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Controlled buccal delivery of buprenorphine

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Buprenorphine is a potent opiate agonist-antagonist used in the treatment of both acute and chronic pain. Like many opiates, it has low oral bioavailability due to both presystemic metabolism in the wall of the gastrointestinal tract and extensive first pass metabolism. Controlled delivery of analgesics results in good pain relief and a lower total requirement for the drug. Buccal delivery offers advantages in terms of accessibility, avoidance of first pass metabolism and the ability to provide controlled delivery for extended periods of time. Buccal permeation of buprenorphine was measured in vitro and in vivo in the dog model using prototype non-woven and hydrogel systems. The fluxes of drug were identical from solutions and from non-woven systems in vitro, providing a reliable way of applying a drug solution to the mucosa without leaking. A model is described that permits screening of potential buccal systems in vitro to select a system for in vivo use. In vivo, steady-state plasma levels were obtained using both non-woven and hydrogel systems. Steady state was attained in 1 to 1.5 h and was maintained during the time of application of the system. Assuming that the flux in man is similar to that in the dog, controlled buccal delivery of buprenorphine would provide adequate analgesia over an extended period of time.

Key words: Buccal; Buprenorphine; Analgesia; Controlled delivery; Hydrogels

Introduction

Buprenorphine, an opiate agonist-antagonist with 20 to 40 times the potency of morphine [1], is used in the treatment of both acute and chronic pain [2,3]. Like many opiates, it is extensively metabolized in both the gastrointestinal (GI) tract and the liver [4,5] and is therefore a poor candidate for oral delivery. It is currently administered as repeated intravenous or intramuscular injections and as a sublingual tablet. In the control of pain, it has been reported that administration of an analgesic at a constant rate results in both optimal patient comfort and a reduced total amount of analgesic [6]. Controlled delivery of buprenorphine may therefore, offer advantages in pain management.

The buccal route offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic metabolism in the GI tract are avoided. The area is obviously very accessible for placement and removal of a delivery device. Polymeric systems with an impermeable backing could deliver drug in a unidirectional fashion to the mucosa and avoid loss due to swallowing. The ultimate aim would be to develop a small, thin, flexible device

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that would adhere to the mucosa during normal activities, including eating and drinking. Buccal delivery also offers the advantage of rapid absorption, which would obviously be necessary in the control of pain, and buprenorphine is known to be efficacious as a sublingual tablet [7]. The use of a device that provides rapid, long-lasting and adequate pain control by noninvasive means could offer considerable advantages in pain management.

In the present study, the buccal absorption of buprenorphine was assessed in vitro in modified Ussing chambers [8]. Three different prototype systems, one non-woven and two hydrogels of varying water content, were assessed in vitro and in vivo in the dog. Hydrogels have previously been used for the buccal delivery of diclofenac sodium in both the dog and man [9,10], and similar fluxes were measured in both species. Preliminary results of the current studies have been presented [11,12].

Materials and Methods

Materials

Buprenorphine hydrochloride was obtained from Diosynth (Bensenville, IL) and was used without further purification. Radioimmunoassay (RIA) kits were purchased from Diagnostic Products Corporation (Los Angeles, CA). *t*-Butyl peroctoate was from Pennwalt, Buffalo, NY, 2-hydroxyethyl methacrylate (HEMA, Lot #64622) was obtained from Polysciences, Inc., Warrington, PA, and monomer:macromer mix was kindly supplied by Dr. K. F. Mueller of Central Research, Ciba-Geigy Corporation, Ardsley, NY. All other reagents were of HPLC or analytical grade and were used as purchased.

Methods

Analytical methodology

HPLC. Buprenorphine was quantitated by reverse phase high performance liquid chromatography (HPLC) on a C-18 column (3 cm, 3 μm particle size; Perkin-Elmer, Norwalk, CT) with fluorescence detection using an excitation wavelength of 213 nm and a 360 nm emission cut-off filter. The mobile phase (60/40 acetonitrile / 0.01M KH_2PO_4, 0.01% TEA, adjusted to pH 3 with phosphoric acid) was pumped isocratically at a flow rate of 1.5 ml/min. Standards were made up in the same solution as the samples being assayed. The standard curve was linear over the concentration range 25 ng/ml to 20 μg/ml, using an injection volume of 15 μl.

RIA. Buprenorphine in Tris-phosphate saline [13] was measured using a modification of a commercially available kit. Briefly, 50 μl of sample (or standard) was incubated with 100 μl of [^{125}I]buprenorphine and 100 μl of antiserum at room temperature for 1 h. Separation of antibody-bound from free buprenorphine was accomplished by the addition of a second antibody (goat anti-rabbit gamma-globulin), and centrifugation at 25°C (1500×*g* for 30 min). The pellet, containing antibody-bound material, was counted using a gamma counter (Minaxi Gamma Model 5000, Packard Instrument Company, Downers Grove, IL). The amount of buprenorphine was calculated from the standard curve which ranged from 0.05 to 15 ng/ml. Samples were assayed undiluted or at a dilution of 1:5 or 1:20. The assay was validated at all dilutions studied and stability of buprenorphine was confirmed in buffer stored at −70°C for up to 21 days prior to analysis.

Solubility of buprenorphine hydrochloride

The solubility of buprenorphine HCl was determined by the addition of excess drug to either phosphate buffers [14,15] or physiological buffer (Tris-phosphate saline) with initial pH values between 4 and 8. The vials were capped, vortexed and placed in a shaking water bath at 25°C for 24 h. 1.5 ml of solution was removed, centrifuged in a microfuge (Model 235B, Fisher Scientific, Springfield, NJ) at 15000×*g* for 2 min at room temperature and diluted for determination of buprenorphine by HPLC. The pH of the solutions was measured to give the final pH of the solutions.

Buprenorphine flux across buccal mucosa in vitro

Male New Zealand White rabbits (2–4 kg) were sacrificed by carbon dioxide inhalation and beagle dogs of either sex (7–11 kg) were sacrificed by an intravenous overdose of Nembutal® and exsanguination. All animal experimentation was performed according to protocols approved by Ciba-Geigy's Animal Care Committee. Buccal tissue was removed by blunt dissection, separated from underlying muscle, rinsed in buffer and mounted in modified Ussing chambers (WPI, Sarasota, FL). Equilibration was in 10 ml Krebs-Henseleit buffer [16], containing 10 mM glucose. The pH was maintained at 7.4 by bubbling with 95% O_2/5% CO_2 and the temperature was maintained at 37°C by water-jacketing. The tissue was equilibrated for 30–60 min before drug donor solution was added to the mucosal side and fresh buffer was added to the serosal side. Samples (0.5 ml) were taken at intervals from the serosal side and the volume replaced with buffer. Samples were assayed for buprenorphine content by RIA or HPLC. Due to the low solubility of buprenorphine at neutral pH, some flux studies were performed at pH 4 using Tris-phosphate saline buffer. To monitor tissue viability, transepithelial potential difference and short-circuit current were measured by salt bridges of 2% agar in Krebs-Henseleit buffer in contact with Ag/AgCl electrodes connected to a voltage current clamp (DVC-1000, WPI, Sarasota, FL) via a preamplifier.

Preparation of hydrogel discs

The hydrogels were prepared by copolymerization of HEMA with a macromer synthesized by the reaction of polytetramethylene glycol (Polymeg®) with isophorone diisocyanate in a 1:2 ratio [17]. Both 90:10 (monomer:macromer, wt/wt) and 80:20 hydrogel systems were assessed. 90:10 and 80:20 hydrogels were prepared by the addition of HEMA to a 70:30 monomer:macromer mixture. After degassing for 30 min, 0.2 wt% of *t*-butyl peroctoate was added as initiator. The solution was placed between two Mylar®-covered glass plates with the appropriate Teflon® spacer around the perimeter. The polymer was crosslinked by placing the mold at 80°C for 1 h. After cooling, the polymer was removed and washed with 5 changes of 8 l of distilled water. Discs were punched from the water-washed polymer, and remaining monomer was removed by Soxhlet extraction in ethanol overnight. The extracted discs were dried in a vacuum oven at 45°C for 24 h.

For drug loading, the dried discs were weighed, placed in a solution of buprenorphine HCl (15 wt% in 70% ethanol/30% 0.01 M KH_2PO_4, pH 4) and stirred at 45°C for 72 h. The loaded systems were removed, rinsed briefly in 70% ethanol and dried for 48 h at room temperature in a vacuum desiccator. Before use, the systems were placed in a 95% humidity chamber for 48 h at room temperature.

Dissolution testing

The release profiles of the systems were determined using dried discs in a standard dissolution apparatus with stainless steel baskets (Vanderkamp 600, Van-Kel Industries, Chatham, NJ). Dissolution was determined in 500 ml of distilled water at 32°C. At various time intervals, 0.8 ml of the solution was withdrawn from the reservoir and assayed for buprenorphine content by HPLC.

Systems application in vitro

The fluxes of buprenorphine across canine buccal mucosa were measured from both non-woven and hydrogel discs in vitro. Buprenorphine (220 µl of 10 mg/ml buprenorphine hydrochloride in 10 mM KH_2PO_4) was pipetted onto the surface of the non-woven material. The system was applied to the buccal mucosa and mounted in the Ussing chamber. Hydrogel discs, prepared as described above, were applied to the mucosal surface, backed with Parafilm® and mounted in the Ussing chamber. In all experiments, the total exposed surface area was 1 cm^2.

Buccal absorption in vivo

Beagles (7–11 kg) of either sex were fasted overnight and had free access to water until the time of experimentation. They were anesthetized with sodium pentobarbital (approximately 25 mg/kg) via a 22 G Abbocath® in the cephalic

vein and additional doses were administered to maintain anesthesia during the course of the experiment. Cannula patency was maintained with an i.v. drip of sterile lactated Ringers (1 ml/min). Blood samples (3 ml) were drawn into heparinized Monoject® syringes and plasma, obtained following centrifugation ($2000 \times g$ for 10 min), was placed in microfuge tubes and frozen in a dry ice-ethanol bath. Samples were stored for up to 3 weeks at $-70°C$.

To determine the i.v. pharmacokinetics of buprenorphine, a 0.30 mg bolus of buprenorphine HCl in 1.5 ml of lactated Ringers solution was injected through a second catheter placed in the saphenous vein. The bolus was followed by 5 ml of lactated Ringers to insure injection of the total dose. Plasma samples were obtained over a 4 h period and assayed for buprenorphine content by RIA. The fit of the plasma profile to a biexponential equation was modelled using R-Strip (Micromath, Inc.) with a y^2 weighting, and pharmacokinetic parameters were determined for each animal.

To determine buccal delivery of buprenorphine, beagles were anesthetized as described above, and a zero time blood sample was taken. The inner cheek was blotted dry with gauze, the appropriate device(s) was placed on the cheek and the area covered by an impermeable backing membrane held in place by a peripheral adhesive (Super Polygrip, Dentco, Inc., Jersey City, NJ). The device was left in position for 2 to 4 h. Blood samples were taken at intervals during the application of the device and after its removal. All plasma samples were assayed for buprenorphine content by RIA. Results are expressed as the mean ± 1 SEM.

Results

Solubility of buprenorphine hydrochloride

At the end of the 24 h incubation period all vials contained undissolved material which was removed by centrifugation. The solubility of buprenorphine was highly pH dependent with the highest solubility seen at low pH (17.3 mg/ml at pH 4.2). The solubility at neutral pH was considerably lower (52 μg/ml at pH 7.3) (Fig. 1). Essentially, similar solubilities were measured in USP, phosphate, and physiological (TPS) buffers, except at pH 4.2 when the solubility was considerably lower in TPS (4.2 mg/ml).

Buprenorphine flux across buccal mucosa in vitro

The flux of buprenorphine in vitro was measured across buccal mucosa obtained from both rabbit and dog. The donor solutions were at saturation (4.3 mg/ml) in TPS buffer, adjusted to pH 4 with isotonic citric acid. Steady-state fluxes were calculated by linear regression using the asymptotic region of the cumulative amount/time curve and the time lag (to steady-state) was determined from the intercept on the abscissa. The steady-state fluxes and time lags were 4.2 ± 0.6 μg/cm^2/h and 2.7 ± 0.1 h ($n=6$) in the rabbit and 22.3 ± 6.0 μg/cm^2/h and 1.6 ± 0.4 h ($n=4$) in the dog, respectively. In the rabbit, steady-state flux was linearly related to donor concentration over the range 0.04 to 4.3 mg/ml (Fig. 2, $r=0.998$). The addition of sodium azide (10 mM), a metabolic inhibitor, to the mucosal solution at the same time as the drug caused the abolition of the transepithelial potential difference and an approximately 10-fold increase in the flux of buprenorphine, with no attainment of steady-state within the experimental time period.

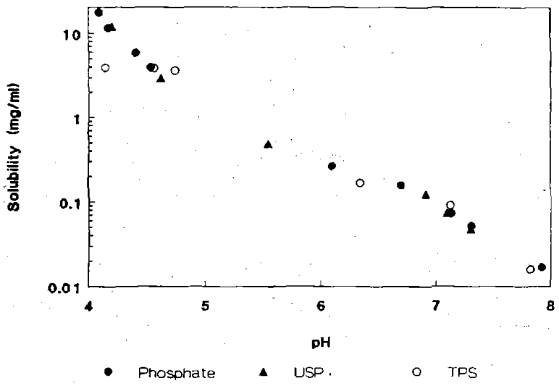

Fig. 1. Solubility of buprenorphine hydrochloride in phosphate, USP phosphate and physiological (TPS) buffers.

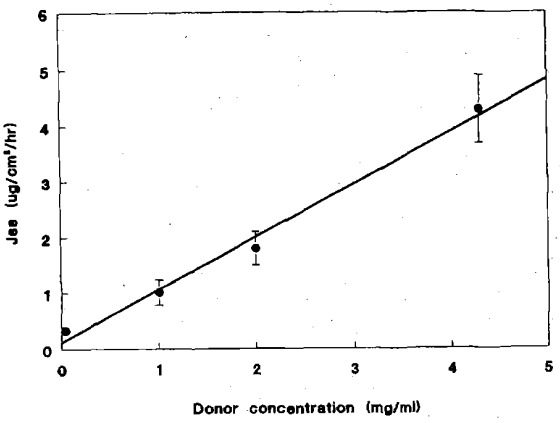

Fig. 2. Relationship between donor concentration and steady-state flux of buprenorphine across rabbit buccal mucosa in vitro. The number of experiments was between 4 and 6.

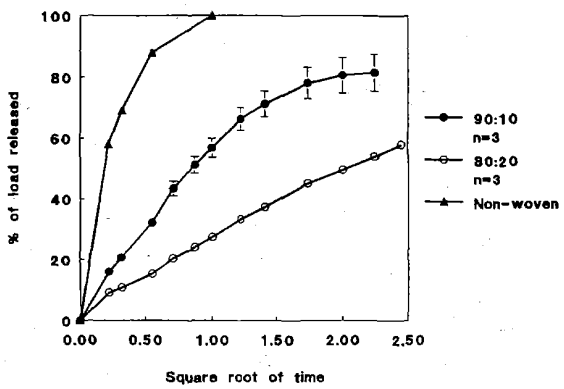

Fig. 3. Dissolution of buprenorphine from non-woven and hydrogel systems as a function of the square root of time in hours.

Dissolution of buprenorphine from systems

The hydrogel discs were 1.9 cm^2 and 0.138 mm thick. The release profiles of buprenorphine from 90:10 and 80:20 hydrogel discs were linear with the square root of time for 1 and 2 h, respectively (Fig. 3). The release rates were 432 ± 25 and 173 ± 5 $\mu g/cm^2/h^{-1/2}$ for the 90:10 and 80:20 discs, respectively ($n=3$, for each system).

Drug release from these monoliths that are initially swelled with water may be described by the equation:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8 \exp(-D[2n+1]^2\pi^2 t/L^2)}{(2n+1)^2\pi^2} \qquad (18)$$

where: M_t = total amount of drug released at time t, M_∞ = total drug loaded into hydrogel, D = drug diffusion coefficient, and L = thickness of hydrogel.

The diffusion coefficient for buprenorphine can be calculated using an early time approximation of the above equation:

$$\frac{M_t}{M_\infty} = 4\frac{(Dt)^{1/2}}{\pi L^2}$$

This equation is accurate to within 1% for $M_t/M_\infty < 0.6$.

The diffusion coefficients for buprenorphine were $6.6 \pm 0.72 \times 10^{-5}$ and $2.2 \pm 0.14 \times 10^{-6}$ cm^2/h for the 90:10 and 80:20 hydrogels, respectively.

Flux from systems in vitro

Steady-state flux across dog buccal mucosa from a solution of buprenorphine (10 mg/ml in 10 mM KH_2PO_4, pH 4) was 87.1 ± 30.3 $\mu g/cm^2/h$ with a time lag of 1.3 ± 0.33 h, $n=7$ (Fig. 4). The permeability coefficient was $2.42 \pm 0.84 \times 10^{-6}$ cm/s. The steady-state flux from the same solution loaded onto a non-woven chamber was 78.7 ± 26.4 $\mu g/cm^2/h$ with a time

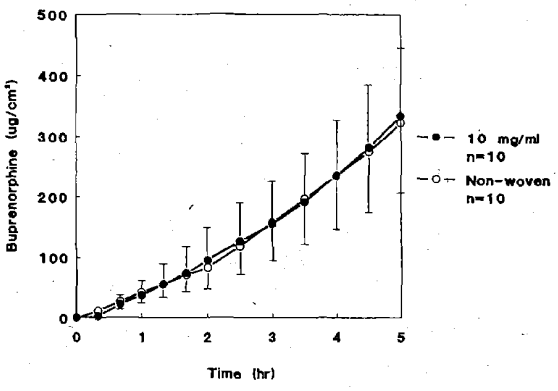

Fig. 4. Cumulative flux of buprenorphine across dog buccal mucosa from a solution of 10 mg/ml ($n=10$) and from 220 μl of a 10 mg/ml solution loaded on to a non-woven system ($n=10$).

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