PERCUTANEOUS ABSORPTION: CONTROLLED DRUG DELIVERY FOR TOPICAL OR SYSTEMIC THERAPY

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The current conventional methods of introducing drugs into the systemic circulation include intravenous, intramuscular, or oral administration. Drug administration via the oral route can result in variable systemic levels of the active form of the drug, both within and among individuals, as a result of the variable absorption or release of drug from the formulation, variation in pH of the gastrointestinal tract, differences in food intake, or initial entry of drug into the portal circulation. Injections or infusions of drugs avoid some disadvantages of the oral route; however, neither of these forms of drug administration fills the need for prolonged unattended duration of drug availability. Continuous infusion therapy is acknowledged as a superior mode of drug administration for certain conditions, and thus we have initially investigated the possibility of fulfilling such a need by using skin as a port of entry for continuous input of drugs into the systemic circulation.

The skin is one of the most impenetrable tissues of the body, for it functions as a barrier against invasion by microorganisms, viruses, and many toxic chemicals, and simultaneously limits the escape from the body of physiologically essential components such as water. As a result of its dual barrier role, skin has seldom been regarded as a suitable route for administration of drugs to the systemic circulation. Examination of the causes of skin impermeability, and of the factors which may modify it, has opened up approaches to using this organ as a route for administering medication to the systemic circulation and also has surfaced the possibility of optimizing therapy (with regard to drug concentration and time of exposure) for the treatment of topical disorders.

Using human skin in vitro mounted as a membrane in a permeation chamber, we have confirmed that for the drugs we have so far examined, the main factors that modify transdermal permeation include:

1. The stratum corneum, which is frequently as much as 5 orders of magnitude less permeable to most substances than the dermis and thus offers the principal barrier to skin permeation [1]. The skin appendages (sweat glands, hair follicles, sebaceous glands) in the human skin probably contribute little to sustained drug permeation through intact skin.

2. The physiochemical properties of the drug, such as its molecular size, pH, oil/water partition coefficient, and polarity [2].

3. The vehicle in which the drug is dissolved, which may modify the permeation of the drug through skin by affecting its release from the vehicle and subsequent partition into the stratum corneum.

4. The physical form of the drug (ionized or non-ionized); the non-ionized form of a drug permeates more freely than the ionized.

5. Hydration of the skin, which facilitates absorption and permeation of water-soluble drugs.

6. The lipid content of the skin.

7. Use of sorption-promoting agents.

8. Regional variations in skin properties, which result in modification of percutaneous absorption of drugs.

The results of in vitro skin permeation experiments designed to evaluate the importance of the above-mentioned factors, have indicated that it is feasible to administer drugs topically in a form such that the skin content of the drug is maximized (for topical therapy) or the skin content of the drug is minimized and maximum transdermal permeation of drug is attained (for systemic therapy).

We have initiated development of transdermal therapeutic systems which, when applied to the surface of intact skin, will deliver drugs continuously and unattended to the systemic circulation at the appropriate predetermined rate. Knowledge of the factors which govern transdermal permeation of a drug, including the vehicle of choice, etc., are built into the design of the system so that the drug is released from the system in a profile which will optimize the required therapeutic effect and elicit minimal unwanted side effects.

The percutaneous absorption of certain of the drugs we have examined in vitro, using skin from human cadavers, has been followed in vivo. For the drugs ephedrine and scopolamine we find good agreement between percutaneous absorption in vitro and in vivo, indicating that for these two compounds there is little metabolism of the drug by the skin, and that cutaneous blood flow does not limit the appearance of drug in the systemic circulation.

For scopolamine we have developed a transdermal therapeutic system which is a multilaminate structure of small size (up to 2.5 cm² in area and 0.2 mm thick) that can be worn comfortably at a fixed...
location in the postauricular area, a region which provides for adequate drug permeability.

The system has been designed to provide controlled administration of scopolamine to the surface of intact skin, such that the system controls the availability of drug to the systemic circulation, for prevention or treatment of motion-induced nausea. The clinical data indicate that by controlling the systemic levels of this drug one can obtain a therapeutic effect and reduce the incidence and severity of unwanted parasympatholytic effects associated with the conventional forms of administering this drug parenterally or orally.

Scopolamine also produces a local effect at the site of application, namely, inhibition of sweat gland function. By changing the physical form of the drug presented to the skin surface and its pattern of administration, it is possible to maximize this local effect of scopolamine and minimize the throughput of drug to the systemic circulation.

In conclusion, it now appears feasible to use skin as a route of entry for drugs into the systemic circulation, such that we can provide controlled circulating levels of the drug for up to one week duration following a single application of a therapeutic system. The concept of sustained delivery of drugs at a predetermined rate for treatment of topical disorders requires controlled clinical pharmacologic studies with each drug to define the optimum pattern of drug administration required to elicit the desired therapeutic effect.

REFERENCES