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DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEMS

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INTRODUCTION

The year 1981 brought to the brink of maturity a technology for the rate-controlled administration of drugs through intact skin. The first such system to be marketed was ALZA's Transderm®-Scōp scopolamine product for the prevention of motion sickness. Subsequently Transderm®-Nitro, a dosage form that provides rate-controlled administration of nitroglycerin, received FDA approval for the prevention of angina. Other dosage forms for administering nitroglycerin systemically through intact skin (Nitro Disc®, Nitro-Dur®) also received FDA approval.

Transderm®-Scōp scopolamine is a useful and effective product but not one with a major market potential. Nonetheless, this product broke important ground for programmed transdermal drug therapy. It demonstrated to

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skeptical physicians that delivery of drugs through intact skin could provide reliable, highly effective therapy with fewer side effects than the same drug in oral or injectable form. Moreover, its three-day continuous action after one application was unique--an order of magnitude greater than the duration of action of scopolamine in its usual dosage forms (i.e., 72 hr vs 6 hr for injections and tablets). Finally, the transdermal product's acceptance by patients was enthusiastic, diminishing doubts on that important issue.

Transderm®-Nitro system for preventing angina is a product with a much larger market potential. The transdermal scopolamine system had eased its path through the regulatory process. After a single application, this rate-controlled form of nitroglycerin provides at least 24 hours of continuous protection from angina--with a drug whose half-life in the body is only a few minutes. Moreover, our data indicate that duration of Transderm®-Nitro use could likely be extended to two days following one application.

With these and other transdermal systems on the market, we appear poised for rapid expansion of this new technology. How reasonable are these expectations? Specifically, for how wide a variety of drugs will rate-controlled transdermal delivery be appropriate? Some insight into the answers to these questions may be gained by reviewing some of the work of a dedicated group at ALZA, which has been responsible over the past 9 years for the research, development, clinical testing, and regulatory submissions for the first rate-controlled transdermal drug delivery form. (Subsequently

the group at ALZA worked closely with the excellent CIBA-GEIGY manufacturing and marketing staff to launch the scopolamine and nitroglycerin transdermal products in the U.S.)

Regimen Dependence of Drug Actions

In assessing the future of transdermal delivery, we should start by looking at what the technology can provide in the way of new regimens--and what these regimens can do to improve therapeutic results. We now have systems capable of delivery, after one application, of 0.5 mg scopolamine over 3 days, and of 5 mg or 10 mg of nitroglycerin over 24 hours. In addition, systems are under development to release other drugs at controlled therapeutic rates for up to 7 days. Occluding the skin continuously for longer than that will likely cause unacceptable problems; for one thing, the strateum corneum layer of skin sloughs and regenerates at a rate such that 7 days of adhesion appears to be the duration limit for one application of a transdermal system.

Even with that current limitation, rate-controlled regimens providing multiday therapy from one application of the dosage form confer an unprecedented drug delivery capability. What does their availability mean to developers of pharmaceutical products and to patients using them? As a partial answer to that question, one must review the concept of the regimen-dependent actions of drugs, as opposed to their dose-dependent actions. It is known that the amount of drug administered influences both the number and magnitude of drug actions.

It is less well-known, perhaps, that the timing or rate of drug input can also influence those factors; yet a number of investigators have reported striking examples of regimen-dependent actions. I shall discuss two recent reports of that kind.

Nau and his co-workers (1) recently reported that the embryotoxicity of valproic acid (VPA) in mice is markedly dependent on its regimen of administration. The half-life of this widely used anti-epileptic drug is only 0.8 hr in the mouse, compared to 8 to 16 hr in humans. Nau et al. administered it in the same total dose to mice on days 7-15 of gestation in two different regimens: (1) by injection once daily and (2) by continuous infusion from implantable pumps. With the continuous infusion, drug levels were maintained within the concentrations used for therapy. The once-daily injections caused valproic acid concentrations in plasma to peak and decline quickly (Figure 1); for long periods between injections, the drug was undetectable. In humans the peaks are only one-tenth as high and the drug is not totally eliminated from the plasma between doses. Thus, extrapolating the results of mouse toxicity data to humans can give rise to two types of errors: the higher peak levels in mice may lead to overestimating the human toxicity of VPA; or conversely, the long periods of no detectable drug in mice may lead to underestimating its human toxicity. With the continuous infusion of VPA (Fig. 2) Nau found that a higher total dose was required to produce embryotoxicity than with a single daily administration, as shown by resorptions and exencephaly (Figs. 3 & 4).

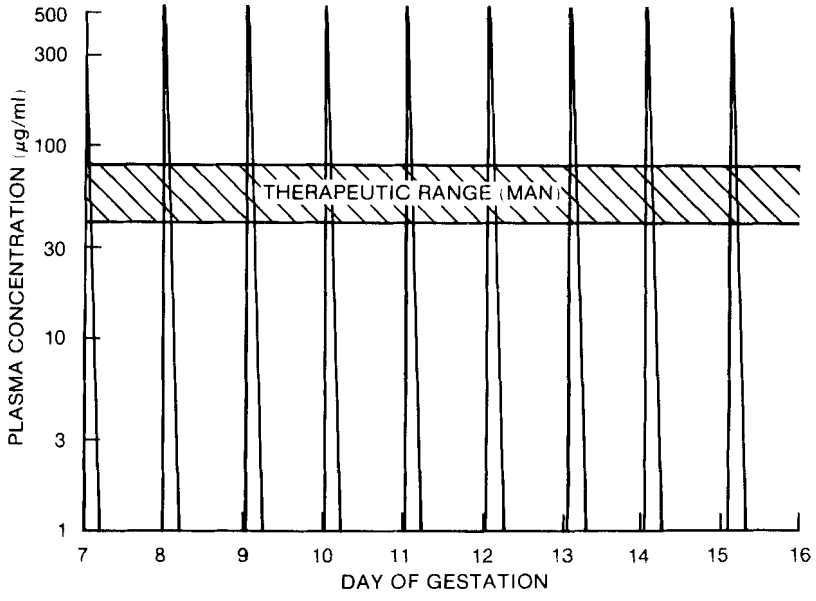

Figure 1. Plasma concentrations of valproic acid in mice vs. time following subcutaneous administration of the drug (400 mg/kg) once a day during days 7-15 of gestation. The curves were drawn through experimentally determined values. Shaded area indicates human plasma concentrations observed during pregnancy, which are lower than those observed in nonpregnant adult epileptics.

Sikic et al. (2) had previously observed a similar effect associated with continuous infusion of the anticancer drug bleomycin to mice with lung carcinoma. When identical doses were administered in three different 7-day regimens (injections twice daily, injections twice weekly, and continuous subcutaneous infusions), different results were obtained. Results associated with drug infusion differed in two ways from results obtained with the other regimens: the drug's pulmonary toxicity (Fig. 5) was less (e.g., fewer

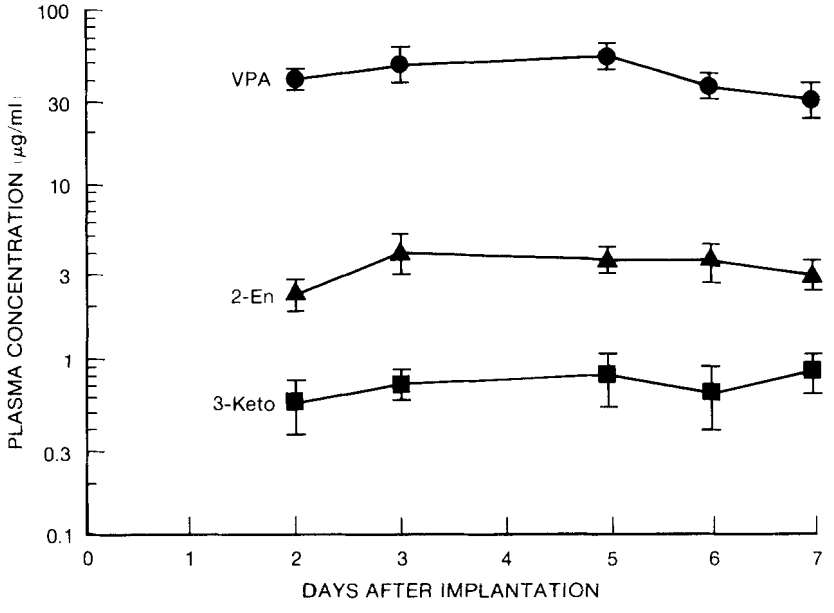

Figure 2. Concentrations of valproic acid (VPA) and its two principal metabolites--2-en(2-propyl-2-pentenoic acid) and 3-keto(2-propyl-3-oxo-pentanoic acid)--in mouse plasma following constant rate application of the drug via ALZET® osmotic pumps in the mouse. On day 7 of gestation, two mini-osmotic pumps containing 400 mg sodium valproate/ml water and delivering 1 µl/hr drug solution were implanted subcutaneously in each mouse. Due to the increasing body weight of the mice the dose decreased from 600 mg/kg/day on day 7 to 500 mg/kg/day on day 15. The means ±S.D. (n = 4-6 animals) are given at each point.

deaths, less pulmonary fibrosis); and tumor size was smaller (Fig. 6).

For these two drugs, Figs. 3-5 show that, with a constant rate of drug delivery, the dose-response curve for adverse effects (i.e., embryotoxicity and pulmonary fibrosis)

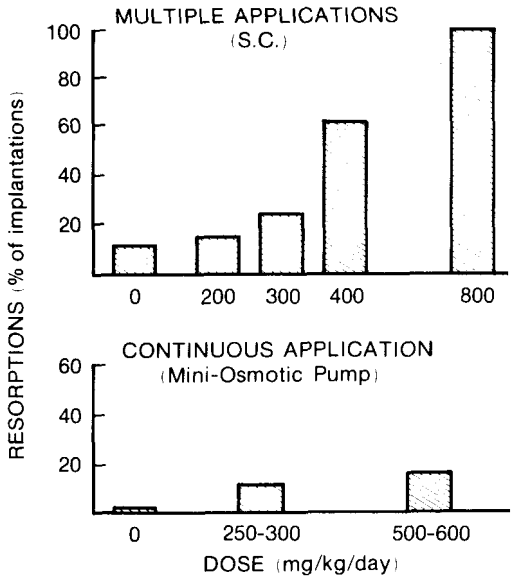

Figure 3. Resorption rates (in % implantations) observed in mice following valproic acid (VPA) administration on gestational days 7-15, either subcutaneously once each day or continuously at a constant rate via an mini-osmotic pump implanted on day 7.

shifts to the right. On the other hand, Fig. 6 shows that constant-rate delivery causes the dose-response curve for bleomycin's therapeutic effect to shift to the left. That shift clearly indicates that changing the regimen for administration of bleomycin can selectively improve the risk/benefit ratio of the drug. These experimental results, moreover, confirm the clinical impression obtained during treatment of testicular and cervical carcinoma.

The regimen-dependent pharmacodynamics of these two drugs opens up the possibility of conducting clinical trials--using rate-controlled drug dosage forms--to provide

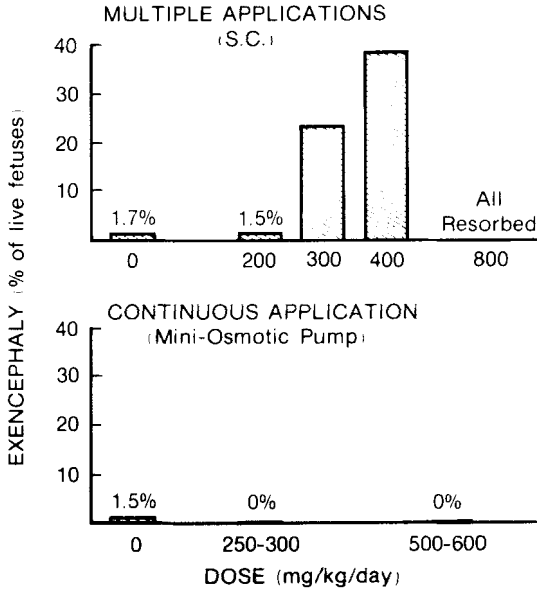

Figure 4. Incidence of exencephaly (in % of live fetuses) observed in mice following administration of VPA to the dams between gestational days 7-15, either subcutaneously once each day or continuously at a constant rate of application via an osmotic pump on day 7.

a rationale for developing a dedicated, constant-rate dosage form to elicit bleomycin's full therapeutic effect while minimizing side effects.

Choice of Drugs for Transdermal Therapy

Such toxicologic and clinical studies should precede the development of any type of rate-controlled drug delivery system--to make sure it is a rational candidate for such delivery. In the case of scopolamine, when we developed the rate-controlled transdermal system, we did not have available

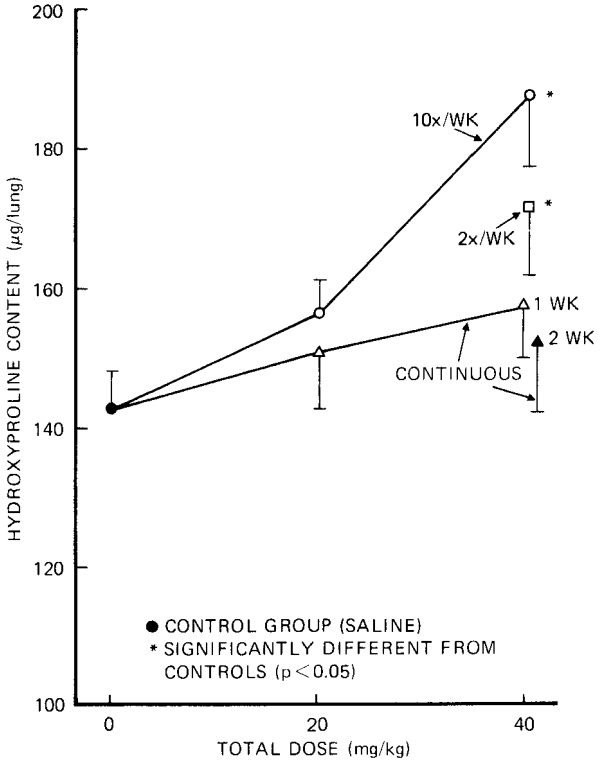

Figure 5. Effects of various schedules and doses of bleomycin on pulmonary toxicity in nontumored animals, as measured by lung hydroxyproline content 10 wks after treatment. All regimens lasted for one week except the continuous infusion (▲), which lasted two weeks. It was given via an implanted pump and the other regimens via subcutaneous injections. Controls received saline. Mean ±S.E.; n=10.

the small ALZET® pumps (3,4) that Nau and Sikic used in their animal studies. Only in the later stages of Transderm®-Scōp scopolamine development did we have specialized, rate-controlled, experimental equipment available for use in clinical studies: wearable, ALZA-developed, rate-controlled infusors (5) and the OSMET™ modules--rate-controlled experimental oral dosage

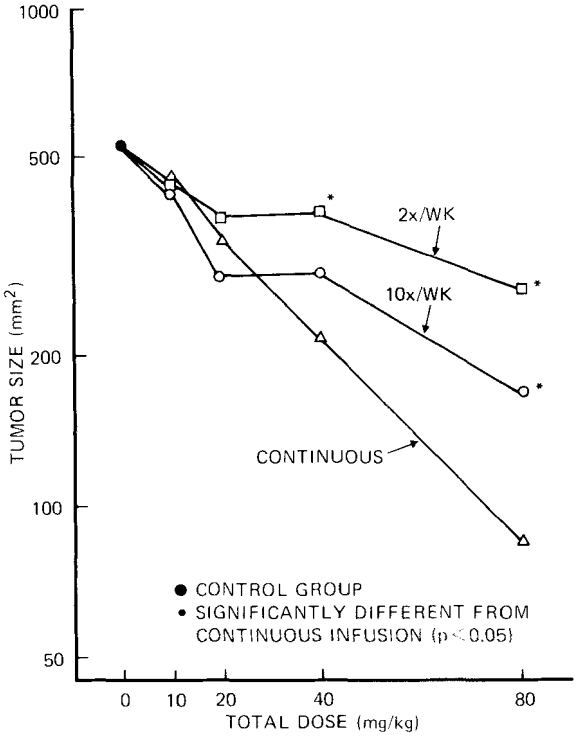

Figure 6. Dose-response curve of bleomycin antitumor effect against Lewis lung carcinoma with 3 schedules of administration. These measurements were made on day 15 after implantation, but are representative of differences which existed throughout the course of tumor growth. (See Figure 5 for details.)

forms (4). (In modified form, the infusors are now available from Travenol for therapeutic use.)

Thus, we were not able to do as formalized an investigation of the effects of rate control on the pharmacodynamics of scopolamine as is now possible. Instead we monitored blood concentrations of the drug (as reflected by its urinary excretion rates)--and their correlation with various pharma-

cologic effects--at intervals following a 200 µg intramuscular injection of scopolamine hydrobromide (6). These studies demonstrated two things: the potential for improvement of the drug's selectivity of action (i.e., decreasing its unwanted pharmacologic actions) by controlling its blood levels (Fig. 7); and the minimum blood concentrations that would provide a full anti-emetic effect. Data from these studies were later useful in designing the required profile of drug release for the system.

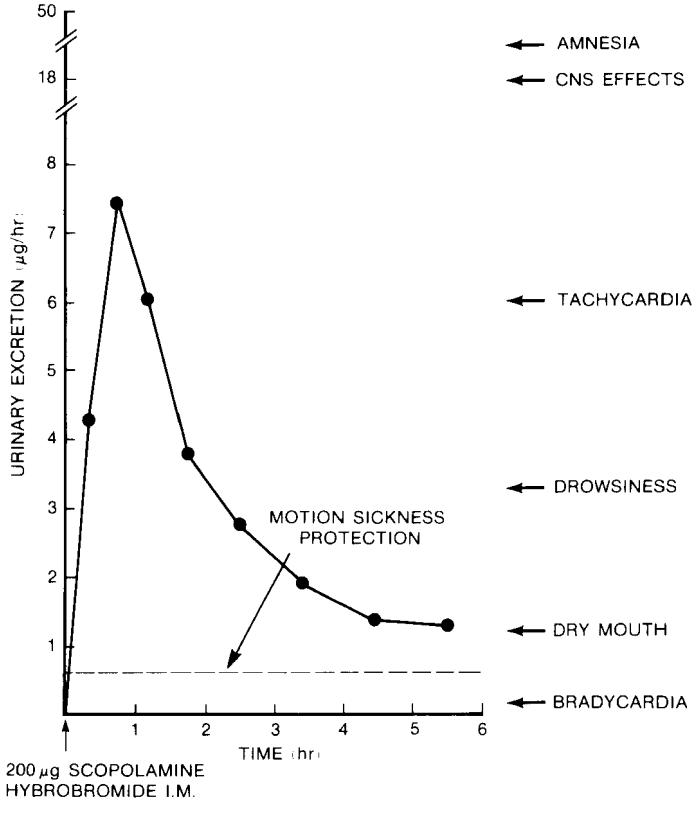

Figure 7. Relationship between rate of urinary excretion of scopolamine and its pharmacological effects: 10% of a parenteral dose of scopolamine is excreted in the urine unchanged.

The reasons for the decision to utilize the transdermal route for scopolamine's rate-controlled delivery were several--and they apply to other drugs as well. Need for prolonged treatment with an agent having a short half-life was one reason; scopolamine has a half-life of less than an hour, but its continuous transdermal administration can provide multiday dosage intervals. That capability offers promise for improving therapy in numerous situations requiring prolonged, round-the-clock treatment. For example, it should be useful for administering certain drugs that cause difficulties in patient compliance when they are given in conventional dosage forms, either because of inconvenient regimens or unacceptable side effects (7). (With scopolamine these effects can include dry mouth, drowsiness, cycloplegia, and hallucinations.) One of the most important contributions of the transdermal route is bypass of the gastrointestinal tract and delivery of drug directly into the bloodstream (7). Thus, it provides an alternate route when nausea (as in motion sickness) or unconsciousness makes oral therapy impossible. The skin also bypasses gastrointestinal tract influences that make absorption unreliable; these include variable acidity, motility, and food content, as well as unpredictable metabolism by the liver on the first pass (7).

In addition, rate-controlled delivery of drug through skin offers unique safety factors. One arises from the ability to terminate therapy quickly (7), if indicated, because of the ready removal of the transdermal dosage form to terminate drug input. Moreover, like other rate-controlled

drug dosage forms, transdermal delivery can substantially reduce the total dose needed for therapy (7). Transderm®-Scop system, for example, delivers only 0.5 mg scopolamine over 3 days vs. about 2.5 mg over 3 days from 6-hourly administration of 200 µg injections or tablets. Thus, side effects from the transdermal scopolamine system form are minimal, though its efficacy exceeds that of oral dimenhydrinate (8).

Just one of the factors discussed above may provide a strong rationale for developing a transdermal dosage form for a particular drug--provided the drug has suitable pharmacological and physico-chemical properties. The latter include stability, molecular weight less than 1000, melting point less than 200°F, solubility in both mineral oil and water greater than 1 mg/ml, and pH of 5 to 9 in a saturated aqueous solution. Some of these properties affect the most essential capability of the drug--namely its permeation of skin in therapeutically potent amounts over an acceptable area. Another requirement for acceptability, of course, is the drug's freedom from localized irritating or allergenic effects.

Thus, a considerable general knowledge of the drug's properties is required before the decision can be made to develop it in transdermal form. Prior to the first steps in product development, detailed data are needed on the rate-controlled pharmacology of the drug (its rate-controlled pharmacokinetics, pharmacodynamics, therapeutic index, and potency--e.g., effective parenteral dose). Also essential are data on its permeation rates through skin *in vitro* at various body sites under various conditions.

Design Considerations for Transderm®-Scop Scopolamine

Few quantitative data are available on permeation rates of specific drugs through skin. It has, however, been established that the principal barrier to permeation resides in the stratum corneum (9). That tissue comprises dead, partially desiccated epidermal cells. Little information, however, is available on factors (e.g., stratum corneum thickness, skin temperature, occlusion) that influence permeation of drugs through--or immobilization of drugs in--skin *in vivo*. To quantify these factors for scopolamine we developed an *in vitro* test method using whole skin, epidermis, or dermis removed from cadavers and mounted as membranes in a diffusion chamber. (These techniques have been described in reference 10.) We developed a mathematical model that is predictive of permeation of a drug through skin, based on certain of the physicochemical properties of the drug mentioned previously.

Our results showed that permeation of scopolamine through skin varied widely--not only between body sites on one individual but also between the same site on different individuals (9). The most permeable area tested was that behind the ear (Fig. 8), where flux of the drug through skin was in the range of 20 $\mu g/cm^2/hr$. In that area a fivefold difference in permeation rates existed between individuals with the most permeable and least permeable skin (9).

These wide inter-individual differences were of concern because of their potential for causing variations in the amount of drug actually absorbed into the bloodstream from a

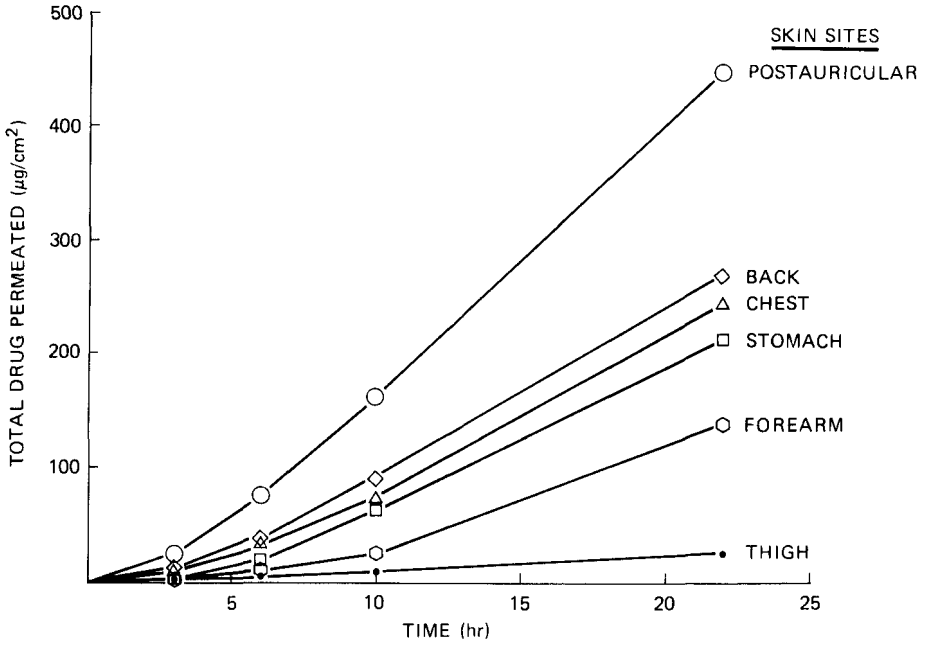

Figure 8. Permeation of scopolamine free base through human skin obtained from various body areas, in vitro, at 30°C.

rate-controlled transdermal dosage form. Such variations could be of critical importance for a drug--in this case scopolamine--that had a narrow therapeutic index. Thus, the aim was to assure that the system and not the skin would control systemic scopolamine administration.

In clinical studies, prototype transdermal systems of various sizes--delivering at proportionally different rates--were utilized to discover what input rate of drug was required to maintain the desired therapeutic effect; it was found that 5 μg/hr would do so. A system of appropriate size (2.5 cm^2) was then selected for placement in the postauricular area and the delivery rate (2.0 $\mu g/cm^2/hr$) was fixed to provide the required rate of drug input. On this

skin site, the 2 μg/cm^2/hr delivery rate of the system is much slower than the rate at which even the least permeable skin can absorb the drug; thus, control of systemic drug input for all subjects resides securely in the system.

To achieve precise control of delivery rate, a laminate (Fig. 9) comprising (from the outside in) the following four functional layers was developed: an impermeable backing; the drug in a reservoir of mineral oil; a rate-controlling microporous membrane; and a contact adhesive also containing scopolamine. (A fifth layer is a peel strip that protects the adhesive in the package; it is removed prior to system application.)

The purpose of adding drug to the adhesive during manufacture is to provide an initial drug release rate higher than the steady-state rate of 5 μg/hr, in order to saturate binding sites for scopolamine in skin. Previous studies had

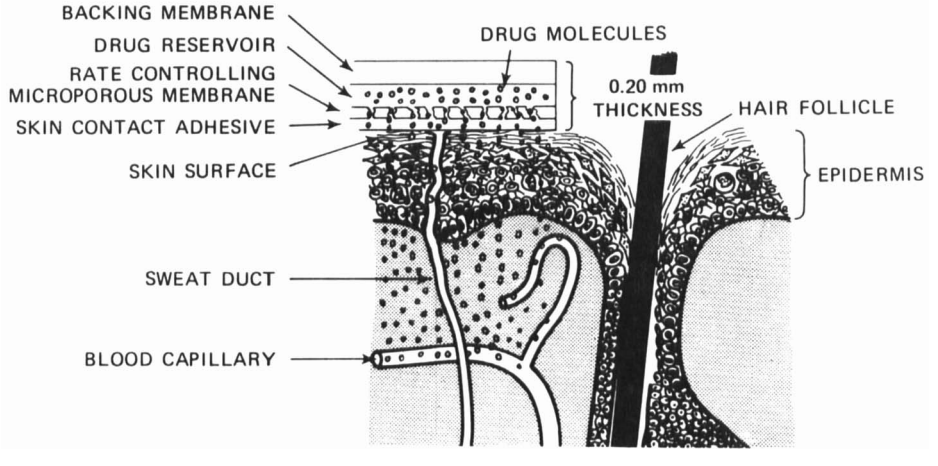

Figure 9. Schematic diagram of controlled flow of drug from Transderm®-Scop through skin into the systemic circulation.

shown that drug input to the circulation does not reach the required steady-state of 5 µg/hr until these sites are saturated. The priming dose released for this purpose is about 140 µg, delivered within a few hours after application of the system. Thereafter the concentrations of scopolamine maintained in blood are equivalent to those produced by a closely controlled I.V. infusion at a rate of 5 µg/hr (6,11).

Considerations in Design of Transderm®-Nitro System

The precision of systemic drug input provided by the scopolamine system is necessary for drugs that have a narrow therapeutic index. Nitroglycerin has a wider therapeutic index than does scopolamine; hence, development of a new transdermal delivery system for the cardiovascular drug followed a different course.

Topical administration of the drug for systemic therapy had previously been used in the form of ointments. Their use is somewhat imprecise, however, due in part to variations in the thickness and area of applications made by patients. In addition, ointments can be messy and inconvenient to apply.

One of the objectives in the development of a new dosage form for nitroglycerin was to make use of the drug more convenient. A second objective was to deliver the drug in appropriate amounts that would be reproducible, within patients, for each skin application. The wide therapeutic index of the drug indicated that provision of a ceiling on rate the of drug input to the circulation would suffice to

meet these objectives. Thus, the first possibility explored was whether nitroglycerin could be delivered satisfactorily from a monolithic system without any rate-controlling membrane (Figs. 10 & 11). Studies showed, however, that such systems released drug at widely different and unpredictable rates over the course of the dosage interval (12). Moreover, variations of as much as sixfold can appear in the concentrations of drug in blood, depending on the permeability of the subject's skin (12). Among patients with highly permeable skin, the input to the circulation from such monolithic dosage forms can lead to overdosing.

To achieve a more precise and more reproducible flow of drug from the dosage form to the circulating blood in patients, a rate-controlling membrane of ethylene vinyl acetate compolymer (EVA) is incorporated in the Transderm®-Nitro

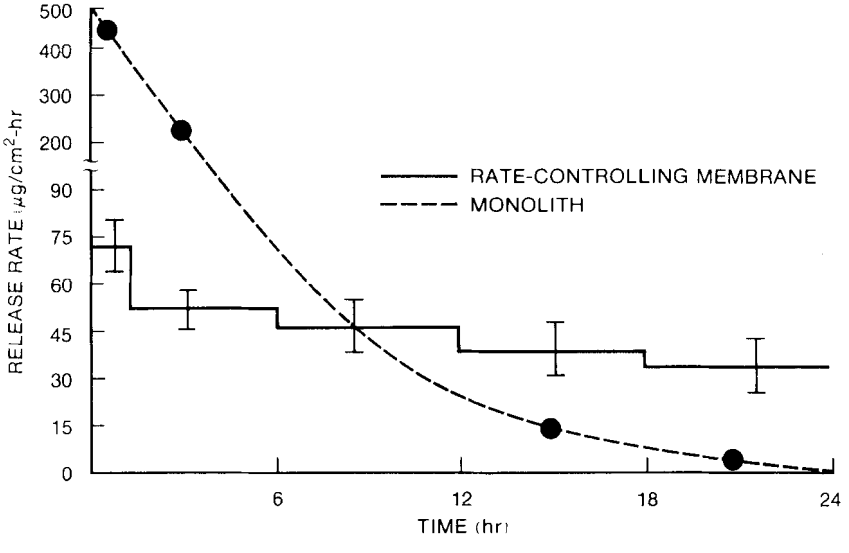

Figure 10. Comparison of nitoglycerin release rate of Transderm®-Nitro system and monolithic system.

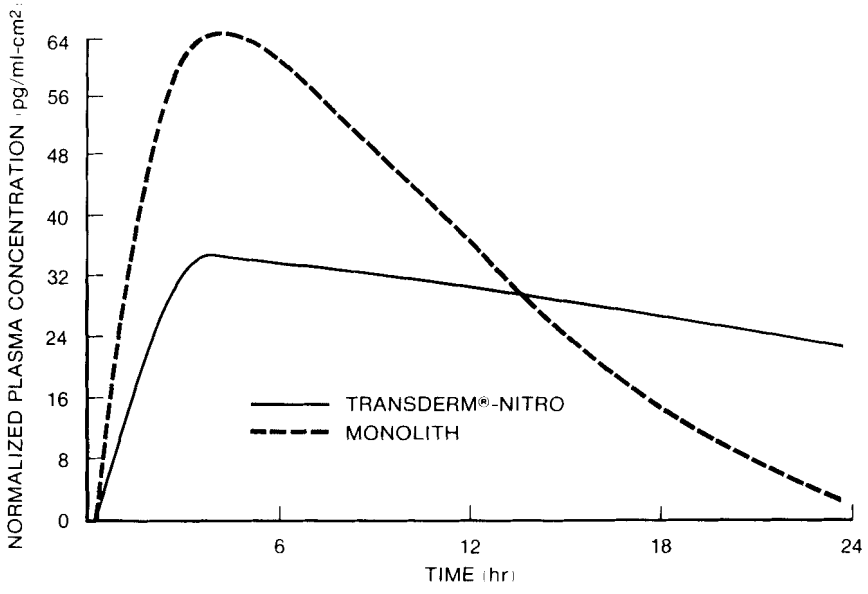

Figure 11. Comparison of nitroglycerin serum levels resulting from placement of Transderm®-Nitro system and monolithic system on highly permeable skin.

system. This system provides a constant nitroglycerin release rate of 40 to 50 μg/cm^2/hr *in vitro* (Fig. 10), which establishes a safe upper limit on the rate of systemic absorption of nitroglycerin. When the system is placed on skin of average permeability, steady absorption of drug occurs at a rate of approximately 25 μg/cm^2/hr *in vivo*, which is somewhat less than the *in vitro* release rate. One can calculate that for patients whose skin is five times as permeable as normal (a not unanticipated condition), the rate of nitroglycerin absorption from Transderm®-Nitro would not exceed 36 μg/cm^2/hr. Conversely, peak serum levels would be much higher with the wearing of a monolithic dosage form on skin of higher permeability (Fig. 11) than with the rate-controlled Transderm®-Nitro.

Over 24 hr, plasma concentrations of drug during wearing of Transderm®-Nitro systems of 10 cm^2 area (which deliver 5 mg nitroglycerin over 24 hr) ranged from 110 pg/ml to 160 pg/ml--compared with a peak value of 2,000 to 3,000 pg/ml associated with use of sublingual tablets, which decayed to zero within minutes (12). Figure 12 shows that 24-hour nitroglycerin levels maintained by one application of this system were equivalent to those resulting from three precisely measured daily applications, at 8 hr intervals, of 0.5 inches of nitroglycerin ointment applied over 10 cm^2 of skin (13). For a drug with such a wide therapeutic index as that of nitroglycerin, this degree of control is fully adequate to provide a safety factor against overdosage.

The Transderm®-Nitro system is available in 10 cm^2 or 20 cm^2 sizes, delivering, respectively, 5 mg or 10 mg of

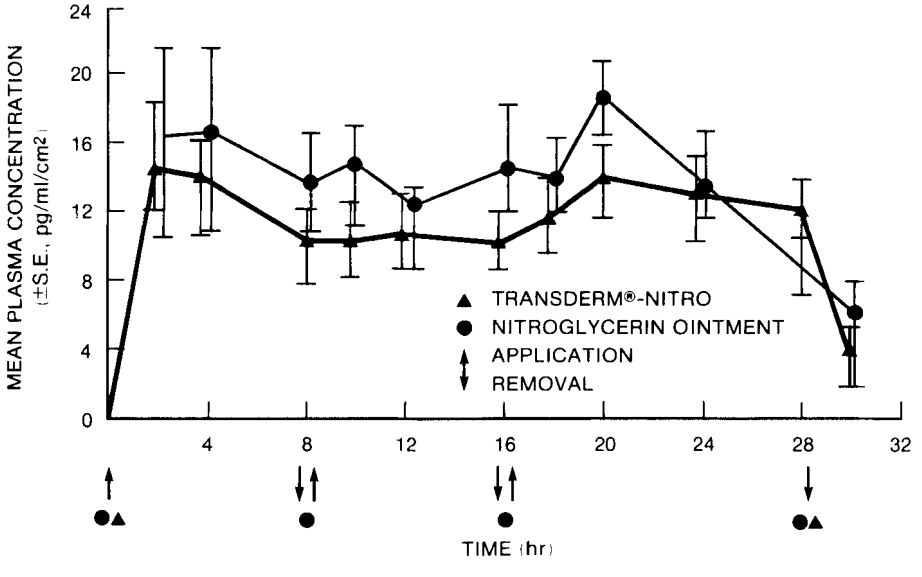

Figure 12. Comparison of standardized plasma levels of nitroglycerin from Transderm®-Nitro and nitroglycerin ointment.

drug over 24 hr. Thus, patients can be titrated to their effective rate of drug input. The systems are most often worn on the chest; more than one can be used as need dictates. Sublingual tablets may still be taken to abort any acute attacks of angina.

The Transderm®-Nitro system, like the Transderm®-Scōp system, has a four-layer structure and provides a priming dose at the inception of therapy. The drug reservoir contains nitroglycerin on lactose in silicone medical fluid, with colloidal silicone added to increase the viscosity. The drug passes through the rate-controlling EVA membrane by thermodynamic activity, moving toward the area of lower concentration. In storage, about 8% of the system's drug content passes into the adhesive, and is released as a priming dose when the system is applied to skin. Well-controlled clinical studies have shown that this system produces a significant reduction in number and intensity of angina attacks in patients (13).

Recapitulation and Conclusions

Let us now briefly recapitulate the applicability of this technology. To ascertain its suitability for a specific drug, one should first acquire or review data on the regimen-dependence of the drug's beneficial or adverse effects. Some of the techniques for accomplishing this on the animal level I have already mentioned, in discussing the outcome of the valproic acid and bleomycin studies. If rate-control appears likely to change the agent's

therapeutic ratio significantly, then its therapeutic index, potency, and physicochemical properties should be reviewed to determine if the transdermal route is appropriate for its rate-controlled delivery. If so, then system design may proceed; a variety of membranes and adhesives are available, depending on system specifications. Once the system is developed, the clinical testing and regulatory procedures will present some differences from those utilized for drugs in more conventional forms. It seems fair to note, however, that these differences have not in any way slowed up the regulatory review or decision-making process for transdermal products.

In summary, you should consider that a rationale exists for the rate-controlled transdermal delivery of potent, nonirritating, nonallergenic agents whose administration causes one or more of the following problems:

1) Patient compliance difficulties--e.g., in chronic treatment of an asymptomatic disease

2) Troublesome side effects or unreliable therapeutic action with repetitive dosing in conventional dosage forms (e.g., scopolamine)

3) Need for frequent dosing in conventional dosage forms because of the drug's short biological half-life

4) Gastric irritation with oral therapy

Despite these cogent reasons for its use, transdermal therapy will never replace oral therapy. The latter will continue to serve for the majority of medications. Nevertheless, for appropriate drugs, transdermal drug delivery can provide remarkable precision of drug input and prolonged (1-7 day) therapy from one application. Moreover, this technology illustrates the much broader potential for rate-controlled delivery of drugs in general--which can be effected by many forms for administration, via many routes. Rate-control can enhance the value of some existing agents and rescue from oblivion new drug candidates having regimen-dependent problems of side effects or compliance.

At present only 1 in 8 of new drug candidates ever reaches the market. If rate-controlled delivery can raise this number to 2 in 8 it will have achieved a 100% increase in R&D productivity. That is a figure that emphasizes the importance of evaluating the regimen-dependent actions of drugs of interest in early R&D stages.

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