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Report

Improved Buccal Delivery of Opioid Analgesics and Antagonists with Bitterless Prodrugs

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Buccal delivery of opioid analgesics and antagonists is a useful way of improving bioavailability relative to the oral route. These compounds taste bitter, however. Various prodrugs of nalbuphine, naloxone, naltrexone, oxymorphone, butorphanol, and levallorphan, in which the 3-phenolic hydroxyl group was esterified, lacked a bitter taste. This taste difference was not due to differences in water solubility, suggesting that for these compounds the phenolic functional group is important for interaction with the taste receptor. In rats, nalbuphine, naloxone, and naltrexone administered buccally as prodrugs exhibited up to 90% bioavailability. In dogs, the bitter taste of buccally administered nalbuphine and naloxone caused salivation and swallowing, and bioavailability was low. Buccal dosing of the prodrugs of these compounds caused no adverse effects and the bioavailability ranged from 35 to 50%, a significant improvement relative to the oral bioavailability, which is 5% or less. The feasibility of buccal prodrug delivery using an adhesive patch formulation was demonstrated.

KEY WORDS: buccal absorption; opioid analgesics; narcotic antagonist; prodrug; taste; nalbuphine.

INTRODUCTION

A characteristic feature of the 3-hydroxymorphinan opioid analgesics and antagonists is their low oral bioavailability and high first-pass metabolism. This limits the usefulness of oral administration for most of these compounds. Bioavailability can be substantially improved, however, by buccal or sublingual dosing, because when administered by these routes the drug is not exposed to the metabolic enzymes of the intestines and liver during absorption. For example, in rats the buccal bioavailability of nalbuphine was as high as 60% of the dose, whereas the oral bioavailability was less than 1% (1). Similarly, oral bioavailability of the opioid antagonists, naloxone and naltrexone, was less than 1% in rats, but buccal bioavailability was approximately 70% (2). Sublingual buprenorphine bioavailability in postoperative patients was reported to be 50–60% (3). Buccal morphine bioavailability and postoperative analgesia scores were equivalent to those for intramuscular morphine (4).

Discomfort due to bitter taste was a common complaint from patients administered morphine buccally (5). Various other structurally similar opioid analgesics and antagonists also taste bitter. This characteristic could preclude buccal and sublingual administration. Therefore, we undertook studies to find a way to deliver opioid analgesics and antagonists buccally or sublingually, and to retain a high bioavailability, but without a bitter taste.

Taste is a physiological response that occurs when a chemical taste stimulant interacts with a taste receptor. When the stimulant concentration at the surface of the taste receptor exceeds a certain threshold concentration, a taste is perceived (6). One approach that has been used to mask unpleasant taste is to administer the drug in an insoluble form so that the solution concentration cannot exceed the threshold taste concentration. For example, hydrophobic ester prodrugs of bitter antibiotics were used to reduce their bitterness so that they could be used in oral liquid pediatric formulations (7,8). But it is also possible that a prodrug could be devoid of bitter taste because of less interaction with the taste receptor than the parent drug, irrespective of solubility considerations. We have found that prodrugs of several opioid analgesics and antagonists are bitterless, in contrast to the active drugs. In this case, however, this phenomenon is not apparently related to the aqueous solubilities of the drug and prodrug.

The purpose of these studies was to demonstrate the feasibility of delivering opioid analgesics and antagonists in tasteless prodrug forms. Prodrugs of various 3-hydroxymorphinans were prepared and evaluated for taste. Prodrugs of the analgesic nalbuphine and the narcotic antagonists, naloxone and naltrexone, were subjected to further characterization. Buccal bioavailability of nalbuphine, naloxone, and naltrexone was measured in rats using solution vehicles and in dogs using an adhesive patch formulation containing various prodrugs. Prodrug hydrolysis rates in rat and dog plasma were also determined.

MATERIALS AND METHODS

Materials

Nalbuphine HCl, naltrexone HCl, naloxone HCl, and oxymorphone HCl were from DuPont Pharmaceuticals. Bu-

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torphanol and levallorphan were kindly supplied by Bristol Myers and Hoffman La Roche, respectively. Prodrugs were synthesized and characterized as described previously (9,10). Hydroxypropylcellulose (Klucel EF) was supplied by Hercules, and polycarbophil (Carbopol 934P) was from B. F. Goodrich.

Taste Analyses

Compounds were evaluated for bitter taste on a quantal (bitter or not bitter) basis. This was generally performed with a few crystals of the drug substance placed on the tongue with the subject's wetted fingertip. Most compounds were tasted by three volunteers, and for each compound every examiner reported the same response.

Prodrug Hydrolysis in Plasma

Rates of nalbuphine, naloxone, and naltrexone prodrug hydrolysis in rat and dog plasma *in vitro* were determined using methods previously reported (9,10). Briefly, the prodrug was added to plasma and incubated at 37°C for various times. Samples were then extracted and analyzed by high-performance liquid chromatography (HPLC) for unchanged prodrug or for the hydrolysis product, nalbuphine, naloxone, or naltrexone. For acetylsalicylate prodrugs, deacetylation in plasma is much more rapid than hydrolysis of the salicyloyl moiety (10). Results presented here represent the rates of drug appearance.

Bioavailability Studies

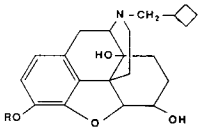
Bioavailability of the active drugs after prodrug or drug dosing were determined in rats and dogs. Groups of male Lewis rats were administered nalbuphine HCl, naloxone HCl, or naltrexone HCl intravenously (1 ml/kg) at doses of 5.6, 6.9, and 5.8 μmol/kg, respectively. Buccal doses in rats were equimolar to the i.v. doses. Buccal dosing was performed after ligation of the esophagus, which prevents swallowing of the dosing solution. The dosing solution (0.25 ml/kg) was applied between the cheek and the lower gum using a syringe and blunt needle. In each experiment rats were anesthetized with urethane (700 mg/kg, i.p.) and restrained to minimize movement. There were five to eight rats in each group. Blood samples were collected into heparinized test tubes after cutting the tip of the tail. Plasma nalbuphine, naloxone, and naltrexone concentrations were determined by HPLC after solvent extraction using previously described procedures (1,2). The area under the plasma drug concentration vs time curve (AUC) from 0 to 6 hr was calculated for each rat. Bioavailability was calculated as the ratio of $AUC^{buccal}/AUC^{i.v.}$, using the average $AUC^{i.v.}$ and individual AUC^{buccal} values.

Bioavailability was also determined in female beagle dogs, fasted overnight prior to dosing. Nalbuphine HCl and naloxone HCl were administered intravenously at doses of 2.5, and 3.0 μmol/kg, respectively. The buccal doses were 10.2 μmol/kg for nalbuphine and its prodrugs and 11.8 μmol/kg for naloxone and its prodrugs. In the dog studies adhesive patch formulations were administered. The patches were composed of the following: prodrug HCl/hydroxypropylcellulose/polycarbophil/polyethylene glycol 400 (25/66.2/5.4/3.4 weight ratio). The dry powders were triturated in a mortar, and after a uniform mixture was formed, the PEG 400 was added and levigated with the dry mixture. The powder was then pressed in a hydraulic press at 220°F under 25,000 psi for 10 min. From the thin films, patches were cut to an oval shape (roughly 3 × 5 cm) containing the desired dose. Dosing was accomplished by placing the patch between the cheek and the lower gum after moistening the dog's mouth with water. The patches became adhesive when wet. The mouth was held closed for 8 min, during which the patch dissolved. Blood (5 ml) was collected by jugular venipuncture. Plasma nalbuphine or naloxone concentrations were determined by HPLC. Bioavailability was calculated as a ratio of buccal and i.v. $AUC^{0-\infty}$, corrected for the differences in dose. There were three dogs in each group. For the bioavailability studies, the levels of unchanged prodrug in plasma were not determined. The analytical methods for drug determination used electrochemical detection, which requires the free 3-hydroxy group.

RESULTS AND DISCUSSION

We previously demonstrated that in rats various opioid analgesics and antagonists had very low oral bioavailability and that the bioavailability was significantly greater when the drugs were administered buccally (1,2). Buccal delivery of the active drugs may be unacceptable, however, because these compounds taste bitter. In our taste evaluations, nalbuphine, naloxone, naltrexone, oxymorphone, butorphanol, and levallorphan were all unpleasantly bitter. However, various nalbuphine prodrugs esterified in the phenolic 3-hydroxy position were all devoid of the bitter taste (Table I). Water solubility was apparently not a taste-determining factor, since both nalbuphine HCl and free base were bitter, and some water-soluble HCl salts of prodrugs were bitterless. Pivalate prodrugs of other opioid analgesics and antagonists were prepared for taste evaluation, to see whether the

Table I. Bitterness of Nalbuphine and Various Nalbuphine Prodrugs



R	Salt	Taste
H–	Free base	Bitter
H–	HCl	Bitter
$(CH_3)_3CCO$–	Free base	Not bitter
$(CH_3)_3CCO$–	HCl	Not bitter
$(CH_3CH_2)_3$ CCO–	HCl	Not bitter
$CH_3(CH_2)_{10}$ CO–	Free base	Not bitter
C_6H_5CO–	HCl	Not bitter
2-$CH_3C_6H_4CO$–	Free base	Not bitter
2-$NH_2C_6H_4CO$–	HCl	Not bitter
2-OHC_6H_4CO–	Free base	Not bitter
2-$CH_3COOC_6H_4CO$–	Free base	Not bitter
2-$CH_3COOC_6H_4CO$–	HCl	Not bitter
CH_3SO_2–	Free base	Not bitter
CH_3OCO–	Free base	Not bitter[a]
4-$CH_3OCOC_6H_4NHCO$–	HCl	Not bitter

[a] Not bitter initially, but bitter taste developed within 1 min.

Table II. Bioavailability (Mean ± SD) of Nalbuphine, Naloxone, and Naltrexone Administered Buccally in Drug or Prodrug Form to Rats and Dogs

Compound	Hydrolysis half-life in plasma *in vitro* (hr)		Buccal bioavailability (%)[a]		t_{max} (hr)	
	Rat	Dog	Rat[b]	Dog[c]	Rat	Dog
1. Nalbuphine			63.1 ± 22.5	10.6 ± 1.7	1.3 ± 1.2	0.5 ± 0.0
2. Nalbuphine-3-pivalate	0.68	17.5	44.7 ± 8.7	34.8 ± 11.2 (1)	1.1 ± 0.8	0.3 ± 0.1
3. Nalbuphine-3-acetylsalicylate	0.21	3.5	86.6 ± 28.8 (2)	41.4 ± 11.9 (1)	1.3 ± 0.6	1.0 ± 0.4
4. Nalbuphine-3-salicylate	0.21	3.5	92.7 ± 33.4 (2)		2.2 ± 1.9	
5. Naloxone			68.8 ± 22.0	15.5 ± 2.1	0.4 ± 0.1	0.3 ± 0.1
6. Naloxone-3-pivalate	0.03	0.5	51.5 ± 14.4	34.2 ± 12.4	2.8 ± 1.2	0.5 ± 0.0
7. Naloxone-3-acetylsalicylate	0.02	0.9	26.5 ± 9.6 (5,6)	51.1 ± 2.9 (5)	1.5 ± 2.0	1.0 ± 0.7
8. Naltrexone			62.4 ± 12.0		0.6 ± 0.2	
9. Naltrexone-3-pivalate	0.05	2.0	59.9 ± 16.9		1.0 ± 0.6	

[a] Represents bioavailability of nalbuphine, naloxone, or naltrexone. Numbers in parentheses indicate groups that were significantly different ($P < 0.05$).

[b] All were administered as HCl salts in H_2O except 3 and 4, which were administered as the free base dissolved in 0.15 *M* citric acid and 0.03 *N* HCl, respectively.

[c] Administered as HCl salts in adhesive patch formulations.

same phenomena were applicable to other members of the 3-hydroxymorphinan series. Naloxone, naltrexone, butorphanol, and levallorphan were bitter, but the respective 3-pivalate prodrugs were not. Therefore, phenolic prodrugs offer the advantage of lack of a bitter taste when administered via the oral mucosa. For this use, it is important that the prodrugs be absorbed more rapidly than they are hydrolyzed so that a bitter taste does not develop. For example, the methyl carbonate ester of nalbuphine was tasteless initially, but bitterness developed within a minute, presumably because of hydrolysis within the fluids of the mouth.

For prodrugs to be useful for buccal delivery, it is necessary that they be well absorbed, as previously demonstrated for the active drugs, and that they be hydrolyzed to the active drug after absorption. Plasma hydrolysis rates and buccal bioavailability were therefore evaluated for several prodrugs of nalbuphine, naloxone, and naltrexone in rats and dogs. Results are summarized in Table II. Plasma hydrolysis rates *in vitro* are indicative of the relative stability of the prodrugs, but *in vivo* the mucosal membrane and erythrocytes probably also contribute to hydrolysis (9). The pivalate, acetylsalicylate, and salicylate prodrugs were empirically judged to be stable enough to resist hydrolysis within the mouth but would be rapidly hydrolyzed systemically. Aceylsalicylate prodrugs are rapidly deacetylated in plasma *in vitro,* and hydrolysis of the resultant salicylate prodrug is rate-limiting for drug appearance (10).

In rats, the possibilities for absorption were maximized by ligating the esophagus to prevent swallowing and by administering the drugs in solution. Leaking from the mouth was still possible but was not observed. Bioavailabilities of the nalbuphine, naloxone, and naltrexone were generally as high when prodrugs were administered as when the drugs were administered (Table II). Representative plots of plasma drug concentrations vs time are given in Fig. 1. The average times of the maximum plasma concentrations (t_{max}) are also reported in Table II. The value of t_{max} is influenced by the drug or prodrug absorption rate, the prodrug hydrolysis rate, and the drug elimination rate. T_{max} values were generally similar for drugs and prodrugs, indicating rapid prodrug hydrolysis *in vivo*. In animals dosed with either drug or prodrug the terminal drug decay half-life was often longer than in animals dosed intravenously, suggesting that buccal absorption may have been prolonged. Prolonged absorption phases were also observed for buccal morphine in humans (4) and sublingual buprenorphine in rats (11) and humans (12).

In the dog studies rapidly dissolving adhesive patch formulations were administered. Administration of nalbuphine or naloxone when not in prodrug form was obviously unpleasant since the dogs salivated excessively and tried to

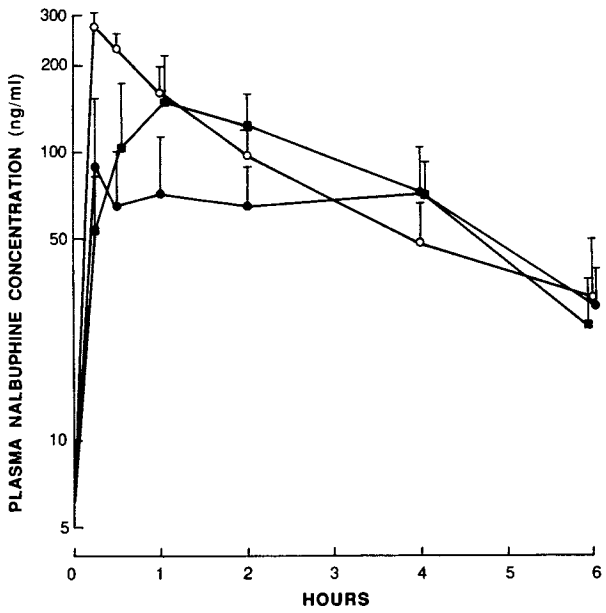


Fig. 1. Representative data (mean + SD) in rats comparing plasma nalbuphine concentrations after i.v. nalbuphine (○), buccal nalbuphine (●), or buccal nalbuphine-3-acetylsalicylate (■) dosing.

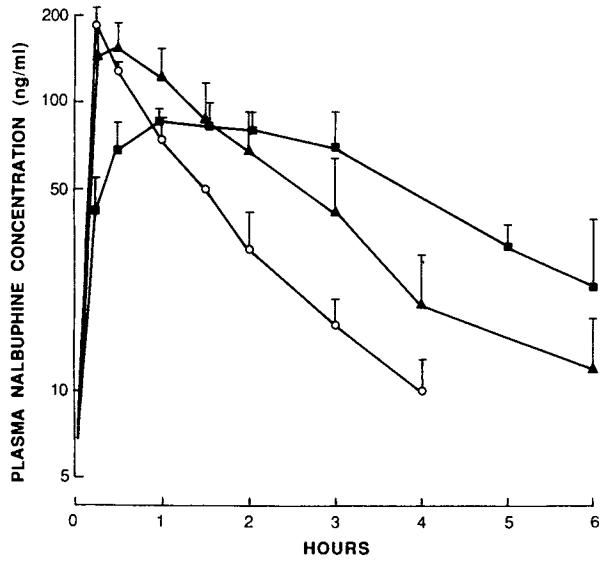


Fig. 2. Comparison of nalbuphine disposition in dogs administered nalbuphine i.v. (○), nalbuphine-3-pivalate buccally (▲), or nalbuphine-3-acetylsalicylate buccally (■) (mean + SD).

expel or swallow the patch. Bioavailability was low (Table II) because of loss of the patch due to expulsion or swallowing. In contrast, the prodrug patches were administered without any visible adverse consequences. Bioavailability generally ranged from 35 to 50% (Table II). Representative plasma nalbuphine concentration vs time profiles for dogs are shown in Fig. 2. For some prodrugs (e.g., nalbuphine-3-pivalate), plasma drug concentrations peaked rapidly, indicative of rapid absorption and prodrug hydrolysis. For other prodrugs (e.g., nalbuphine-3-acetylsalicylate), the peak in plasma drug concentrations was delayed, and the plasma concentrations were prolonged. This could be due to prolonged absorption or could represent rate-limiting prodrug hydrolysis. The oral bioavailability of nalbuphine in dogs is only approximately 5% (13) and that of naltrexone is less than 5% (10), because of extensive first-pass metabolism. The acetylsalicylate and salicylate prodrugs, but not the pivalate prodrugs, were effective in increasing oral nalbuphine and naltrexone bioavailability by blocking first-pass metabolism (9,10). Therefore, if the acetylsalicylate or salicylate prodrugs were swallowed, the bioavailability could also be greater than when the active drugs are administered orally. However, this would not be the case for the pivalate esters; swallowing would lower bioavailability. High buccal bioavailability and rapid absorption using the pivalate esters in dogs demonstrates that the patch formulations were effective in providing good mucosal contact and quick drug release to the membrane. Optimizing the formulation and instructing patients not to swallow for several minutes after dosing might lead to further improvement of bioavailability.

In conclusion, we have shown that prodrugs of opioid analgesics and antagonists are preferred for delivery via the oral mucosa because they do not taste bitter. The prodrugs appear to be inherently tasteless, irrespective of solubility considerations. Pivalate, acetylsalicylate, and salicylate esters of nalbuphine, naloxone, and naltrexone provided good bioavailability buccally in rats and dogs and can be administered in patch formulations. Buccal administration represents an attractive alternative to oral delivery, where bioavailability is low, and may be more patient acceptable than injections.

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