TRANSDERMAL DRUG DELIVERY

Controlled transdermal drug delivery was introduced to the world in 1981 when D-TRANS® transdermal technology was combined with scopolamine for the treatment of motion-sickness. Since that time, other medications have been incorporated into transdermal delivery systems including clonidine, fentanyl, estradiol, nicotine, testosterone, nitroglycerin and oral contraceptives. The advantages of treatment with such products include the avoidance of hepatic first pass metabolism and GI tract biotransformation. Consequently, drugs delivered through the skin require smaller, less frequent doses in order to achieve a therapeutic effect, which may improve patient compliance.

One disadvantage of transdermal drug administration is that effects are delayed due to the amount of time needed for the compound to diffuse through the stratum corneum. Other drawbacks include the potential for local irritation, systemic toxicity, and potential overdosage if transdermal delivery systems are applied over multiple skin sites. The increasing number and popularity of medications being prescribed as transdermal patches compels health professionals to recognize their misuse as sources of toxicity and overdose. Thus, it is important to understand the delivery mechanisms and factors that affect penetration into the general circulation.

PHARMOKINETICS

To understand how drugs permeate the skin, the structure of the skin needs to be understood. The outermost layer, the epidermis, is composed of five cell types: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum germinatum (see Figure 1).

Figure 1: Epithelial layers of the epidermis

It is the keratinized layer of the stratum corneum that provides the rate limiting step to drug permeation. In the 1984 article on cutaneous toxicity, Wester showed that the head, neck, axilla and scrotum are the areas of greatest absorption. Transcutaneous flow across the stratum corneum occurs via passive diffusion down a concentration gradient. Cleansing of the skin between applications actually enhances the drug's systemic delivery by increasing the skin's hydration; moisture facilitates the diffusion of any portion of the drug that is already partitioned within the epidermis. Increased cutaneous blood flow also augments absorption by maintaining the concentration gradient for diffusion and may occur in the setting of fever, exercise or certain autonomic disorders.

CLINICAL PHARMACOLOGY

The transcutaneous delivery system currently in use is the D-TRANS® transdermal technology, developed by the Alza Corporation. The patch comprises a backing layer, a drug reservoir, a rate controlling film and an adhesive backing. It is able to deliver up to 20 mg per day through intact skin for up to one week. This technology is used to deliver the three most commonly abused patch formulations: Duragesic® (fentanyl), Catapress® TTS (Clonidine), and NicoDerm® CQ (nicotine).
Backings are typically made of polyurethane sheets and the rate controlling films are composed of ethylene vinyl acetate. A higher percentage of vinyl acetate increases the lipophilicity of the membrane. A polyester film coated on one side with fluropolymer can serve as a release liner. Forthcoming advances in transcutaneous drug delivery technologies include patches that utilize low-level electrical energy to deliver small, pulsatile, precise amounts of a drug through intact skin. This method allows for the possibility of patient controlled delivery and is in phase III development as a fenatryn delivery system. Another mechanism being pursued is a small screen with microprojections that creates superficial and painless pathways through the stratum corneum. One method used to enhance transdermal drug delivery is iontophoresis: the application of an electric current to the skin in order to facilitate the movement of large polar molecules (e.g. insulin) through the epidermis. The process of iontophoresis employs ultrasonic irradiation to increase transcutaneous absorption. Chemical enhancers such as propylene glycol also improve penetration.

CLINICAL TOXICOLOGY
The 2002 AAPCC annual report documented 193,822 dermal exposures, including twenty-two deaths. Nine of the fatalities involved exposure to a fentanyl patch. Four deaths resulted from dermal exposure, another four were from ingestion and one followed a parenteral exposure. As of July 31st, 2003 one cinnodine patch exposure, twenty-eight fentanyl patch exposures and two nicotine patch exposures have been reported to the Regional Center for Poison Control and Prevention serving Massachusetts and Rhode Island, (as compared to four, ten and four respectively by the same time in 2002). The Duragesic® (fentanyl) system provides continuous seventy-two hour drug delivery. Once the system is cut or damaged, delivery can no longer be controlled. Sequelae are those typical of opiate agonists; pinpoint pupils and depression of the respiratory and central nervous systems may be seen. Uncontrolled delivery may yield fatal outcomes, as evidenced by case reports where patches were scraped, heated and inhaled. Overdose has resulted from simultaneous exposure to multiple patches, biting or aspiration of a patch, placement of patches in buccal cavities, and in the case of a funeral home employee who obtained a patch from a deceased patient.

According to a study performed by Marquardt et al., a three day old 10 mg patch was found to have 4.46-8.44 mg of fentanyl remaining. Using a Vd of 4 L/Kg and a potential lethal concentration of 3.7 mcg/kg, a lethal dose of 1,036 mcg can be calculated for a person who weighs 70 Kg. This amount is less than the observed fentanyl residue in a three day old patch.

MANAGEMENT
Management of transdermal exposures does not differ from the standard management of a toxic reaction to the substance contained within the delivery system. For example, patients who have ingested a fentanyl patch typically respond dramatically to standard naloxone therapy. One caveat is that repeat dosing might be required secondary to prolonged absorption. Danger arises when these systems are compromised (i.e. the patches are broken, burned, ingested) and delivery is uncontrolled. Consequently, a thorough body examination, including buccal cavities and all body cavities, should be performed if any suspicion of ingestion exists.

Cleansing the skin between drug applications has been shown to enhance drug delivery, because the increased hydration facilitates diffusion of any remaining drug already partitioned within the epidermis. Elevated temperature, exercise and autonomic disorders are also known to augment transcutaneous drug delivery by increasing cutaneous blood flow and may precipitate an overdose. Additionally, placement of a patch over broken skin should also be avoided. This information should be communicated to patients and their families at the time of prescription.
REFERENCES

13. 2002 Annual Rep of the Amer Assoc of Poison Control Centers TESS.
14. Regional Center for Poison Control and Prevention serving Massachusetts and Rhode Island.