Etorphine Is an Opiate Analgesic Physicochemically Suited to Transdermal Delivery

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INTRODUCTION

Pain is an unavoidable symptom for most patients suffering terminal forms of cancer. A goal of therapy for such patients is to provide relief of the pain and at the same time allow the patient to function normally. The mainstay of pain management is the narcotic analgesics. However, when given orally, narcotics require frequent dosing and undergo severe first-pass metabolism (1,2); in some patients they induce nausea and vomiting, and in others, constipation (1–3). Irrespective of how given, narcotics have short durations of action. The maintenance of a pain-free state with discrete dosages is thus accompanied by intense, cyclical variations in blood levels. Early in the cycle the drugs leave patients somnolent and may even depress respiration. Later, pain breaks through. Further, since narcotics are addictive, they tend to be used sparingly and in less than optimum amounts even when treating the terminally ill (1–4). A means of sustained delivery capable of leveling swings in serum levels offers advantage over current therapy. However, continuous intravenous administration is hardly the answer, as it too is beset with problems. Therefore, an alternative means of administering these drugs to achieve protracted pain relief with minimal side effects is desirable. Transdermal delivery fulfills these requirements, and patches are being developed to deliver the opioid, fentanyl, for cancer pain management. We report here on the feasibility of transdermally delivering the opiate, etorphine.

The feasibility of delivering a narcotic transdermally rests on its skin permeability (5–7) and on its local toxicity. Relationships between skin permeability coefficients and *in vitro* partition coefficients (7,8) establish the principle transport phase of the stratum corneum as a lipoidal phase, and one previous report describes its barrier function for narcotics (9). Fentanyl and sufentanil can be delivered through the skin based on their physicochemical properties and low dose (9,10). Because etorphine is ~10,000 times more potent than morphine, this drug, too, augers as a compound of transdermal utility. It has already been successfully tested for pain control by intramuscular injection (11,12). Its low toxicity against selected mammalian cell lines relative to other narcotics tested (13) heightens interest in its transdermal delivery.

MATERIALS AND METHODS

Skin Permeation Studies. In vitro studies were performed to measure quantitatively the permeability coefficient of etorphine hydrochloride through skin tissue. Excised skin from hairless mice (SKH-hr-1 strain supplied by Skin Cancer Hospital, Temple University, Philadelphia, PA), 120 to 150 days old, was mounted between the donor and the receiver reservoirs of a diffusion cell. Large areas of abdominal and dorsal skin of the mouse were blocked out into a total of six square sections. Each section was excised with surgical scissors; adhering fat and other visceral debris were removed carefully from the undersurface with a scalpel. Alternatively, human abdominal cadaver skin, obtained at autopsy, was stored in a −20°C freezer and then thawed at room temperature as needed.

The skin sections were mounted carefully between the half-cells of diffusion cells (SIDE-BI-SIDE DC-100B, Crown Glass Co., Inc., Somerville, NJ). Each half-cell had a 3-ml capacity and was individually jacketed. Water maintained at 37°C within a circulating temperature bath was passed through the jackets to keep each total cell at an even temperature. Stirring of the medium within each chamber was achieved by magnetic stirring bars placed in cylindrical depressions within the cell chambers near their openings. Each chamber was fitted with a glass-stoppered sampling port at its top for the addition or removal of medium within the chamber.

After the receiver compartments were filled with 2.8 ml of isotonic TRIS buffer (1.21%, 0.1 *M* in 0.6% NaCl) at pH 7.4 (ionization approximately 30% at pH 7.4, 37°C, $pK_b \approx 7.8$), 2.8 ml of [^{3}H]etorphine · HCl solution (radioactivity, 0.125 μCi/ml; Amersham, Allington Heights, IL) in this same buffer (100 μl of etorphine hydrochloride stock solution in ethanol evaporated to dryness and then reconstituted in 18 ml of buffer) was added to the donor compartment. The pH of the donor solution measured 7.3; the slight pH differential between the donor and the receiver was ignored. The cell contents were stirred at 150 rpm. At predetermined times, 1-ml samples were withdrawn from the receiver compartment and transferred to scintillation vials for determination of radioactivity. To maintain the same volume on the receiver compartment, 1 ml of Tris buffer was added after each sample was withdrawn. Concentrations of etorphine in the samples as a function of time were determined after making adjustments for dilution occasioned by sampling.

The data obtained from experiments were plotted as the cumulative disintegrations per minute collected in the receiver compartment as a function of time. The permeability coefficient for a given experiment was calculated from the average rate of change in amount penetrating the membrane,

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Table I. *In Vitro* Permeability Data for Etorphine, Indicating Average Permeability Coefficients and Lag Times for the Respective Runs

Type of skin	No. of diffusion cells	P (cm/hr)	T_L (hr)
1. Mouse	6	$2.9\ (\pm 0.6) \times 10^{-3}$	3.6 ± 1.5
2. Mouse	5	$4.6\ (\pm 1.0) \times 10^{-3}$	2.9 ± 2.4
3. Mouse	6	$3.5\ (\pm 0.4) \times 10^{-3}$	3.7 ± 1.4
4. Cadaver	6	$3.6\ (\pm 0.9) \times 10^{-3}$	3.1 ± 1.3

dM/dt, over the period of 4 to 24 hr, a period of relatively steady flux, using Fick's law:

$$\frac{dM}{dt} = J_T = P \cdot A \cdot \Delta C \qquad (1)$$

where $dM = V \cdot dC$ is the incremental amount of etorphine penetrating per unit time, dt, after the permeation has reached a steady state. The ratio, J_T, is thus the pseudo-steady-state flux (μg/hr) across the skin; P is the permeability coefficient (cm/hr); A is the area between compartments available for diffusion, 0.64 cm^2 in the present study; and ΔC is the concentration differential across the membrane, which was taken to be the donor phase concentration. All concentrations are expressed in units of disintegrations per minute per cubic centimeter.

The following equation, based on the estimated permeability and the saturation concentration, was used to get the maximum daily amount which can be delivered per unit area (milligrams):

$$M_{24} = P \cdot C_s \cdot 24 \qquad (2)$$

where M_{24} is in milligrams per day, P is in centimeters per hour, C_s is in milligrams per milliliters and there are 24 hr/day. This rate per unit area is then divided into the daily dose to estimate the size patch which would be needed to deliver a therapeutically adequate quantity of etorphine.

Solubility Measurement. An excess of cold etorphine cocrystallized with tritium-labeled etorphine was equilibrated with citrate–phosphate buffer (pH 7.4) at 25°C. The buffer was prepared from stock solutions containing 0.1 *M* citric acid and 0.2 *M* Na_2PO_4, respectively. Ten milliliters of the citric acid solution was added to 90 ml of the sodium phosphate solution to prepare 100 ml of buffer at pH 7.4. Sufficient time was allowed for the solution medium to reach equilibrium with the suspended solid, then the slurries were filtered (Millipore, 0.45 μm) and the radioactivity of the clear supernatant was measured.

RESULTS

The cumulative amounts of etorphine penetrated through the hairless mouse skin (or cadaver membranes) were plotted as a function of time, and steady-state fluxes were determined from the slopes using linear regression analysis. Correlation coefficients ranged from 0.96 to 0.986. Lag times were calculated by extrapolating the steady-state curves to the time axis. Results of these determinations are summarized in Table I. The permeability coefficients were calculated using Eq. (1). Similar values were obtained for the permeability coefficients of hairless mouse and human cadaver skin. Irrespective of skin type, the steady-state phase occurred between 6 and 9 hr. The average lag time, T_{Lag}, for the three mouse experiments was 3.5 hr, hardly different from the 3.1 hr seen with human skin.

The independently determined solubility of etorphine in citrate–phosphate buffer at pH 7.4 was 0.218 mg/cm^3. The octanol/water partition coefficient (K_p) of etorphine at pH 7.4 was determined to be 13.

DISCUSSION

Based on past experience, the permeability coefficient of mouse skin was expected to be higher than for human cadaver skin, but this was not observed for the one section of cadaver skin studied. The absolute values are high in both instances, suggesting the compound has near-optimum physicochemical properties for a skin penetrant of such size (molecular weight of the free base, 411.52). This finding surprised us considering the relatively high melting point of etorphine, 215°C. In the past melting and partition coefficients appeared highly correlated, as, to some extent, both reflect hydrophobicity. Etorphine seems to break from this pattern. Thus the concern expressed in the literature about toxicity of etorphine splashed on the skin may be valid.

As shown in Table II, our results indicate etorphine has a permeability similar to meperidine and fentanyl and superior to morphine and its analogues. The opiates have shown little promise for transdermal delivery because their required doses are large and inconsistent with their low innate abilities to permeate skin (9). Etorphine is an exception by rea-

Table II. *In Vitro* Permeability Data Obtained on Human Cadaver Skin for Etorphine and Six Other Narcotics[a]

Drug	$J_{\text{saturated solution}}$ (μg/cm^2/hr)	P (cm/hr)	T_L (hr)	K_p (octanol/water)
Sufentanil	0.40 ± 0.06	$1.2\ (\pm 0.1) \times 10^{-2}$	2.0 ± 0.8	2840
Fentanyl	0.26 ± 0.05	$5.6\ (\pm 0.9) \times 10^{-3}$	1.9 ± 0.8	717
Meperidine	0.60 ± 0.14	$3.7\ (\pm 0.9) \times 10^{-3}$	1.2 ± 0.2	38.9
Etorphine	0.79 ± 0.20	$3.6\ (\pm 0.9) \times 10^{-3}$	3.5 ± 1.7	13.0
Codeine	0.09 ± 0.04	$4.9\ (\pm 1.2) \times 10^{-5}$	7.6 ± 1.3	2.95
Hydromorphone	0.032 ± 0.006	$1.5\ (\pm 0.2) \times 10^{-5}$	9.9 ± 2.4	1.28
Morphine	0.006 ± 0.002	$9.3\ (\pm 3.6) \times 10^{-6}$	5.2 ± 2.4	0.70

[a] Literature data from Refs. 9 and 14.

son of its low dose and relatively high partition coefficient, with attending high permeability. The listed partition coefficients for all compounds in Table II were measured at pH 7.4, and thus none are the intrinsic partition coefficients of the respective free bases. Nevertheless, permeabilities and partition coefficients are in the exact same rank order.

Using the solubility and permeability coefficient determined in this work, the size of a patch needed to deliver etorphine would be of the order of 50 cm^2, using 1 mg as the probable total daily dose. This size is calculated from the equation

$$\text{Area} = \frac{1}{C_s \cdot P \cdot 24} \tag{3}$$

where C_s is the total solubility of etorphine (mg/cm^3) at pH 7.4, P is the permeability (cm/hr) at the same pH, and 24 is the hours per day. While 50 cm^2, of itself, is not altogether too large, the size of the patch might be greatly reduced through judicious formulation and choice of enhancers. Thus, because of etorphine's extreme potency, relatively low cytotoxicity *in vitro* (13), and facility in permeating the skin, etorphine appears to be a favorable candidate for transdermal delivery.

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