DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(4), 627-646 (1983)

CONTROLLED RELEASE OF SCOPOLAMINE FOR PROPHYLAXIS OF MOTION SICKNESS

S. KUMAR CHANDRASEKARAN

ABCOR, INC.
WILMINGTON, MA 01887

I will present to you a biomedical approach to the development of a transdermal delivery system for scopolamine. Our mission was to develop a system that would administer scopolamine systemically to offset the effects of motion sickness, and at the same time would not engender any unwanted pharmacological actions that are normally associated with this potent drug.

Just a little chemistry to show what the drug looks like that everyone has been talking about this morning and early this afternoon. Scopolamine is a belladonna alkaloid with a pK of 7.35; the water solubility at 30°C of the base is about 75 mg/mℓ and of the hydrobromide salt 520 mg/mℓ.

The first procedure was to determine the permeation characteristics of this drug through human skin. The technique we followed was to mount a piece of cadaver skin between two aqueous filled solution compartments. We maintained adequate sink conditions on one side and adequate source conditions on the other, and measured the transport characteristics of the tissue per se. These measurements were conducted as a function of pH, solubility, and temperature, and a representative set of data is shown in Figure 1. The scopolamine concentration in aqueous solution presented on the abscissa in milligrams per millimeter, and the transdermal scopolamine flux on the ordinate. There is a linear relationship between concentration and flux, justifying further that the processes that really govern transport through skin are not active in nature, but are essentially passive diffusion processes that could be amply described by Fick's Law.

The next step was to determine the transport resistance offered by the various parts of skin, and the results are shown in Table 1. We used two forms of the drug scopolamine -- the base form and the salt form. The transport flux through the epidermal part of the skin, which essentially contains the stratum corneum, is very

0363-9045/83/0904-0627$3.50/0

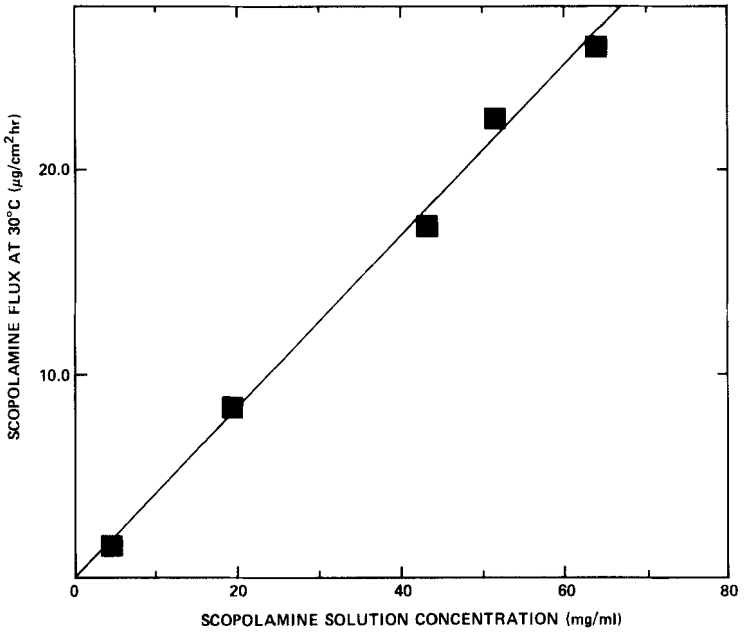


Fig. 1: Effect of Concentration on Scopolamine Flux through Human Epidermis (Epidermis A)

TABLE 1

Permeation Behavior of Scopolamine

From Saturated Aqueous Solutions

Drug form	Skin	Skin thickness (cm)	Steady state flux ($\mu g/cm^2 hr$)
Free base	Whole skin	.0953	6.0
	Epidermis	.0051	6.7
	Dermis	.0889	1342
Salt	Whole skin	.0953	0.8
	Dermis	.0889	5710

close to the flux through whole skin, again justifying what was brought out this morning, namely, that the topmost layer of skin provides the resistance to drug transport. On the other hand, if one gets rid of the epidermis, and essentially looks at the hydrated dermis, the flux rate through this tissue is almost an order of magnitude higher. On the other hand, the transport rate of the salt form through

whole skin is considerably lower than the base form in the case of scopolamine. More important, if we look at the dermis, the flux is very much greater for the salt form compared to the base form. This may be related to the higher water solubility exerted by the salt as compared to the base.

These measurements, we should mention again, are steady state measurements. It is extremely interesting to determine the transport processes taking place during this transient period before steady state is established. One way to monitor the transient domain is by performing a set of sorption measurements; namely, taking a piece of tissue (stratum corneum if you would), and equilibrating it in an aqueous solution of drug, and subsequently monitor the partition of the drug between the solution and the skin tissue (Figure 2). The sorption isotherm is non-linear in nature, and we have correlated the results utilizing a dual-mode sorption model; namely that the total amount of drug at any point within the sorption isotherm is really composed of two parts, the dissolved part and the immobilized part. The sum of these two components determines the concentration of the drug in the tissue. It is important to point out, however, that the transport is governed primarily with

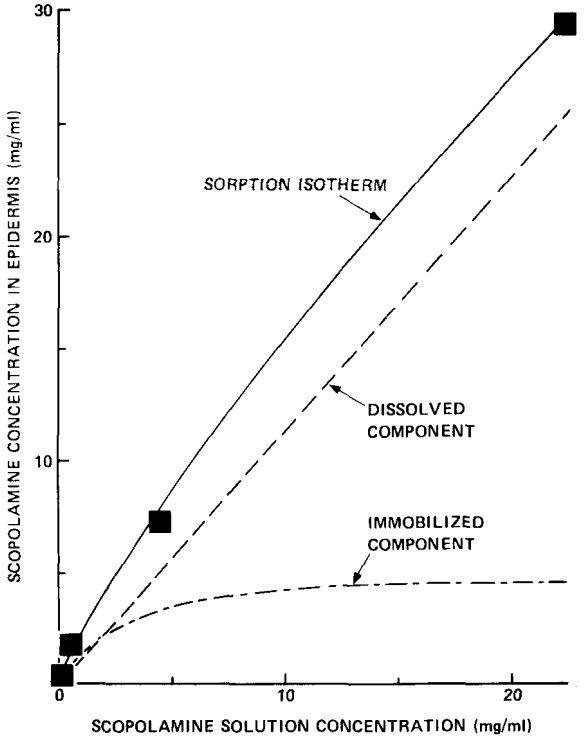


Fig. 2: Scopolamine Sorption Isotherm in Human Epidermis In Vitro (Epidermis A)

TABLE 2

SCOPOLAMINE SOLUTION CONCENTRATION C, mg/ml	STEADY STATE DIFFUSION COEFFICIENT, D_{SS} $cm^2/sec \times 10^{10}$
64.0	5.0
51.4	5.2
43.1	4.8
19.5	5.0
4.4	4.6

SCOPOLAMINE DIFFUSION COEFFICIENTS

(EPIDERMIS A)

the dissolved part which is readily being diffused. The immobilized part, on the other hand, is really contributing to what drug is immobilized in the tissue and is not readily available for transport.

From the dual-mode sorption model, we can correlate two types of diffusion coefficients. We have a steady state diffusion coefficient, which is a coefficient that one normally applies in the steady state domain. On the other hand, there is the transient or time lag diffusion coefficinet, the value of which is lower than the steady state diffusivity but which approaches the steady state value once the immobilization sites have been saturated. Typical results showing the effect of concentration on drug diffusivity are presented in Table 2.

The steady state diffusivity values average somewhere around 5×10^{-10} cm^2/sec. and seem to be independent of concentration. For those of you not familiar with transport through synthetic membranes, this value is several orders of magnitude lower than transport, say, through silicone rubber. The time lag diffusion coefficient is considerably lower than the steady state diffusivity and approaches the steady state value as the concentration increases. As the concentration increases, it tends to saturate the drug binding sites, and the difference between these two diffusion coefficients eventually approaches unity. In Figure 3, the ratio of the steady state and time lag diffusion coefficients are plotted as a function of scopolamine concentration. The solid line is predicted by theory, whereas the solid squares are the experimental data points; the agreement between theory and experiment is reasonably good. It would therefore appear that for scopolamine, this type of modeling of the sorption isotherm appears to have considerable promise.

This morning, Dr. Kligman mentioned a procedure of extracting the so-called lipid components of the stratum corneum by use of a mixture of chloroform and methanol.

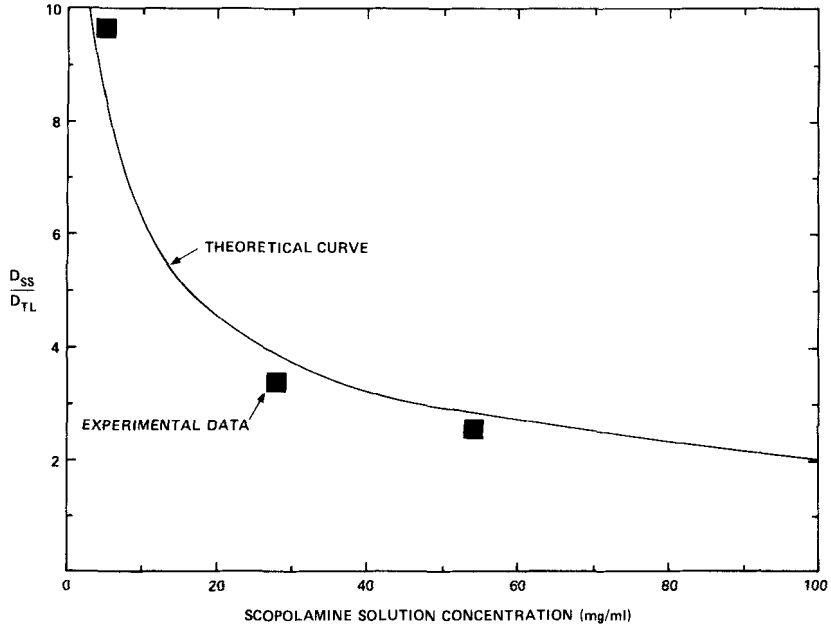


Fig. 3: Effect of Drug Concentration on D_{SS}/D_{TL} (Epidermis A)

The sorption isotherm when a tissue of stratum corneum was subjected to such a treatment and subsequently rehydrated is shown in Figure 4. The data points both for the control epidermis that hasn't seen such a treatment and the one which has seen the treatment are very similar, suggesting now that the sorption characteristics of the stratum corneum doen't seem to be dependent upon whether the tissue has been subjected to an extensive lipid extraction or not. On the other hand, as also pointed out by Dr. Kligman this morning, the transport rate through the "lipid-free" epidermis is enhanced several orders of magnitude, even though the sorption characteristics of the tissue remained essentially unchanged (Table 3).

These results indicate that the interstitial lipid phase of the stratum corneum is the cause of the exceedingly low apparent diffusivity of scopolamine and in this regard acts as the principal permeation barrier. Selective removal of the lipid phase of the tissue enhances the transdermal permeation rate of scopolamine by orders of magnitude without causing any change in the equilibrium sorption isotherm, suggesting that scopolamine sorbed by the skin is localized predominantly within the protein phase of the tissue.

During our examination of the transport characteristics of the skin to scopolamine, we faced the issue that I am sure many of you who are looking at transdermal medication face: Are the transport characteristics good enough? Or do we need other novel techniques to enhance the transport characteristics? In that regard, we went through a whole list of enhancing agents which unfortunately I will not be able to describe to you. However, I do have some experimental data which you may find

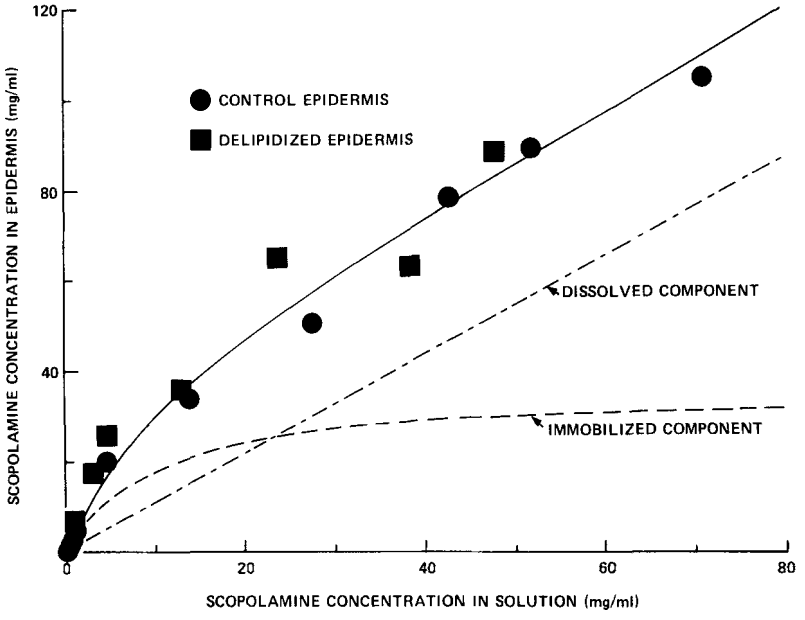


Fig. 4: Effect of Delipidization on Scopolamine Sorption Isotherm

TABLE 3

Effect of Delipidization on

Scopolamine Diffusion Coefficients

Tissue	Average steady state diffusion coefficient (cm^2/sec)
Control epidermis	4×10^{-10}
Delipidized epidermis	2×10^{-7}

exciting regarding the use of the agent dimethylsulfoxide. What we did in this case was essentially do an initial screening set of experiments and determine that 80% dimethylsulfoxide in water was indeed reasonably optimal in enhancing the transport characteristics of scopolamine. In this regard, what I describe to you are some additional interesting experiments that we did using 80% dimethylsulfoxide. A typical sorption isotherm with scopolamine concentration in solution presented on the abscissa and scopolamine concentration within the stratum corneum on the ordinate is shown in Figure 5. The filled-in triangles here represent the scopolamine dissolved in water; the filled-in circles here are where the solution concentration

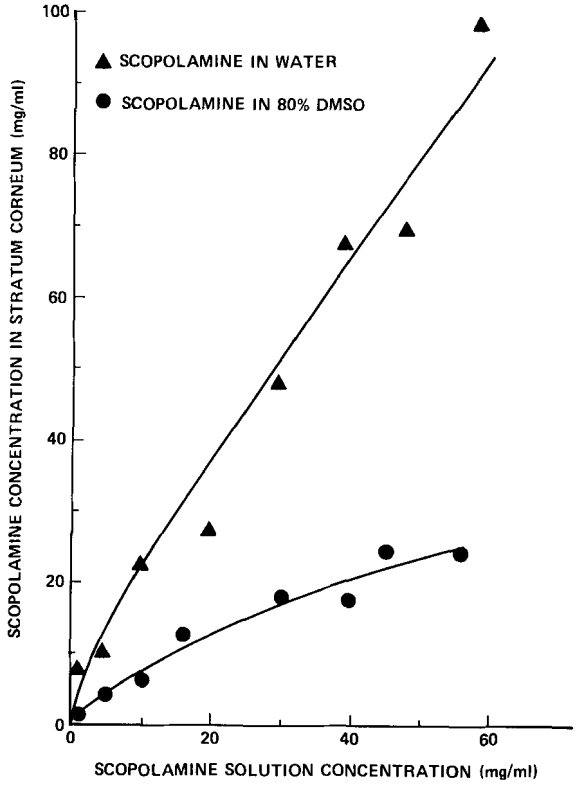


Fig. 5: Scopolamine Sorption Isotherms in Human Stratum Corneum

is in 80% dimethylsulfoxide. There seems to be a difference between these two sorption isotherms, and more drug seems to be absorbing into the tissue when the scopolamine is dissolved in dimethylsulfoxide.

But one has to be careful because even though one may do experiments at the same concentration in two different solutions, the activity or chemical potential of the drug may be widely different. If the abscissa is altered to read activity or chemical potential for scopolamine in solution, we find that the data points are essentially superimposed on the same line (Figure 6).

In another set of experiments we studied the mechanism by which dimethylsulfoxide enhanced the transport characteristics of scopolamine. The results of the permeation of scopolamine through stratum corneum (cadaver 1) from both aqueous and 80% DMSO donor solutions into receptor solutions of the same respective solvent are presented in Table 4. In the presence of DMSO, the steady state flux of scopolamine appears to be lower compared to the control experiment. Using the partition coefficients computed from the sorption isotherm, and the measured thickness of the stratum corneum at the termination of the experimentation, the steady state diffusivity was now determined by dividing the measured steady state in vitro transdermal flux by the computed gradient in the stratum corneum of dissolved drug. From aqueous solu-

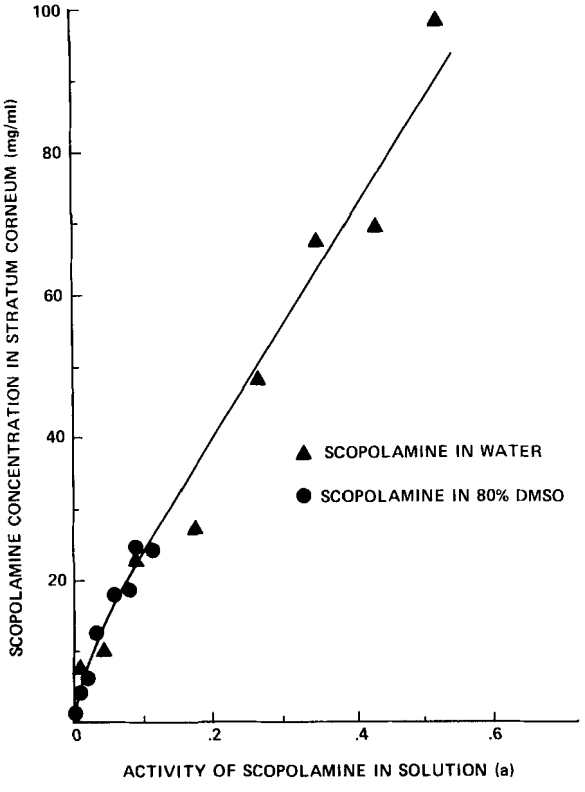


Fig. 6: Normalized Scopolamine Sorption Isotherms in Human Stratum Corneum

TABLE 4

PERMEATION OF SCOPOLAMINE THROUGH STRATUM CORNEUM IN VITRO (CADAVER 2)

Donor/Receptor Combination	Nature of Donor Solution	Scopolamine Concentration in Donor (mg/ml)	Scopolamine Activity at t=0*	Nature of Receptor Solution	Scopolamine Flux, J ($\mu g/cm^2 hr$) (5→9 hrs)
A	Water	11.7	0.117	Water	6.8
B	80% DMSO	11.5	0.023	80% DMSO	3.0
C	Water	11.7	0.117	80% DMSO	35.1
D	80% DMSO	11.5	0.023	Water	13.7

*Calculated using 100 mg/ml as saturation for scopolamine in water, and 502 mg/ml as saturation for scopolamine in 80% DMSO.

tions, the diffusivity of scopolamine in stratum corneum approximates 6×10^{-10} cm^2/s and is in good agreement with results published earlier, whereas from 80% DMSO solutions, the steady state diffusivity approximates 15×10^{-10} cm^2/s, indicating a decrease in the transport resistance offered by the stratum corneum in the presence of DMSO.

The permeation characteristics of scopolamine through stratum corneum (cadaver 2) are presented in Table 4. The flux of scopolamine with water in the two compartments of the permeation cell approximates 6.8 $\mu g/cm^2$ hr, whereas at a similar concentration of scopolamine at 11.5 mg/mℓ, the flux with 80% DMSO in both compartments is 3.0 $\mu g/cm^2$ hr. The result of normalizing these flux values for skin thickness and the activity of scopolamine in the donor solution are shown in Table 5. Under the experimental conditions of having water in both the compartments, the normalized flux approximates 0.3 μg/cm hr, whereas with 80% DMSO the normalized flux is 0.7 μg/cm hr. The 2.3-fold increase in the normalized flux in the presence of DMSO directly reflects a 2.3-fold increase in the scopolamine diffusivity through the stratum corneum; this enhancement compares well with the 2.5-fold increase in drug diffusivity measured previously using stratum corneum from cadaver 1.

Analysis of the fluxes, under conditions when a gradient of DMSO concentration is impressed across the stratum corneum, is more complex; the variables measured are shown in Figure 7. The presence of 80% DMSO on one side of the stratum corneum versus water on the other side causes an osmotic pressure gradient of about 320 atm; when a DMSO gradient of opposite sign to that of scopolamine is impressed across the skin, bulk flow of water into the receptor solution decreases the donor solution volume by about 3 mℓ in 9 hours (Figure 7a, C). At the same time, DMSO migrated from the receptor into the donor solution, resulting in a gradual increase in the DMSO concentration in the scopolamine-rich donor solution (Figure 7c, C). A consequence of this rise in the DMSO concentration was the increase in drug solubility in the donor solution, resulting in a net decrease in scopolamine activity (Figure 7d, C).

The opposite phenomenon occurred when the impressed gradient of DMSO was in the same direction as that of scopolamine; there was bulk flow of water from the receptor into the scopolamine donor solution and, consequently, dilution of the concentration of scopolamine (Figures 7a and 7b, D). Simultaneously, DMSO permeated from the donor to the receptor compartment, resulting in a decrease in the DMSO concentration in the donor solution (Figure 7c, D). The decrease in DMSO concentration offset the decrease in scopolamine concentration, resulting in an almost constant activity level of scopolamine in the donor solution (Figure 7d, D).

The representative transport fluxes of scopolamine during the experimentation described above are shown in Figure 8. The permeation rate of scopolamine is time dependent and, more surprisingly, the flux of drug under conditions when the impressed concentration gradient of DMSO if of opposite sign to that of the drug, is about two to three times greater, compared to when the gradient of drug and DMSO are in the same direction. However, in either case, the permeability of the skin to scopolamine is increased by at least one order of magnitude compared to the permeation rate in the absence of a transdermal gradient of DMSO.

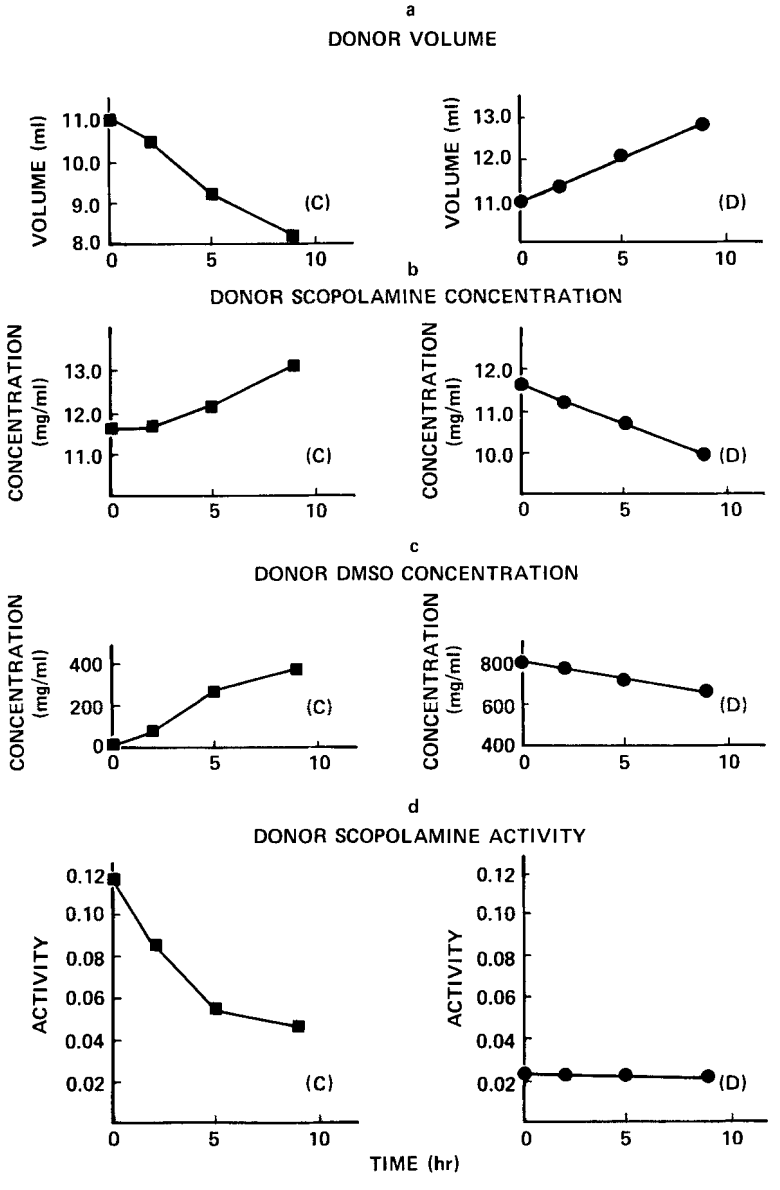


Fig. 7: Variation of Volume, Concentration, and Activity with Time

These fluxes were normalized with respect to the skin thickness and activity (percent saturation) gradients of scopolamine across the stratum corneum during the permeation experiments. The results of these computations are presented in Figure 8 and Table 5. After a time period of about four hours, the normalized fluxes are quite similar at approximately 4 μg/cm hr and appear independent of whether the

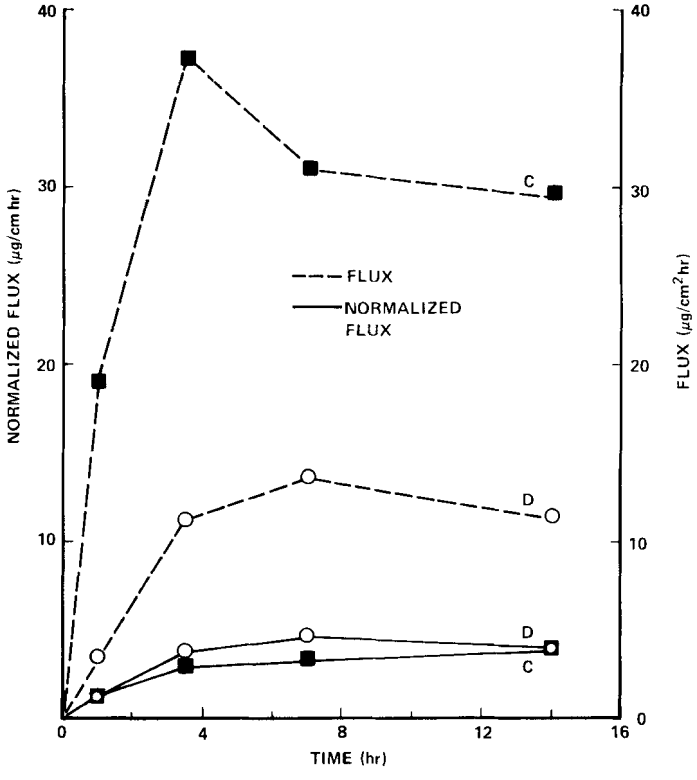


Fig. 8: Scopolamine Fluxes through Human Stratum Corneum

TABLE 5

SCOPOLAMINE FLUXES THROUGH STRATUM CORNEUM
NORMALIZED FOR ACTIVITY GRADIENT AND THICKNESS

Donor/Receptor Combination	Nature of Donor Solution	Nature of Receptor Solution	Scopolamine Activity Gradient, Δa	Stratum Corneum Thickness ℓ(cm)	Normalized Flux, $\bar{J}$* (μg/cm hr)
A	Water	Water	0.114	0.00432	0.3
B	80% DMSO	80% DMSO	0.023	0.00508	0.7
C	Water	80% DMSO	0.049	0.00534	3.8
D	80% DMSO	Water	0.022	0.00737	4.5

*Computed as $\bar{J} = J\ell/\Delta a$

impressed gradient of DMSO concentration is of the same or opposite sign to that of the drug.

This apparent independence of the direction of the DMSO concentration gradient on its ability to enhance the permeation rate of scopolamine is surprising. These results suggest an alteration in the stratum corneum microstructure caused by the presence of a DMSO concentration gradient. Photomicrographs of stratum corneum cross sections after exposure to water, 80% DMSO, and a concentration gradient of 80% DMSO are shown in Figure 9. The tissues were prepared using the routine paraffin embedding procedure; namely, the tissues were placed in 10% buffered formalin, dehydrated with graded alcohol, cleared in xylene, and infiltrated with paraffin. Marked swelling, distortion, and intercellular delamination are apparent in the stratum corneum only when it is subjected to a concentration gradient of DMSO; these changes are partially reversible following complete extraction of the tissue with water (Figure 10). These effects may be caused by the development of very high osmotic stresses produced within the stratum corneum as both water and DMSO are transported into the tissue.

Fortunately, when all is said and done, we didn't require a permeation enhancer for the drug scopolamine, because for several reasons explained by Dr. Kligman this

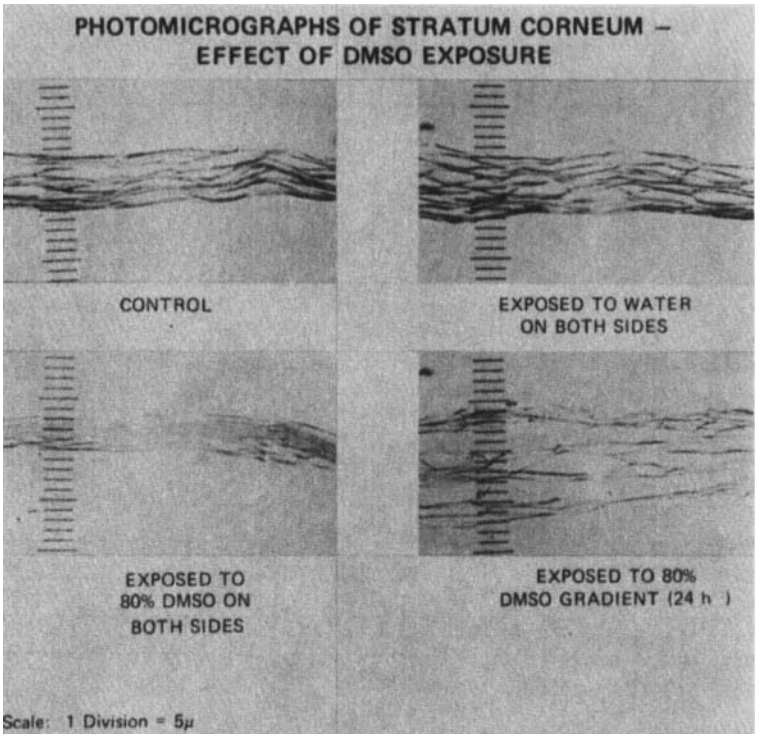


Fig. 9: Photomicrographs of Stratum Corneum Effect of DMSO Exposure

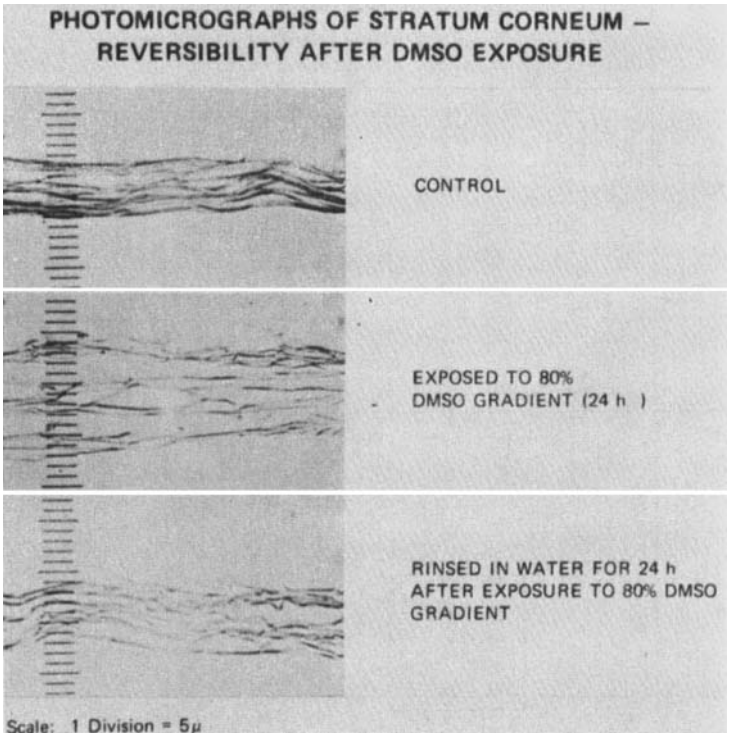


Fig. 10: Photomicrographs of Stratum Corneum Reversibility after DMSO Exposure

morning, we found that the post-auricular region was indeed very permeable to the drug. In Table 6, the permeation characteristics of scopolamine through skin excised from the post-auricular region is compared to that excised from the thigh, and the results show that the post-auricular skin site demonstrates adequate drug permeability to enable us to proceed further with the design of a transdermal drug delivery system.

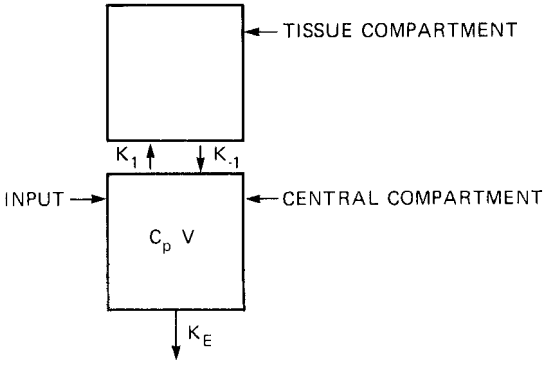
Dr. Smolen discussed various pharmacokinetic parameters, and in this respect we wanted to determine the fate of the drug once it reached the systemic circulation. On the basis of very rigorous pharmacokinetic studies, we have concluded that a two-compartment open pharmacokinetic model was adequate to correlate the pharmacokinetic parameters of the drug scopolamine (Figure 11). Now having a good idea of the permeability characteristics of the skin, and the pharmacokinetic characteristics of the drug, we proceed further to put together a transdermal system The transdermal system is essentially a multilaminate system (Figure 12). We have a rate-controlling microporous membrane to separate a unit activity source of scopolamine from the skin surface. Furthermore, we have determined that the microporous membrane should not be placed directly on the skin surface for two reasons. One is that the skin is relatively rough, and even though the microporous membrane is relatively flexible, the external contact between the membrane and the skin surface is still not perfect.

TABLE 6

Permeation and Immobilization

of Scopolamine in Epidermis

Skin	Scopolamine in donor (mg/ml)	Epidermal thickness (cm)	Scopolamine in epidermis (mg/ml)	Scopolamine steady state flux ($\mu g/cm^2 hr$)
Thigh	4.6	.0106	16.9	4.7
	16.9		25.7	15.5
Postauricular	4.6	.0084	7.4	10.0
	16.9		13.9	24.3



$C_p = Ae^{-at} + Be^{-bt}$

WHERE A = 35.0 μg/hr

B = 0.3 μg/hr

a = 0.67 hr^{-1}

b = 0.07 hr^{-1}

Fig. 11: Two Compartment Pharmacokinetic Model for Scopolamine

So we needed something to bridge the gap between the membrane and the skin surface. Furthermore, what we also wanted to do was to try and find a means by which we could saturate the skin binding sites for scopolamine rapidly and thereby reduce the time before steady state is achieved.

Thus, on the dermal side of the rate-controlling membrane is an adhesive gel containing scopolamine; this gel layer serves both as an adhesive to secure the system on the skin surface and as a priming dose drug reservoir to provide an initial priming dose of drug prior to the establishment of a controlled input of drug to the

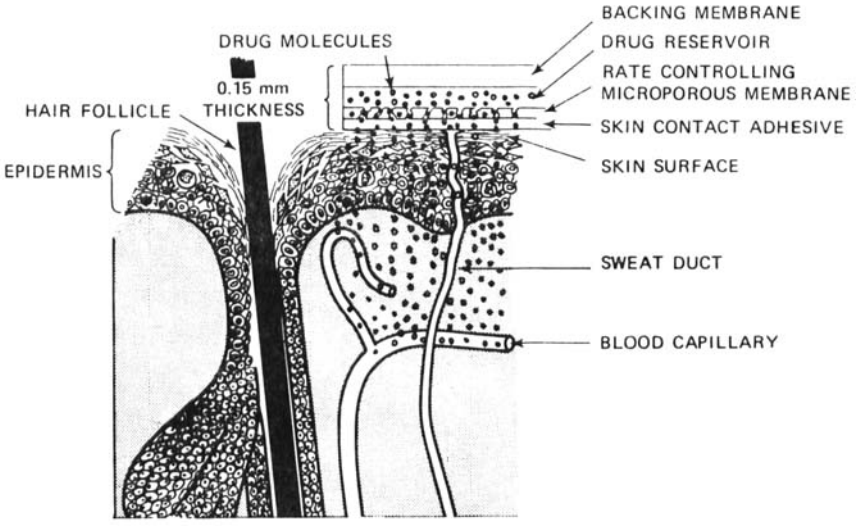


Fig. 12: Schematic Diagram of a Transderman Therapeutic System in Place on Surface Intact Skin

skin surface. A typical in vitro release rate/time profile of scopolamine from a transdermal therapeutic system into an infinite sink at isotonic and isothermal conditions is shown in Figure 13. The data points represent values experimentally measured, and the solid line represents the profile predicted by theory, assuming that the transport characteristics of scopolamine from the system are determined by molecular diffusion through the various elements of the multilayer laminate.

We performed a very interesting set of experiments by placing the scopolamine system on humans and subsequently stripping the skin site with scotch tape to determine the drug concentration profile. Two main conclusions surface from these results, both lucidly explained by Dr. Kligman this morning. The first is that the concentration is very much higher near the surface, consistent with the concentration gradient one would expect from a passive diffusion system. Secondly, the stripping of the stratum corneum layers becomes more difficult as one moves deeper into the tissue.

Based on the sorption and permeation behavior of scopolamine in human skin in vitro, and drug elimination kinetics, a mathematical model was developed for estimating and optimizing the temporal pattern of scopolamine delivery from a transdermal therapeutic system through human skin in vivo. The delivery of scopolamine from a transdermal therapeutic system into and across human skin in vivo has been developed, assuming that drug transport occurs by normal Fickian diffusion, with partition equilibrium of penetrant being maintained at the interlayer boundaries.

For the prediction of scopolamine permeation through human skin in vivo, on the basis of in vitro permeation measurements, it was assumed that stratum corneum thickness was 40 μ, and steady state scopolamine diffusivity was 5×10^{-10} cm^2/sec.

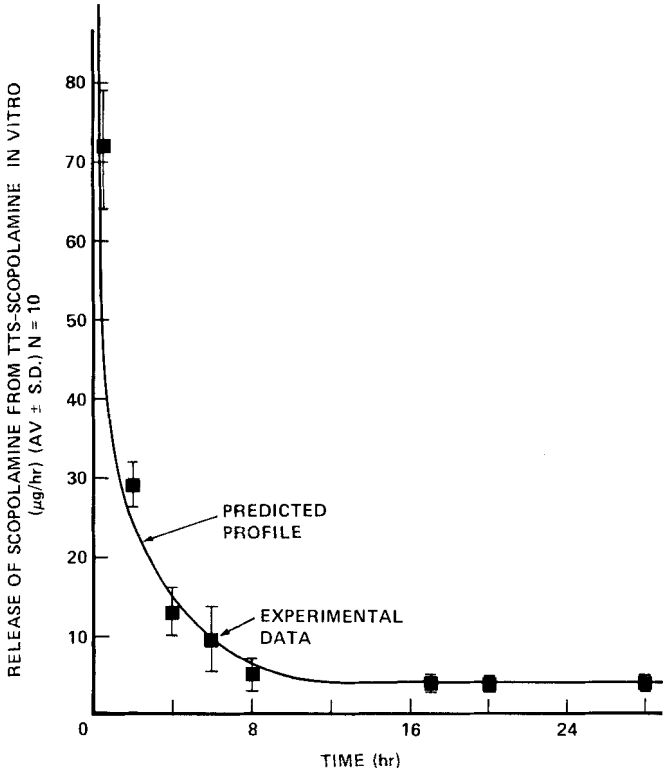


Fig. 13: Scopolamine Release Rate Profile Comparison of Theory and Experiment

From the two-compartment pharmacokinetic model, the excretion rate constant was estimated to be 0.62 hr^{-1}. The predicted urinary excretion rate profile for a single 24-hour application of the transdermal therapeutic system scopolamine is shown in Figure 14.

To follow the rate of scopolamine input to the systemic circulation in vivo, we monitored its rate of urinary excretion. Since only 10% of the drug is recovered in the urine in the free form following intramuscular or intravenous administration, we assumed that percentage recovery would be similar during transdermal administration. The measured urinary excretion rate of scopolamine during a single 24-hour application of the transdermal system (Figure 14) indicated good agreement between theory and experiment.

In Figure 15, the predicted urinary excretion rate profile of scopolamine, for three successive 24-hour applications of the transdermal system in different skin sites is compared with in vivo data. Again, the agreement between theory and experiment is good.

The model has been useful in optimizing the design of the therapeutic system. It has been especially valuable in regard to the provision of the priming dose of drug, which serves to saturate the immobilization sites for scopolamine within the

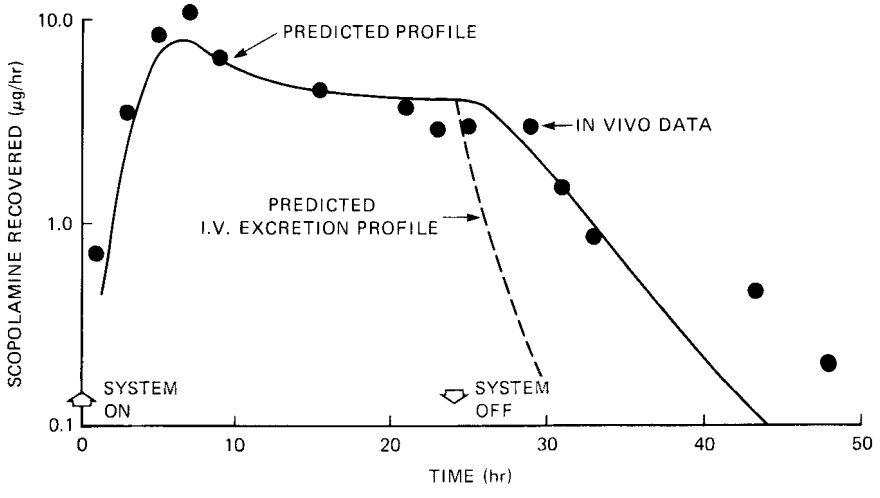


Fig. 14: Scopolamine Extretion Rate: Comparison of Theory and In Vivo Data

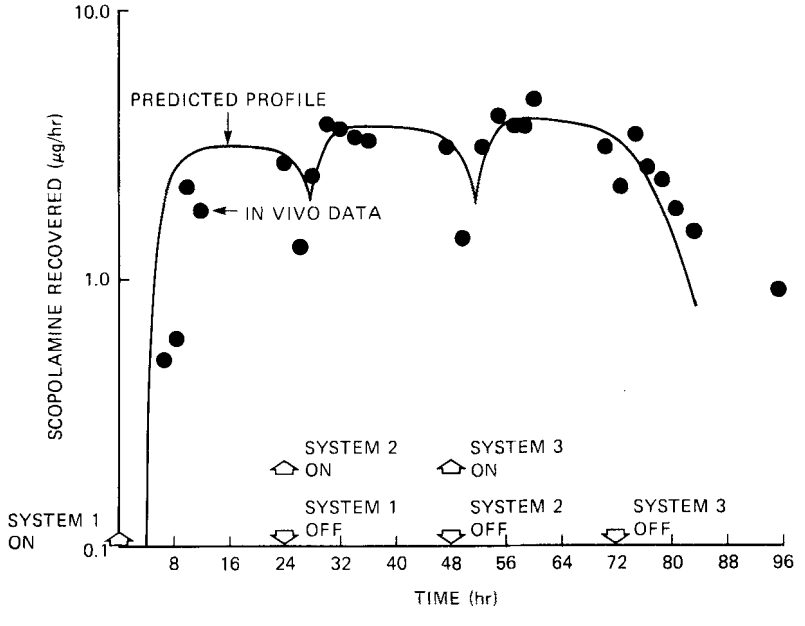


Fig. 15: Scopolamine Excretion Rate after Multiple Applications: Comparison of Theory and In Vivo Data

stratum corneum. Saturation of these sites permits rapid establishment of steady-state in urinary excretion rate of drug.

The goal of the development effort was to deliver scopolamine at the rate that would give the beneficial effects of control over motion sickness, but none of the side effects normally associated with the drug. The pharmacological effects exerted by scopolamine are shown in Figure 16. The concentration profile

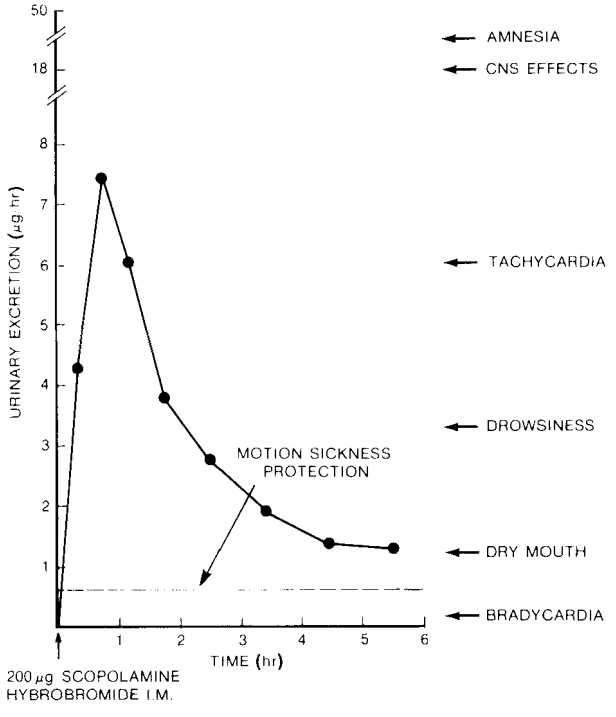


Fig. 16: Relationship between Rate of Urinary Excretion of Scopolamine and Its Pharmacological Effects

shown in this figure was obtained after intramuscular administration of 200 micrograms of scopolamine hydrobromide. Based on these results, we were able to define the rate of scopolamine input required to maximize the sensitivity of the antiemetic action.

To determine whether the scopolamine system provided an exact analog to a closely monitored i.v. infusion, we compared urinary excretion levels of scopolamine prevailing during its delivery by TTS-scopolamine or a controlled intravenous infusion at approximately the same rate.

Rates of urinary excretion of scopolamine peaked within 12 to 24 hours following TTS application, then decreased slightly, and thereafter held constant throughout the remainder of the 72-hour wearing of the system (Figure 17, dashed lines). During i.v. infusion (Figure 17, solid lines), excretion of unchanged scopolamine attained a steady rate within the first 12 to 24 hours, which was maintained throughout the 72-hour infusion. Drug excretion rates associated with the i.v. infusion and TTS varied significantly only during hours 12 through 24 of scopolamine administration and after its discontinuation (Figure 17).

During each mode of scopolamine administration, subjects reported a dry mouth as the only significant pharmacological effect. A moderately dry mount developed 12 to 24 hours following TTS application but decreased so that it was barely

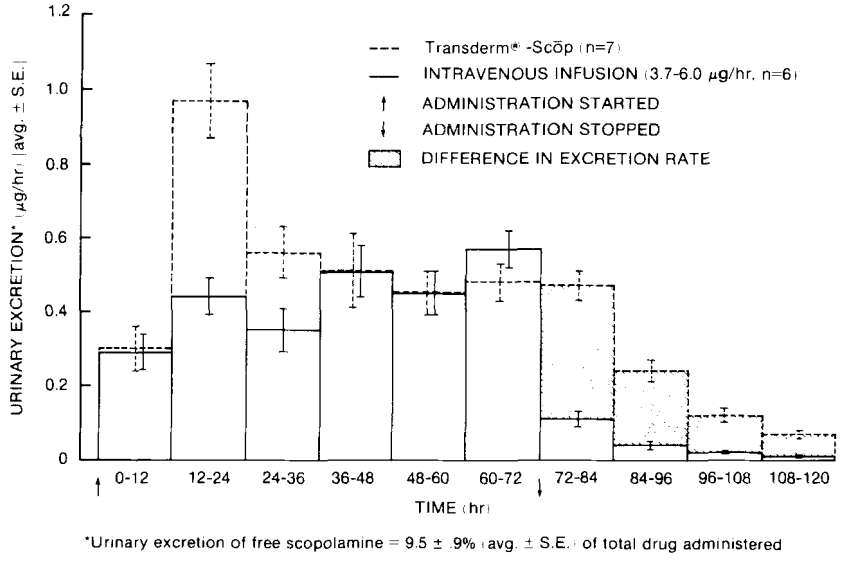


Fig. 17: Urinary Excretion of Scopolamine Base during and following Transdermal and Intravenous Administration

noticeable at the time of removal of the system. During scopolamine infusion, subjects reported experiencing a mildly dry mouth continuously. It appears that the concentration of scopolamine that elicits the dry mouth side-effect is very little higher than that needed to attain protection against motion sickness.

The data indicate that TTS-scopolamine controlled the drug's excretion as well as intravenous administration. The higher rate of scopolamine excretion during the first 24 hours of TTS use is attributable to the initial priming dose provided by incorporation of scopolamine into the adhesive contacting the skin. Because skins have differing capabilities for concentrating scopolamine, a slight overshoot or undershoot can occur in the rate of drug input during hours 12 to 14 following TTS application. This over/undershoot is very small with respect to the wide oscillations of urinary excretion seen with intramuscular injections (Figure 16).

Following cessation of transdermal scopolamine administration, the cutaneous depot of drug manifests itself in a rate of urinary excretion that initially declines rather more slowly than the rate observed following cessation of intravenous administration, a difference that appears to be without pharmacological consequence.

Conclusions

The anti-emetic effect of TTS-scopolamine has been documented elsewhere for a variety of conditions of motion; two-thirds of the people experienced transient dry mouth and one-sixth experienced some drowsiness. Other central effects of scopolamine were observed infrequently, as was mydriasis.

A point deserving emphasis is that, with rate-controlled delivery, the total scopolamine dosage producing a satisfactory therapeutic effect is only about one-fifth of that required with pulse-entry (first-order) dosage forms such as injections. The usual intramuscular dose of scopolamine administered for motion sickness is 200 µg, and its six-hourly repetition would presumably be required under conditions of continuous motion. Thus, the total dose over three days from this first-order dosage form would be 2.4 mg versus programmed delivery of 0.5 mg over three days from TTS-scopolamine. In addition to a reduction in total dosage, the TTS-scopolamine avoids dose-related peaks in plasma concentration (reflected by the urinary excretion curve shown in Figure 16). Therein lies the mechanism by which rate-controlled administration increases the selectivity of scopolamine's actions.

Another point deserving emphasis is that the TTS-scopolamine's duration of three days is many times longer than the pharmacokinetic half-life of the drug, which is less than one hour. The therapeutic system form, instead of the intrinsic kinetic properties of the drug, provides the therapeutically important attribute of duration of action.