CHAPTER 24

Clinical Considerations of Transdermal Drugs

SOLOMON SOBEL

1. INTRODUCTION

Mountain climbers have been known to say that they are challenged by a peak basically "because it is there." Analogously, researchers and manufacturers may try to apply technologies just because they are available.

In considering the usefulness of the transdermal method for drug administration, one must ask what advantages and disadvantages does the giving of a drug through the skin have over other routes?

Certain classes of drugs are more amenable to the practical use of transdermal approaches in therapy. Particularly, metabolic and endocrine drugs are frequently excellent candidates for novel routes of administration. These drugs are often used as replacement therapies. Thyroid products in hypothyroidism, insulin in diabetes mellitus, estrogens in the menopause, testosterone in eunuchoid states, and growth hormone in pituitary dwarfism are good examples of these replacement treatments. There are a few reasons why the nature of these deficiency disorders provides an impetus for the development of new ways of giving drugs. First, deficiency problems may often require lifelong treatment. Second, these conditions may start in childhood, and it may be hard for youngsters to take medicine by conventional methods such as injection. Moreover, the drugs are
frequently peptides requiring routes that avoid the gastrointestinal tract. One seeks methods that will be effective and safe, while achieving good compliance and minimal discomfort to the patient.

2. CURRENT PROGRESS

Recent approaches include polymeric implants that release peptides slowly, nasal administration of drugs, and transdermal administration.

Two recent drug products considered by the Food and Drug Administration (FDA) are illustrative of therapeutic issues which make transdermal administration a valuable route of administration. One is a transdermal therapeutic system for administering estradiol. The other, an investigational product, is a transdermal therapeutic system for testosterone.

2.1. Estrogen Replacement Therapy

The indications for estrogen replacement therapy include the relief of hot flushes and vaginal dryness and the maintenance of bone mass. Less clearly, estrogens may help prevent heart and blood vessel disease.

The cardiovascular protective effect is not an approved indication but bears some discussion in view of the differing effects that the various ways of giving estrogen have on some of the known risk factors of cardiovascular disease.

Estrogens (e.g., estradiol, estrone, and estriol) are steroids. There are also chemical agents such as diethylstilbestrol which are nonsteroidal and have potent estrogenic effects. This discussion will be limited to steroidal estrogenic substances. The bioavailability by mouth of unmodified steroidal estrogens is very limited because of poor gastrointestinal absorption. However, estrogens when conjugated are readily absorbed. The most widely used conjugated estrogen products contain mostly estrone sulfate and equilin sulfate.

Another approach to improving gastrointestinal absorption has been to alter the physical state of an estrogen suspension. "Micronization" used in a marketed estradiol-containing product increases its absorption. Presumably, the particle size stimulates absorption by intestinal lymphatics. This method, however, results in the conversion by intestinal wall enzymes of the potent estradiol to the significantly less potent estrone.

Estrogens are also given vaginally. This method affords good relief of dryness, but the absorption is very variable so this is not a good method for systemic use.

There are also intramuscular preparations which require monthly injections. Implantable forms such as the estrogen pellet have not been approved; there are questions about their pharmacokinetic profiles and dosage.

Finally, a transdermal product has been recently approved.