in a variety of phenomena including chemical carcinogenesis, sex steroid hormone biotransformation, and perhaps even the pharmacologic inactivation of topically applied drugs.

The skin's function as an excretory organ, although probably minimal, may nonetheless be important. Daily shedding of hair and epidermal cells as well as continuous secretion of sweat and sebum all provide potential avenues of excretion for drugs and other substances. There is some evidence that chlorinated hydrocarbons and heavy metals such as arsenic may be partially excreted in this way. Furthermore, certain heavy metals can be detected in scalp hairs by sensitive techniques such as atomic absorption spectroscopy (17).

The skin's relative impermeability to topically applied compounds dictates that to be effective such agents must be applied frequently and in rather large concentration. Therefore, a patient with a generalized skin disease such as psoriasis or atopic dermatitis who is treated with a topical corticosteroid may easily use a 0.5–1.5-g equivalent of hydrocortisone per day, assuming total body application of a fluorinated corticosteroid such as triamcinolone four times daily.

In contrast, many drugs that are administered systemically for treating skin disease will quickly achieve therapeutic levels in cutaneous tissue and at considerably lower doses. Thus orally administered prednisone in the dosage range of 30–60 mg/day, which is equivalent to 120–240 mg of hydrocortisone, will usually control most acute inflammatory dermatoses. The superior therapeutic effectiveness of systemically administered agents for dermatologic disorders is likely attributable to the relative ease with which circulating drugs can reach the dermis, which in turn is directly related to its rich vascularity. In fact, the entire blood volume circulates through the skin every 10–12 minutes.

Despite the clear-cut superiority of parenterally administered drugs (both in terms of efficacy per unit dose and convenience to the patient), their appropriate use in dermatology is frequently restricted by their potential toxicity. Although a cause of considerable symptomatic and cosmetic discomfort, most dermatologic diseases are rarely life threatening. This demands that the dermatologist give careful consideration to the risk · benefit ratio of the available agents for treating disorders of the skin.

The ideal drug would be able to target specifically to a particular diseased

organ or cell or even to a subcellular organelle such as a lysosome where the pathologic process is occurring. A major advantage possessed by the dermatologist is that the diseased organ is directly accessible for diagnostic and therapeutic purposes. This permits the therapist to apply agents to the diseased organ and to monitor directly, both visually and by palpation, the effectiveness of the administered treatment.

This targeting advantage with topical therapy is for the most part lost with the systemic therapy of dermatologic disease. An exception to this is illustrated by the cytotoxic drug mycophenolic acid, which was previously used in treating severe psoriasis (18). After oral administration mycophenolic acid passes through the liver and undergoes rapid glucuronidation by the microsomal enzyme glucuronyl transferase. In this form mycophenolic acid is pharmacologically inactive. The glucuronidated drug then moves through the circulation to the skin, a tissue that is rich in B-glucuronidase, an enzyme that cleaves the glucuronide moiety from the mycophenolic acid. This restores pharmacologic activity to the parent compound and provides a good example of targeting on the basis of tissue-specific enzyme activity. Similarly, the absence of an enzyme may result in targeting of the toxic effects of a drug. The antitumor agent bleomycin is normally inactivated by an enzyme, bleomycin hydrolase, that is present in all body tissues except the skin and lung. It is thought that bleomycin is particularly toxic to these tissues because of the lack of this enzyme (19). Cutaneous toxicity includes a peculiar sclerodermalike process that may result in ischemic ulceration (20).

PRACTICAL CONSIDERATIONS

The appropriate management of a patient with dermatologic disease requires two major decisions at the outset: (1) selection of the proper drug or drugs, and (2) selection of the appropriate route of administration (topical vs. systemic). These decisions will be influenced by a number of factors including the following: (a) understanding the pathophysiology of the disease being treated, (b) knowledge of the pharmacologic effects and the toxicity of the drugs to be administered, (c) the seriousness of the disease and the extent of cutaneous involvement, and (d) age and general health of, as well as convenience to, the patient. It should be instructive to focus on each of these factors and to see how they may influence therapeutic decisions in a selected number of disorders treated by most dermatologists.

Understanding the Pathophysiology of the Disease Being Treated In recent years much new information about the pathogenesis of pemphigus vulgaris has emerged (21–23). It had long been known that the characteristic histologic

change in the skin of patients with pemphigus was an epidermal blister caused by acantholysis, a pathologic change that damages the intercellular substance, resulting in loss of cellular adhesion (24). Individual keratinocytes (acantholytic cells) can be seen under the microscope in these involved skin areas. The loss of adhesion of the keratinocytes is thought to be essential for blister formation. Thus treatment modalities that can inhibit this pathologic process should be effective in pemphigus. Since pemphigus, like many dermatologic disorders, is actually a form of cutaneous inflammation, it is reasonable to expect that large doses of corticosteroids will have an antiinflammatory effect and hence be therapeutically efficacious in this disease.

Knowledge concerning the mechanism of skin damage in pemphigus vulgaris has also come from studies employing immunofluorescent techniques. Using fluorescein-labeled antibodies, these studies have shown that patients with pemphigus vulgaris have immunoglobulins bound specifically to the intercellular substance of the epidermis as well as circulating antibodies that bind to the intercellular substance of stratified squamous epithelium (25). Furthermore, components of both the classic and alternate complement cascade are found in the epidermis of patients with pemphigus (26). This finding suggests that binding of intercellular antibody to antigen could lead to activation of the complement cascade, culminating in a lytic process such as acantholysis. Others have suggested that the pemphigus antibody can detach epidermal cells without the activation of complement, but rather by activation of a skin proteinase (27).

It is important to emphasize that these findings are frequently helpful in the clinical management of patients with pemphigus. The titers of circulating antibody to intercellular substance may be a useful guide to assessing disease activity and the response to therapy in some patients (28).

The demonstration that pemphigus is associated with circulating antibody to intercellular substance led to the concept that this was a type of autoimmune disorder. This in turn led to the use of cytotoxic (immunosuppressant) drugs in the treatment of pemphigus. Methotrexate, azathioprine, and cyclophosphamide have each been recommended as effective in treating this disease (29–31). In addition, the cytotoxic drugs have been used in combination with corticosteroids in patients with pemphigus. There is good clinical evidence to support the concept that cytotoxic drugs may well have a steroid-sparing effect in selected patients. This has been shown in two ways: (1) cytotoxic drugs frequently reduce the maintenance dose of corticosteroid required for disease control, and (2) the daily administration of cytotoxic drugs combined with alternate-day administration of modest doses of corticosteroid may be sufficient to control milder forms of the disease (32).

The current use of corticosteroids and cytotoxic drugs in pemphigus is therefore the culmination of developing knowledge about the mechanism and