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*Report*

# Transdermal Delivery of Narcotic Analgesics: pH, Anatomical, and Subject Influences on Cutaneous Permeability of Fentanyl and Sufentanil

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The permeation of fentanyl and sufentanil through cadaver skin membranes was investigated using *in vitro* diffusion cell techniques. Neither drug influenced the permeation of the other when they were concurrently applied to the skin membrane. With respect to transdermal delivery, short diffusion lag times of less than 0.5 hr were observed for each compound. Their permeation rates through heat-isolated epidermis and dermatomed (200- to 250-μm) skin sections were essentially the same. However, when the stratum corneum was removed by tape stripping, the respective permeability coefficients were increased >30-fold, establishing the stratum corneum as the principal barrier to their skin permeation. Permeation was also studied as a function of pH. From pH 4 to pH 8 the permeability coefficients of both fentanyl and sufentanil, calculated from the total solution concentration regardless of ionization, increased exponentially. The free base is thus responsible for the relatively facile skin permeation of these drugs. Factoring of the independent permeability coefficients of the ionized and free-base forms was possible, with the latter being over two log orders larger than seen for the protonated species. Permeability coefficients of fentanyl and sufentanil through skin sections obtained from different cadavers varied four- to fivefold. Neither gender nor age was a flux-determining variable for either drug. The permeability coefficients of the drugs through skin sites as diverse as the sole of the foot, chest, thigh, and abdomen were remarkably similar. Their fluxes were sufficient for transdermal administration.

KEY WORDS: narcotics; transdermal delivery; subject variability; percutaneous absorption; fentanyl; sufentanil.

## INTRODUCTION

Fentanyl and sufentanil are synthetic narcotics of the 4-anilinophenylpiperidine class. Fentanyl is estimated to be 80 times more potent than morphine as an analgesic. Sufentanil has a potency about 10 times that of fentanyl (1). Both these drugs can induce profound analgesia and, in sufficient doses, anesthesia. Fentanyl is frequently used as both an analgesic and an anesthetic agent preoperatively because of its rapid onset, short duration of action, and high potency (2,3). Although even more potent than fentanyl, sufentanil's clinical use is limited due to its ultrashort half-life, higher volume of distribution, and narrower therapeutic window (1,4,5). When administered orally, both fentanyl and sufentanil undergo extensive first-pass metabolism (6,7) and thus they are almost exclusively administered parenterally to achieve their effects.

There are disadvantages to intravenous bolus injections of such rapidly metabolized, lipophilic drugs. First, drug action is short-lived, as plasma levels decline rapidly as a result of uptake by tissues and to fast elimination (8–10). Second, in order to sustain the analgesia, large priming doses are often given initially, running the risk of pushing plasma concentrations into the toxic range. A better approach to their administration would be to stabilize their levels by giving them at rates that match their elimination rates from the plasma. This can be achieved by continuously infusing them but also by delivering them transdermally (11–13). The latter is clearly preferable as the patient can be ambulatory. Transdermal delivery also promises to minimize other administration problems generally associated with narcotics, including their all too frequent dosing requirement and even the tendency for their underutilization. Moreover, side effects which derive from the pulsed nature of delivery from discrete dosages can be eliminated.

Michaels *et al.* (14) have studied the *in vitro* permeability of cadaver skin by fentanyl. They report permeability coefficients obtained from saturated aqueous solutions in the range of $0.8–3.5 \times 10^{-2}$ cm/hr (14). More recently, Sebel *et al.* (15) have demonstrated the *in vivo* percutaneous absorption of fentanyl and sufentanil in human volunteers using radiolabeled drug. They observed that 30 to 40% of the transdermally administered dose was recovered in urine after 24 hr. There is no indication in either of these studies that vari-

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ables such as age, gender, skin site, and pH were investigated. The present paper is aimed at elucidating such influences.

Both fentanyl and sufentanil are weak bases (16). The permeation of such drugs through membranes is highly influenced by pH (17,18). Permeation of fentanyl and sufentanil through skin from aqueous media should depend on the respective $pK_a$'s of these substances and the pH of the application medium. Therefore, particular emphasis was placed on evaluating the influence of donor pH on the steady-state permeation rates of these drugs.

## MATERIALS AND METHODS

*Materials.* Fentanyl and sufentanil bases were gifts from Janssen Pharmaceutica (NJ). Citrate phosphate buffers solutions were prepared between pH 4 and pH 7, potassium phosphate buffer solutions between pH 7 and pH 9, and borate buffer solutions at pH 9.5. All buffer solutions were isoosmotic with physiological fluids. The free-base form of each drug was used as the starting material to prepare the solutions to avoid introducing extraneous anions into the donor media. All permeation studies were begun with saturated solutions of the drugs (not suspensions). Each drug solution was prepared from a weighed amount of fentanyl or sufentanil exceeding its solubility. This was dispersed in buffer and stirred overnight to effect saturation. Excess solute was then filtered out and saved for future use to conserve compound. The concentration (solubility) was determined on each solution prior to each study. The reported pH values of the solutions were measured prior to charging the donor chambers of the diffusion cells. Weighed amounts of both drugs were added to the media and the saturation and filtration were done exactly as for a single compound when studying their simultaneous permeation. The solubility of each drug in cosolution was determined by gas chromatographic (GC) assay.

*Skin Preparation and Permeation Procedure.* Human cadaver skin was used in the permeation studies. Samples of whole skin were removed from the abdomen of human cadavers not later than 48 hr postmortem with the aid of a dermatome set at 200-μm thickness. The skins were wrapped in plastic film and stored in a freezer at −20°C. As skin was needed, the frozen sections of skin were thawed and cut into squares before mounting in the diffusion apparatus. The epidermis was isolated from the dermatomed skin by immersing the skin sections in water at 60°C for 30 sec (19). The epidermis was then teased off with forceps. In order to study the permeabilities of these compounds as a function of anatomic site, dermatomed skin samples were obtained from different areas of a single cadaver.

Skin sections (dermatomed skin or isolated epidermis) were mounted carefully between the half-cells of the diffusion cells, each of 3-ml capacity, and fastened with a clamped device spanning the diffusion cell and pressing the edges of the diffusion cells tightly to the skin (Crown Glass two-compartment diffusion chambers). The two half-cells were filled with buffer. Temperature within the diffusion cell was maintained at 37°C by circulating water from a bath (Lauda K-2/RD, Beckman Instrument) through glass jackets around each half-cell. The cell compartments were then rinsed with buffer and the receiver was filled with 3 ml buffer of the same pH as that of the donor medium. The donor compartment was charged with a saturated, buffered solution of one of the permeants at known pH. Stirring was set at 150 rpm throughout the experiment. At predetermined times, 200 μl of receiver content was withdrawn and placed in 15-ml culture tubes. The receiver contents were then brought back to the original volume with 200 μl of prewarmed (37°C) buffer. Samples were taken from the donor compartment at the beginning and at the end of each experiment to assure that the essentials of constant activity and sink conditions were maintained throughout a run (that depletion of donor concentration of a drug did not exceed 10% during an experiment). The samples were assayed by GC using a nitrogen selective detector.

*Fentanyl and Sufentanil Assay.* One hundred microliters of codeine solution containing 14 μg of codeine, the internal standard, 0.5 ml of 2 *M* NaOH, and 4 ml of extracting solvent (hexane:ethanol, 95:5%) were added to each 200-μl sample already in a 15-ml culture tube. The sample was then vortexed (Evapomix) for 5 min to mix the phases intimately and the contents were centrifuged. The organic phase was transferred to another test tube with the aid of a Pasteur pipette and evaporated to dryness at 40°C. The residue was reconstituted in 200 μl of toluene and a 2-μl aliquot of the formed solution was injected into the gas chromatograph.

A Hewlett–Packard 5890 gas chromatograph (Hewlett Packard, NJ) equipped with a nitrogen-phosphorus detector was used. Chromatographic resolution was achieved using a 10-m × 0.32-mm-ID, 0.25-μm cross-linked 50% phenylmethyl silicone-fused silica capillary column. Helium was used as a carrier and makeup gas. The split ratio was 25:1. The gas chromatograph was also equipped with a Hewlett Packard 7673 A autosampler. Peak heights were evaluated on a Hewlett Packard 3390-A integrator.

The flow rates set for the carrier gas and the makeup gas were 2.5 and 45 ml/min, respectively. The column temperature was set at 150°C for the first min and was programmed to reach 255°C at a rate of 10°C/min. The injector and detector temperatures were maintained at 295°C. Aliquots (2 to 3 μl) of the samples were injected and the purge of excess solvent was carried out at a flow rate of 60 ml/min beginning 1 min after the sample was injected and continuing to the end of the analysis. The run time was 15 min. The coefficient of variation of each assay was checked and was never greater than 10%. The lower limit of quantitation for each narcotic assayed was less than 25 ng/ml, with a detection limit lower than 1 ng/ml.

*Data Analysis.* Data were plotted as the cumulative amount of drug collected in the receptor compartment as a function of time. The permeability coefficient for a given run was calculated from

$$\frac{dM}{dt} = J_T = APΔC \quad (1)$$

In this equation $J_T$ is the total flux in the steady state as micrograms per hour; $A$ is the area of the membrane, 0.785 $cm^2$; $P$ is the effective permeability coefficient as centimeters per hour; and $\Delta C$ is the concentration difference ex-

pressed between the diffusion cell's chambers, which was taken as the initial donor-phase concentration in micrograms per cubic centimeter. Since $J_T$ also equals

$$\frac{dM}{dt} = V\frac{dC}{dt} \quad (2)$$

where the term, $V$, is the receiver half-cell volume, 3.0 ml, the permeability coefficient can be directly estimated from the steady-state rate of change in concentration in the receiver half-cell.

The results for fentanyl and sufentanil were statistically evaluated to ascertain if there were significant intra- or interspecies differences in the permeabilities of these drugs as functions of the tested variables. The statistical analysis was performed by the two-tailed Student's $t$ test.

## RESULTS

The 37°C permeability coefficients for fentanyl and sufentanil through dermatomed skin are presented in Table I. These were determined both independently of one another and simultaneously, all on a single section of skin. In this particular experiment, no statistically significant interspecies and intraspecies differences ($P > 0.05$) in the permeability coefficients and lag times of the drugs were evident regardless of whether they permeated alone or together. Permeability coefficients and lag times of fentanyl and sufentanil through heat-separated epidermis and dermatomed cadaver skin prepared from a common cadaver skin section are tabulated in Table II. Permeability coefficients and lag times for fentanyl through the isolated epidermis were no different than found with the dermatomed skin ($P > 0.05$). On the other hand, the permeability coefficients of sufentanil through epidermis and dermatomed skin proved to be statistically different, with dermatomed skin unexpectedly having a higher permeability. This result was substantiated by repeating the study (data not given). In yet another study, the permeation of stripped skin was compared to that of isolated epidermis (Table III). Permeability coefficients found with stripped skin were roughly 50 times greater than for the epidermis.

Permeability coefficients of fentanyl and sufentanil obtained on a single piece of skin as a function of pH are presented in Table IV. The limiting values of the permeability coefficients for fentanyl and sufentanil as the pH was raised were both in excess of $3 \times 10^{-2}$ cm/hr.

A little information was obtained relative to the permeation of fentanyl and sufentanil as a function of subject and, to the extent possible, of gender, age, and race. These data are given in Table V. It can be seen that the permeability coefficients varied considerably from skin to skin and ranged from $3 \times 10^{-3}$ to $17.5 \times 10^{-3}$ and from $5.5 \times 10^{-3}$ to $23.3 \times 10^{-3}$ cm/hr for fentanyl and sufentanil, respectively. Neither gender nor age nor race (two black subjects) seemed to affect the permeation of these drugs. However, on the average, the permeability of sufentanil was 1.4 times higher than that of fentanyl when evaluated over all the skin samples. This ratio is statistically different from one, indicating that sufentanil is the more facile permeant. The latter studies were performed with heat-separated epidermis.

The influence of body site on permeability was tested. The permeability coefficients obtained on skin from a single cadaver at the upper arm, thigh, abdomen, chest, and sole are given in Fig. 1. Remarkably, these were quite the same for each compound. Sufentanil retained its edge in permeability at all sites, whereas fentanyl was less permeable over the sole of foot than at other sites.

Table I. Permeability Coefficients of Fentanyl and Sufentanil Through Dermatomed Cadaver Skin (200 μm) at pH 8.0[a]

| | Donor composition | | |
|---|---|---|---|
| | Fentanyl | (Fentanyl + sufentanil) | Sufentanil |
| Permeability × $10^3$ (cm/hr) | | | |
| Fentanyl | 16.8 ± 0.6* | 17.7 ± 0.6 | — |
| Sufentanil | — | 15.7 ± 1.2 | 14.4 ± 1.3* |
| $T_L$ (hr) | | | |
| Fentanyl | 0.23 ± 0.11 | 0.28 ± 0.15 | — |
| Sufentanil | — | 0.37 ± 0.09 | 0.26 ± 0.02 |

[a] Values are the average ± SD of five diffusion experiments.
* $P > 0.05$.

## DISCUSSION

*Permeabilities of Fentanyl and Sufentanil.* Michaels *et al.* (14) long ago demonstrated that the potent narcotic analgesic, fentanyl, permeated human skin with facility and they related this to a high lipophilicity. More recently, we reported that the permeability coefficients of fentanyl and sufentanil were of the same order of magnitude (20). These two compounds are comparable in molecular size and the latter is even more lipophilic (21). In case fentanyl and sufentanil might be coadministered transdermally to achieve a combined effect, but particularly with an eye to gaining in experimental efficiency, their simultaneous permeation rates through human skin were investigated and compared to their independently determined permeation rates. Simultaneous analysis allowed a direct, intraexperimental comparison of their permeabilities but also provided the opportunity to assess if there was interspecies interaction in the course of their joint diffusion. As evident from Table I, no statistically significant differences in the permeability coefficients of fentanyl and sufentanil were observed when the drugs were used alone and in combination. As expected, the diffusion of the individual molecular species was independent. Also, codiffusion was without effect on the diffusion lag times ($T_L$'s). Since their solubilities were the same when cosaturated as when determined independently, there is obviously no appreciable interaction between fentanyl and sufentanil in the aqueous media. Therefore, to maximize the information gained from each run, all further studies were carried out using fentanyl and sufentanil in combination.

Bronaugh and Stewart have indicated that split-thickness dermatomed skin containing full epidermis and part of dermis should be preferred for percutaneous absorption measurements of all compounds (22). At variance with this recommendation, we have consistently used heat-separated epidermis in our laboratories. Therefore, der-

Table II. Permeability Coefficients of Fentanyl and Sufentanil Through Epidermis and Dermatomed Cadaver Skin at pH 8.0

| Drug | Permeability × $10^3$ (cm/hr)[a] | | $T_L$ (hr) | |
|---|---|---|---|---|
| | Epidermis | Dermatomed | Epidermis | Dermatomed |
| Fentanyl | 10.5 ± 1.7 | 10.2 ± 1.0 | 0.3 ± 0.1 | 0.3 ± 0.2 |
| Sufentanil | 11.9 ± 1.9 | 15.7 ± 0.9* | 0.2 ± 0.04 | 0.3 ± 0.3 |

[a] Values are the average ± SD of four or five diffusion experiments.
* $P < 0.05$.

matomed (200-μm) skin was compared to heat-separated epidermis in the present studies to ascertain the effect of membrane preparation on the permeation rates of these narcotics. The permeability coefficient of fentanyl obtained with heat-separated epidermis was not significantly different from that of dermatomed skin. On the other hand, our data suggest that the permeability coefficient of sufentanil through heat-separated epidermis is lower than that of dermatomed skin. At present it is rather difficult to explain this difference given that the heat-separated epidermis has less aqueous tissue mass. Although the difference is statistically significant ($P < 0.05$), the degree of variability in the skin permeability of sufentanil between the skin preparations is itself not unusual, as can be seen from subsequent experiments. The data in Table I also suggest that when the membrane is heat-separated epidermis, the permeabilities of the two drugs are the same. However, considering data from all skins, sufentanil appears to be a slightly better penetrant.

*Influence of pH on Permeation of Fentanyl and Sufentanil.* The ionization of a basic drug in aqueous solution can be represented by

$$BH^+ \Leftrightarrow B + H^+ \tag{3}$$

where $BH^+$ and B are, respectively, the protonated and nonionized free-base form. At equilibrium, the dissociation rate constant ($K_a$) may be written as

$$K_a = \frac{(C_B)(C_{H^+})}{(C_{BH^+})} \tag{4}$$

and

$$C_T = C_B + C_{BH^+} \tag{5}$$

The total flux through skin during the steady state has contributions from both the ionized and the nonionized species in the donor medium. If sink conditions prevail and if the permeation of the ion and neutral species is independent, the total flux $J_T$ can be simply represented by

$$J_T = J_B + J_{BH^+} \tag{6}$$

where $J_B$ and $J_{BH^+}$ are determined strictly by the activities of the respective species in the donor media. It follows that

$$J_B = P_B A C_B \tag{7}$$

and

$$J_{BH^+} = P_{BH^+} A C_{BH^+} \tag{8}$$

where $P_B$ and $P_{BH^+}$ are the corresponding permeability coefficients for the free-base and the ionized forms, and $A$ is the diffusion area. Combining and rearranging Eqs. (4)–(8), the total flux can be written as (14)

$$\frac{J_T}{AC_T} = P_e = \left(\frac{P_B K_a}{C_{H^+}} + P_{BH^+}\right) \Big/ \left(1 + \frac{K_a}{C_{H^+}}\right) \tag{9}$$

where $P_e$ is the effective permeability coefficient.

The permeability coefficients of the free-base and cationic species of a weak electrolyte permeant through skin can be calculated from Eq. (7) if the $pK_a'$ of the drug and the hydrogen ion concentration is known. The $pK_a'$ values of fentanyl and sufentanil determined in aqueous solution are 8.99 and 8.51, respectively (16). At pH ≈ 3, when the fraction ionized is more than 99.9%, the effective permeability coefficient of both drugs is due mostly to the protonated species. Therefore, the experimentally determined permeability coefficients at this pH approximate to the $P_{BH^+}$'s (Table III). The permeability coefficients of free-base forms ($P_B$'s) at pH 9.0 were then calculated from Eq. (7). This rough means of estimating these pure parameters was based on the assumption that the integrity of the skin was not altered at the extremes of pH, pH 3 and 9, as has been our general observation. The permeabilities of ionized and nonionized species are summarized in Table VI. The contributions of the ionized forms to the total permeabilities of these drugs are so small that one can safely say that the free-base forms are almost entirely responsible for their per-

Table III. Permeability Coefficients of Fentanyl and Sufentanil Through Epidermis and Stripped ($n$ = 25) Cadaver Skin at pH 8.0

| Drug | Permeability × $10^2$ (cm/hr)[a] | | $T_L$ (hr) | |
|---|---|---|---|---|
| | Epidermis | Stripped | Epidermis | Stripped |
| Fentanyl | 0.30 ± 0.11 | 20.2 ± 2.7* | 0.24 ± 0.4 | 0.16 ± 0.1 |
| Sufentanil | 0.55 ± 0.15 | 20.1 ± 2.6* | 1.5 ± 0.4 | 0.23 ± 0.1 |

[a] Values are the average ± SD of four or five diffusion experiments.
* $P < 0.05$.

Table IV. Permeation of Fentanyl and Sufentanil Through Dermatomed Cadaver Skin[a] as a Function of pH at 37°C

| pH | Permeability × $10^3$ (cm/hr)[b] | |
|---|---|---|
| | Fentanyl | Sufentanil |
| 2.88 | 0.30 ± 0.04 | 0.46 ± 0.05 |
| 5.08 | 1.3 ± 0.3 | 2.5 ± 0.1 |
| 6.02 | 5.1 ± 0.8 | 6.2 ± 1.1 |
| 6.95 | 7.1 ± 0.7 | 10.1 ± 0.6 |
| 7.43 | 12.7 ± 3.0 | 15.7 ± 0.8 |
| 7.95 | 22.4 ± 1.7 | 23.1 ± 1.6 |
| 8.52 | 27.6 ± 2.3 | 29.8 ± 3.7 |
| 9.04 | 34.9 ± 6.3 | 34.5 ± 2.5 |
| 9.37 | 32.9 ± 6.3 | 33.7 ± 6.7 |

[a] Site, thigh.
[b] Values are the average ± SD of four or five diffusion experiments for a given pH.

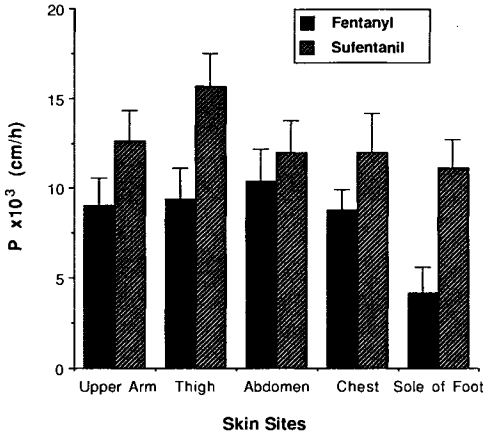


Fig. 1. Permeability coefficients of fentanyl and sufentanil free base through human skin obtained from various anatomic sites of cadaver skin *in vitro* at 37°C.

meation through skin. In fact, by the above approximate estimates, the free-base forms of fentanyl and sufentanil are 218 and 100 times more permeable than their ionized forms, respectively. While the permeability drops off more or less steeply as ionization of fentanyl and sufentanil is induced, there is still measurable flux at the lowest pH studied. These data suggest that the polar pathway is also available for the permeation of ions, albeit to a far lesser extent.

An alternative way of analyzing present data is to plot log ($P/P_{max}$) versus (pH − $pK_a'$) as shown in Figs. 2A and B, where $P_{max}$ is the experimentally determined maximum skin permeability of ionized and nonionized species and $P/P_{max}$ represents the permeability efficiency of a drug. The permeability coefficients increase exponentially as the fraction nonionized increases. Although the fraction ionized increases as the pH of the solution increases, further flux of this drug is limited by its solubility and the plateau is reached beyond pH 9. Similar pH dependencies in the permeation of weakly basic and acidic drugs through skin have been noted previously (14,17,18).

*Permeability as a Function of Different Anatomic Sites and Donor Samples.* Site dependencies associated with the *in vivo* permeation of organic compounds through human skin have previously been reported (23–25). For example, Rougier *et al.* have demonstrated that the *in vivo* permeation of caffeine, benzoic acid, and acetylsalicylic acid appears to be site dependent, with the forehead being the most permeable site of those tested with these compounds. Also, the *in vivo* permeation of scopolamine through human skin varies with anatomic site (25). In contrast with past results on live skin, in our studies, the *in vitro* permeation rates of fentanyl and sufentanil through different sites of skin showed little variation. The permeability of fentanyl through the sole of the foot was lower than for other studied sites of skin, but only by about half (Fig. 1). Since these drugs are quite permeable because their high lipophilicities and consequently favorable partitioning in the stratum corneum, their *in vitro* permeation rates through cadaver skin are relatively uninfluenced by site. This result, if reproduced *in vivo,* suggests

Table V. Permeability Coefficients of Fentanyl and Sufentanil Through Heat-Separated Epidermis at pH 7.4 (37°C)

| Donor (age/sex/race) | Site | $n$[a] | Permeability × $10^3$ (cm/hr) | | Ratio[b] |
|---|---|---|---|---|---|
| | | | Fentanyl | Sufentanil | |
| 1 (M/87/W) | Thigh | 4 | 10.2 ± 1.0 | 15.7 ± 0.9 | 1.54 |
| 2 (M/80/W) | Thigh | 4 | 9.4 ± 1.7 | 15.6 ± 1.9 | 1.66 |
| 3 (M/78/W) | Thigh | 4 | 17.5 ± 1.5 | 20.9 ± 1.4 | 1.20 |
| 4 (M/65/W) | Abdomen | 4 | 5.5 ± 0.9 | 12.4 ± 1.1 | 2.21 |
| 5 (M/NA[c]/W) | Thigh | 4 | 16.1 ± 0.6 | 23.3 ± 1.2 | 1.45 |
| 6 (M/18/W) | Abdomen | 5 | 13.6 ± 2.6 | 15.2 ± 2.9 | 1.12 |
| 7 (F/57/W) | Thigh | 5 | 3.0 ± 1.1 | 5.5 ± 1.5 | 1.83 |
| 8 (F/10/B) | Abdomen | 4 | 11.7 ± 1.2 | 17.4 ± 1.8 | 1.49 |
| 9 (F/66/W) | Abdomen | 5 | 15.2 ± 1.8 | 16.6 ± 1.7 | 1.10 |
| 10 (F/76/W) | Abdomen | 5 | 13.9 ± 3.4 | 16.3 ± 3.8 | 1.17 |
| 11 (F/24/B) | Abdomen | 4 | 8.0 ± 1.9 | 8.4 ± 1.7 | 1.05 |
| Mean | | | 11.3 | 15.2 | 1.43 |
| SD | | | 4.5 | 5.0 | 0.34 |

[a] Number of diffusion experiments.
[b] Sufentanil/fentanyl.
[c] Not available.

Table VI. Drug Fluxes Through Cadaver Skin *in Vitro*

| Drug | Permeability × $10^3$ (cm/hr) | |
|---|---|---|
| | Base form | Ionized form |
| Fentanyl | 65.6 | 0.30 |
| Sufentanil | 45.9 | 0.46 |

that transdermal patches of these drugs can be applied to any convenient body surface.

The permeability coefficients of fentanyl and sufentanil through skin obtained from different cadavers are summarized in Table V. Although a relatively small number of cadaver skin samples ($N$ = 11) was investigated, no trend in the permeation of these drugs as a function of age and gender was observed. These results are in close agreement with previous studies (26) involving *in vitro* permeation of water as a function of age, gender, and race.

The point of the study was to establish the best conditions for transdermal delivery systems of fentanyl and sufentanil. Not surprisingly, the free-base form is the permeable

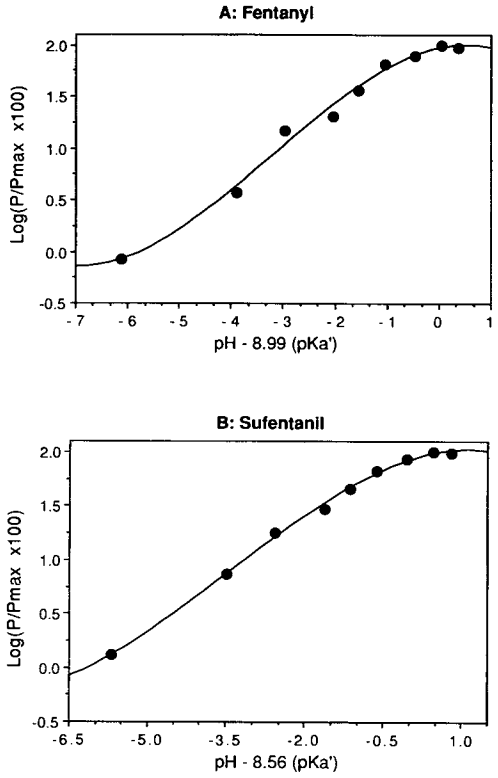


Fig. 2. Relationship of the relative permeability to the bulk pH for fentanyl (A) and sufentanil (B). The relative permeability is expressed as the logarithm of the percentage the permeability coefficient at a given pH is to that at the highest pH, where the value is maximal. These permeability coefficients were calculated from fluxes from saturated solutions without regard to the degree of ionization of the drugs at the specified pH's.

form of each drug. The results of the study continue to point to the feasibility of delivering these drugs at rates consistent with the requirements of pain therapy (14,20). Moreover, it appears that the site which might be chosen to apply the envisioned transdermals is a matter of convenience.

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