CSM UPDATE

Topical agents for the skin: efficacy and safety

Many non-dermatologists who deal with evaluation of drugs believe that systemic toxicity from agents applied to the skin surface requires little or no consideration. This is true for many drugs, including coal tar and dithranol. But serious systemic and local side effects are well recognised with others and may lead to a fatal or near fatal outcome. Two recent examples illustrate this point. A 30 year old man had suffered from autosomal recessive non-bullous ichthyosiform erythroderma since birth. His skin was treated in hospital with 4-12% salicylic acid ointment as a keratolytic applied extensively to the limbs and trunk. The risk of percutaneous absorption was appreciated, and serum salicylate concentrations were measured daily. These were within acceptable limits over a 32 day period. On day 42 the patient developed tinnitus, vomiting, and drowsiness. The plasma salicylate value on the same day was 62.8 mg/100 ml. He recovered after intravenous alkaline diuresis. The second case was a woman of 48 years with extensive chronic plaque psoriasis who had been applying a potent topical corticosteroid, clobetasol propionate 0.05% ointment, twice daily for several years. She developed severe Cushingoid changes and died of pulmonary embolism after deep vein thrombosis.

In both cases toxicity arose because of the greatly reduced barrier function of the stratum corneum in desquamative skin disorders. Small children and infants are especially at risk because of the high ratio of surface area to body mass. When occlusive methods of application are used absorption is also greatly enhanced. Increases of relative humidity from 50 to 100% and of temperature from 10°C to 37°C increase penetration by tenfold and fivefold respectively. The nature of the vehicle greatly affects absorption through the skin. Owing to their greater occlusive effect, ointments generally lead to greater penetration than do creams. The committee also has to be on the lookout for the incorporation of an exotic penetration enhancing agent into the base used for an ostensibly innocuous drug. The formulation of a weak corticosteroid into a base containing such an agent—dimethyl sulphoxide (DMSO) is an extreme example—might lead to the therapeutic equivalent of a sheep with a wolf’s teeth.

In arriving at a decision on a new topical preparation the committee insists that it fulfils the criteria for efficacy and safety no less rigorously than a systemically administered agent. The pharmaceutical industry is now aware of the need for adequately controlled and designed clinical trials for topical dermatological agents. To raise the standard of data submitted to the committee improved methods for measurement of physical properties of the skin are needed, leading to more accurate assessment of both efficacy and safety.

Risk factors in topical therapy:

Infancy and childhood
Application under occlusion
Epidermal integrity reduced by psoriasis, eczema, and other dermatoses
Exotic penetration enhancing factors present in the base
Dose, potency, and duration