(6) J. H. ... Schwartz, and M. I. Surks, *J. Clin. Endocrinol. Me* ...1975).
(7) D. J. Swa... P. Reitberg, I. L. Smith, P. B. Wels, and J. J. Schentag, *J. Pharmacokinet. Biopharm*, in press (1984).
(8) D. P. Reitberg, T. J. Cumbo, I. L. Smith, and J. J. Schentag, *Clin. Pharmacol. Ther.*, in press (1984).
(9) L. A. Bauer and M. Gibaldi, *J. Pharm. Sci.*, **72**, 978 (1983).

*Ian L. Smith**x
Jerome J. Schentag‡
*The Clinical Pharmacokinetics Laboratory
Millard Fillmore Hospital
Buffalo, NY 14209
‡Division of Clinical Pharmacy Science
Department of Pharmaceutics
State University of New York at Buffalo
School of Pharmacy
Amherst, NY 14260

Received November 22, 1982.
Accepted for Publication November 16, 1983.

Transdermal Administration of (15*S*)-15-Methyl Prostaglandin $F_{2\alpha}$ Methyl Ester to Rhesus Monkeys

Keyphrases □ Drug delivery systems—controlled-release transdermal administration, prostaglandins, rhesus monkeys □ Prostaglandins—transdermal delivery system, controlled release

To the Editor:

Drug formulation technology has advanced dramatically in recent years. Controlled-release delivery systems offer a number of distinct advantages in therapeutics, one being the potential for designing delivery systems that release therapeutic agents at preselected rates such that in a given situation blood concentration of a drug can be maintained at the desired level for an extended period of time. This ability to control the rate of drug delivery aids in separating the beneficial effects of a drug from the undesirable side effects. Such delivery systems are particularly useful for drugs with short biological half-lives and/or narrow therapeutic indices. Transdermal delivery systems are one of the most exciting applications of controlled-release technology. We report here our preliminary experiments, which demonstrate that (15*S*)-15-methyl prostaglandin $F_{2\alpha}$ methyl ester (carboprost methyl) is readily absorbed when administered transdermally to rhesus monkeys using a polymeric controlled-release delivery system.

The transdermal delivery system consisted of laminated polymeric membranes with a surface area of 40 cm^2. Carboprost methyl was at a concentration of 16% (w/w) in the inner drug-bearing membrane. This membrane was covered with a rate-controlling membrane which allowed a steady-state release rate of 480 μg/h. Double-sided adhesive tape was applied to the periphery of the transdermal patches for attachment to the skin.

The transdermal patches were placed on the shaved chests of four third-trimester pregnant rhesus monkeys. The animals were anesthetized with ketamine hydrochloride[1], and uterine motility was recorded using a fluid-filled polyethylene catheter[2] inserted transabdominally which was attached to a polygraph[3] using a P-23 Dc transducer[4] (1). Peripheral blood samples were collected from the femoral vein and immediately placed in tubes containing heparin. The plasma was harvested and frozen at −20°C for subsequent determination of (15*S*)-15-methyl prostaglandin $F_{2\alpha}$ by radioimmunoassay (2).

The skin was hydrated prior to applying the transdermal delivery system in three animals: a hot towel compress was used on two animals and the skin was irrigated with water on the third animal. To evaluate the rate of drug absorption without prior hydration, the transdermal patch was applied to one animal immediately after shaving the skin.

Drug absorption was more rapid in those animals whose skin had been hydrated. A plasma prostaglandin concentration of ~1200 pg/mL was attained by 0.5 h after application of the transdermal delivery system in the water irrigated animal. In one animal in which a hot towel compress was used the plasma concentration of prostaglandin was ~2200 pg/mL by 0.5 h. The plasma prostaglandin concentration in the second animal similarly pretreated was ~1100 pg/mL by 1 h and 2300 pg/mL by 3 h. Thus, absorption of the drug was slightly slower in this animal even though the skin had been hydrated in a similar manner. When no attempt was made to hydrate the skin, prostaglandin was not detectable in the blood of the fourth monkey until 3 h after the transdermal delivery system had been applied. At this time the concentration was only 100 pg/mL. Thereafter there was a gradual increase in plasma concentration of prostaglandin to 490 pg/mL at 5 h when the delivery system was removed.

All four animals had an increase in the frequency and amplitude of uterine contractions following application of the transdermal delivery systems. In all cases uterine motility increased gradually without any evidence of a rapid onset of prostaglandin effects. The uterine motility tracing from one of these animals is shown in Fig. 1. The mean time to the initiation of stimulated uterine motility was 90 min (range = 45–150 min). The onset of increased uterine activity was temporally related to the increase in prostaglandin detected in the blood in three of the four animals. In one of the animals the rapid increase in blood prostaglandin (2200 pg/mL at 0.5 h) was not reflected in an immediate increase in uterine motility.

These preliminary results clearly demonstrate that carboprost methyl is readily absorbed transdermally in the rhesus monkey when administered using a polymeric controlled-release delivery system. This was particularly true when the skin was hydrated prior to application of the transdermal patch. It is known that hydration of the skin causes the stratum corneum to swell (3). Thus, the normally tight, dense packing of the cells in this layer is loosened. Presumably, this would facilitate movement of prostaglandin through the stratum corneum into the deeper epidermal and dermal layers. However, it is evident that prostaglandin can be absorbed when no effort is made to hydrate the skin, albeit, at a much slower initial rate.

Transdermal delivery systems are finding more and

[1] Vetalor, Parke-Davis and Co.

[2] PE60, Clay Adams.
[3] Grass.
[4] Strathan.

0022-3549/84/0200-0282$01.00/0

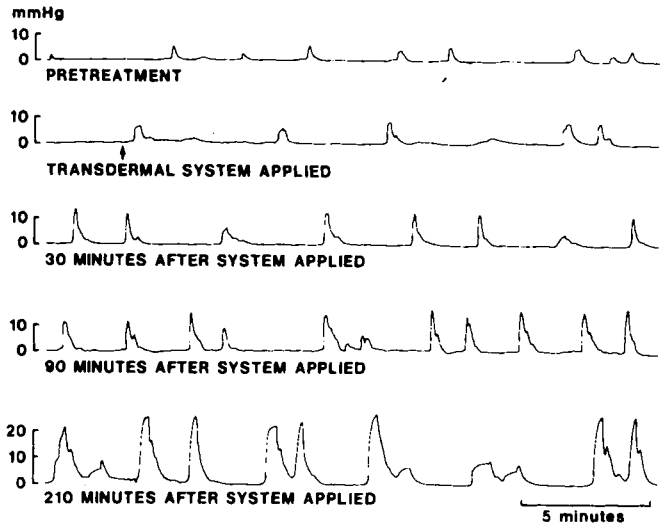

Figure 1—*Uterine motility tracing in a pregnant rhesus monkey (third trimester) treated with a transdermal delivery system containing (15S)-15-methyl prostaglandin $F_{2\alpha}$ methyl ester. Note the gradual increase in the frequency and amplitude of uterine contractions after the delivery system was applied.*

more application for the administration of therapeutic agents (4). A prostaglandin analogue has been shown to be hypotensive when administered transdermally (5). These systems may prove to be especially useful for the administration of prostaglandins for menses induction. The most commonly investigated route of administration for this indication is vaginal (6, 7). One disadvantage to the vaginal route of prostaglandin administration for menses induction is the fact that uterine bleeding is induced as a consequence of the therapy. The time of onset and the amount of uterine bleeding vary among patients. This creates a variable environment for the absorption of prostaglandin from the vagina, and can interfere with drug absorption (7). A transdermal controlled-release delivery system could alleviate these problems.

(1) C. H. Spilman and T. J. Roseman, *Contraception*, **11**, 409 (1975).

(2) J. C. Cornette, D. C. Beuving, and K. T. Kirton, *Prostaglandins*, 12 (Suppl), 53 (1976).

(3) P. Brisson, *Can. Med. Assoc. J.*, **110**, 1182 (1974).

(4) C. D. Black, *U.S. Pharmacist*, **November**, 49 (1982).

(5) J. E. Birnbaum, P. S. Chan, P. Cervoni, F. Dessy, and L. VanHumbeeck, *Prostaglandins*, **23**, 185 (1982).

(6) C. H. Spilman, G. D. Gutknecht, D. C. Beuving, and F. M. Southern, *Contraception*, **21**, 353 (1980).

(7) M. Bygdeman, N. Christenssen, K. Green, O. Vesterqvist, T. J. Roseman, M. E. Tuttle, and C. H. Spilman, *Contraception*, **27**, 141 (1983).

Charles H. Spilman ˣ
Diane C. Beuving
Adelbert D. Forbes
Theodore J. Roseman *
Robert M. Bennett
Fertility Research and Pharmacy Research
The Upjohn Company
Kalamazoo, MI 49001
* Present Address: Travenol Laboratories, Inc.
6301 Lincoln Avenue
Morton Grove, IL 60053

Received September 22, 1983.
Accepted for publication October 25, 1983.

Navel Absorption: Transdermal Bioavailability of Testosterone

Keyphrases □ Absorption—naval, transdermal, bioavailability of testosterone □ Testosterone—transdermal absorption *via* naval, bioavailability □ Bioavailability—transdermal via navel

To the Editor:

The navel (umbilicus) has for many years been widely used as the site for transdermal administration of a number of Chinese drugs, *e.g.*, *Mentha arvensis L.*[1], (1). No bioavailability data are yet available to justify the use of the navel as the site for drug administration.

Recently, a number of systemically active drugs, such as nitroglycerin and scopolamine, have been actively investigated and found to penetrate the skin tissues at a rate sufficient to achieve the therapeutic blood levels required for systemic effects (2–7).

We evaluated the transdermal bioavailability of testosterone through the skin tissues at the navel area[2] and compared the data with that obtained from the transdermal administration on the forearm area (dorsal surface) using four rhesus monkeys as the model animal. [^{14}C]-Testosterone [5 μCi (25 μg)], in 100 μL of acetone, was applied on a skin area (controlled at 0.2 cm^2 by a metal templet) for 5 d. The solvent was quickly evaporated, and the site of drug administration was then covered with a piece of plastic adhesive which remained intact throughout the study. Blood samples (2 mL) were collected in heparinized tubes at 30-min intervals for the first 6 h after administration and then every 24 h up to 9 d. Urine samples were collected daily. The systemic bioavailability and pharmacokinetic profile of [^{14}C]testosterone after topical administration on the navel and forearm skins were then compared using intravenous data as the reference.

The data generated (Fig. 1) suggest that administration *via* the navel yields a relatively faster absorption and also greater systemic bioavailability of [^{14}C]testosterone than administration *via* the forearm. Both routes of percutaneous absorption give well-defined first-order elimination kinetics, which is very much in parallel to that of intravenous administration. It is interesting to note that the systemic bioavailability of [^{14}C]testosterone by navel absorption is relatively close to the level obtained by the intravenous administration of an equivalent dose and is substantially greater than the level achieved by forearm administration. Calculated from Eq. 1, navel absorption of [^{14}C]testosterone has achieved a relative bioavailability of 79.9%, as compared with 49.9% by forearm administration.

$$\% \text{ relative bioavailability} = \frac{\left[\int_0^9 C_c dt\right]_p}{\left[\int_0^9 C_c dt\right]_i} \times 100 \qquad \text{(Eq. 1)}$$

[1] Chemical analysis indicated that it contains menthone, menthol, pinene, and methyl acetate.

[2] Navel area denotes the surface of the navel (Figure 329 in "Structure and Function in Man," 2nd ed., by S. W. Jacob and C. A. Francone, Saunders, Philadelphia, Pa., 1970).

0022-3549/84/0200-0283$01.00/0