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Buccal and oral bioavailability of naloxone and naltrexone in rats

Munir A. Hussain, Bruce J. Aungst, Albert Kearney and Eli Shefter

Du Pont, Medical Products Department, Experimental Station, Wilmington, DE 19898 (U.S.A.)

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Summary

The opioid antagonists naloxone and naltrexone are both known to undergo extensive first-pass metabolism after oral dosing. The buccal route was investigated as a potential alternative to oral administration. Oral and buccal bioavailabilities of naloxone and naltrexone were determined in rats. Less than 1% of oral naloxone or naltrexone was bioavailable, but buccal administration resulted in approximately 70% bioavailability for each drug.

Introduction

Naloxone-hydrochloride (Narcan, Du Pont Pharmaceuticals) is a narcotic antagonist which is used by injection for reversal of narcosis. There are other conditions in which naloxone has shown some beneficial effects, including senile dementia of the Alzheimer's type (Reisberg et al., 1983) and as an appetite suppressant in obesity (Atkinson, 1982). However, presently the only available dosage form is the injectable. Oral administration of radiolabeled naloxone to subjects resulted in plasma radioactivity levels similar to those after i.v. dosing, but plasma naloxone concentrations were negligible (Fishman et al., 1973). This is indicative of extensive first-pass metabolism.

Another narcotic antagonist, naltrexone hydrochloride (Trexan, Du Pont Pharmaceuticals), was recently approved for use in the U.S. for treatment of opioid addiction. Naltrexone is also subject to first-pass metabolism after oral administration. Systemic bioavailability of a single oral dose to healthy volunteers was estimated to be 5–6% by Meyer et al. (1984), and Kogan et al. (1977) estimated oral bioavailability to be 20–22% after acute or chronic dosing. In both of these reports bioavailability was estimated by the method of Vaughan (1975), without i.v. naltrexone administration. With this method the measured area under the plasma concentration vs time curve (AUC) after oral dosing, renal clearance, and a standard value for hepatic blood flow are used to calculate oral bioavailability. Estimates of naltrexone and naloxone oral bioavailability based on comparison of oral and i.v. AUCs have not been reported for man or animals.

For some drugs, the extent of first-pass metabolism is reduced when absorption is via the

Correspondence: Bruce J. Aungst, Du Pont, Medical Products Department, Experimental Station, Building 400, Wilmington, DE 19898, U.S.A.

buccal or sublingual route. Nitroglycerin is the most familiar example, having extremely low oral bioavailability, but providing prompt treatment of acute angina attack when administered sublingually. Other drugs may be well absorbed from the gastrointestinal tract but are poorly absorbed through the buccal or sublingual mucosa (Taraszka, 1970). In this study the bioavailabilities of naloxone and naltrexone were determined after buccal and oral administration.

Materials and Methods

Separate groups of male, Lewis rats were administered naloxone-HCl or naltrexone-HCl i.v., orally, or buccally in aqueous solutions. Rats weighed 250–350 g and were fasted overnight prior to dosing. The naloxone-HCl doses were 2.5 mg/kg i.v. and 25 mg/kg p.o. Naltrexone-HCl was administered at doses of 2.2 mg/kg i.v. and 20 mg/kg p.o. I.v. doses were administered by cardiac puncture and oral doses were administered by gavage. For i.v. and oral dosing, the volume injected was 1 ml/kg.

Buccal dosing was performed on rats in which the esophagus was ligated through a small incision on the neck, which was then closed with surgical staples. This ligation prevents the dosing solution from being swallowed. Rats were maintained on their abdomen with their lower jaw on the surface of the bench. The dosing solution was applied between the cheek and lower gum with a syringe and blunt needle. For both naloxone-HCl and naltrexone-HCl, the buccal dose was 2.2 mg/kg in a volume of 0.25 ml/kg. In each experiment rats were anesthesized with urethane (700 mg/kg, i.p.) and occasionally supplemental ether. There were 5–9 rats in each group.

Blood samples (~ 0.5 ml) were collected into heparinized test tubes after cutting the tip of the tail. Plasma naloxone and naltrexone concentrations were determined by HPLC after solvent extraction using a method similar to those previously described (Derendorf et al., 1984; Meyer et al., 1984; Garrett and El-Koussi, 1985). For naloxone determinations, naltrexone was added to plasma as an internal standard prior to extraction. Nalbuphine (Du Pont Pharmaceuticals) was used as an internal standard for naltrexone determinations. Plasma aliquots (0.2 ml) were buffered with 0.2 ml pH 9 carbonate buffer and doubly extracted into 4-ml vols. of toluene/ethyl acetate/isopropanol (70/29/1). Back extractions into 0.2 ml of 0.3 M phosphoric acid were then performed. The phosphoric acid was injected onto the HPLC. A 25 cm × 4.6 mm reverse phase (Zorbax C_8, Du Pont) column was used. The mobile phase was 11–12% acetonitrile and 0.2% tetrahydrofuran in 0.055 M phosphate buffer at pH 3–4. Electrochemical detection (Bioanalytical Systems) with a glassy carbon electrode and an oxidative potential of +0.98 V was used. Typical retention times for naloxone, naltrexone, and nalbuphine were 5.5 min, 8 min and 11 min, respectively. Calibration curves were made each day an analysis was performed.

Model-independent pharmacokinetic parameters were determined. The terminal plasma naloxone or naltrexone decay rate constants (λ) and half lives ($t_{1/2}$) were calculated by linear regression. The AUC's of each plasma concentration vs time curve from time 0–6 h was calculated using the trapezoidal method. The residual area to time infinity was calculated as C_p^{6h}/λ, where C_p^{6h} is the plasma naloxone or naltrexone concentration at 6 h, the last sampling time. The area under the moment curve (AUMC) was similarly calculated. Then, systemic clearance (Cl_s) and distribution volume (V_d^{ss}) were calculated as:

$$Cl_s = \text{Dose}/\text{AUC}_{0-\infty}$$

$$V_d^{ss} = \text{Dose} \times \text{AUMC}/\text{AUC}^2$$

After oral (o) or buccal (b) dosing, individual values of AUC were calculated and bioavailability (F) was determined by:

$$F = \frac{\text{AUC}^{o,b} \times \text{Dose}^{i.v.}}{\text{AUC}^{i.v.} \times \text{Dose}^{o,b}} \times 100\%,$$

using the average $\text{AUC}^{i.v.}$.

Results and Discussion

Plasma naloxone and naltrexone concentrations after i.v. dosing are shown in Figs. 1 and 2, respectively. Plasma naloxone concentrations decreased monoexponentially. The kinetics of i.v. naltrexone were monoexponential in some rats and biexponential in others. Pharmacokinetic parameters were calculated for each animal and averaged. These are reported in Table 1. Systemic clearance of both naloxone and naltrexone was greater than hepatic plasma flow*, indicating high hepatic extraction and/or extrahepatic metabolism.

Both naloxone and naltrexone have been shown to be well absorbed from the gastrointestinal tract. However, as a consequence of rapid clearance by the gut and/or liver, naloxone and naltrexone undergo extensive first-pass metabolism when given orally. Some rats administered oral naltrexone exhibited secondary peaks in plasma naltrexone concentrations, which presumably were a consequence of enterohepatic recycling. This phenomenon has previously been described for oral naltrexone in monkeys (Shepard et al., 1985). The terminal decay half-life after oral naltrexone could not be accurately estimated, so $AUC_{0-6\,h}$ was used to estimate oral bioavailability. Naloxone concentrations were not detectable in plasma samples taken at times greater than 2 h after oral naloxone. Oral bioavailability of both naltrexone and naloxone was very low (Table 2).

Plasma naloxone and naltrexone concentrations after buccal administration were much more comparable to i.v. concentrations (Figs. 1 and 2). Absorption was apparently rapid, as plasma concentrations peaked within 15 min after dosing. Interestingly, average plasma concentrations of both naloxone and naltrexone were slightly prolonged after buccal doses, relative to i.v. Prolonged buccal or sublingual absorption has also been observed for the structurally similar compounds buprenorphine (Brewster et al., 1981), morphine (Bell et al., 1985), and nalbuphine (Hussain et al., 1986). We previously showed that i.v. nalbuphine disposition was unaffected by the surgical procedure performed prior to buccal dosing. Individual half-lives after buccal dosing could not be accurately estimated. Therefore the average

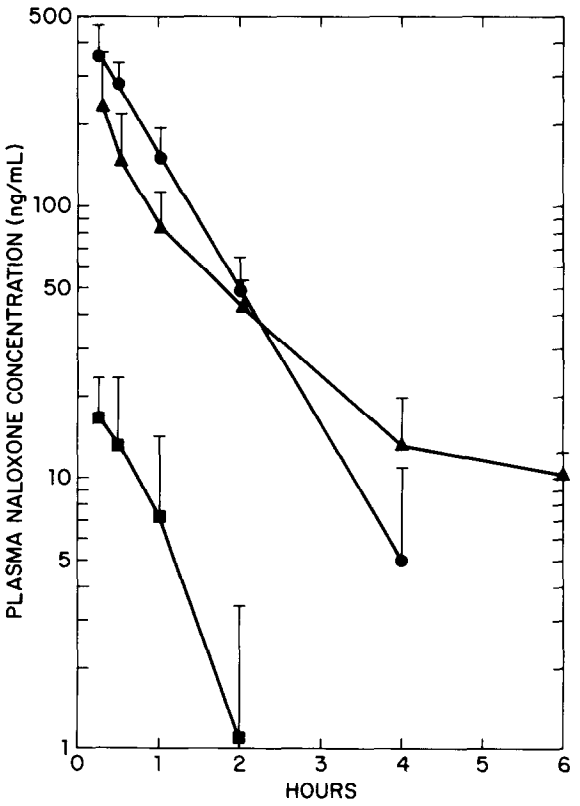

Fig. 1. Naloxone concentrations in rat plasma after 2.5 mg/kg i.v. (●), 25 mg/kg oral (■), or 2.2 mg/kg buccal (▲) naloxone-HCl. There were 9, 5, and 6 rats in the respective groups.

TABLE 1

Naloxone and naltrexone pharmacokinetic parameters (mean ± S.D.) after i.v. administration of naloxone-HCl (2.5 mg/kg) or naltrexone HCl (2.2 mg/kg) to 9 and 5 rats, respectively.

	Naloxone	Naltrexone
λ (h^{-1})	1.15 ± 0.28	0.39 ± 0.05 [a]
$t_{1/2}$ (h)	0.64 ± 0.15	1.80 ± 0.21 [a]
V_d^{ss} (liter/kg)	4.67 ± 2.30	8.29 ± 1.41
Cl_s (ml/min·kg)	85.9 ± 20.0	62.2 ± 11.8

[a] Data represent the terminal decay phase for rats exhibiting biexponential kinetics.

* Hepatic plasma flow in rats administered urethane, ether, or no anesthesia ranged from 0.15 to 0.37 ml/min kg (Tsuji et al., 1983).

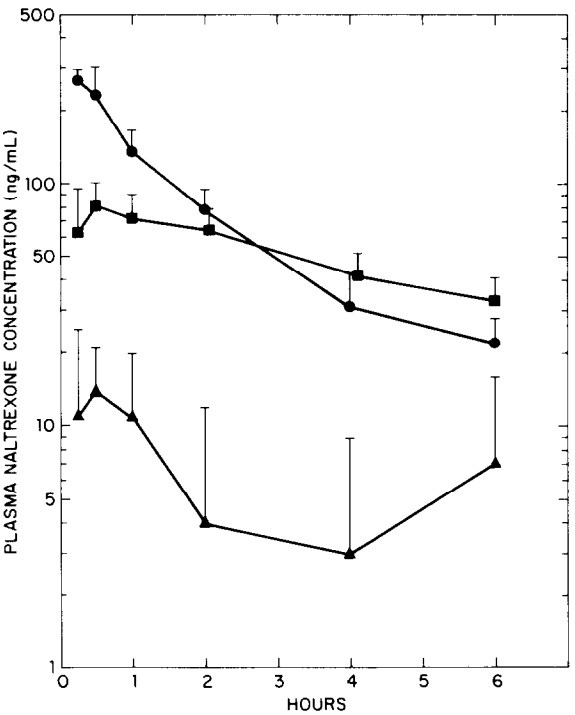

Fig. 2. Plasma naltrexone concentrations (mean + S.D.) in rats administered naltrexone-HCl; 2.2 mg/kg i.v. (●), 20 mg/kg orally (▲), or 2.2 mg/kg buccally (■). There were 5 rats in each group.

i.v. half-lives were used to calculate residual AUC. If the buccal half-lives were significantly longer than i.v., the buccal $AUC_{0-\infty}$ values would be underestimated, and thus bioavailability would be underestimated.

The apparent bioavailabilities of buccal naloxone and naltrexone were greater than 70% (Table 2). First-pass metabolism was avoided. Buccal administration therefore represents a feasible alternative to injections and oral doses for these narcotic antagonists.

TABLE 2

Oral and buccal bioavailabilities (mean ± S.D.) of naloxone and naltrexone in rats

	Naloxone [a]	Naltrexone [b]
F_{oral} (% dose)	0.3 ± 0.3 [c]	0.8 ± 0.7 [c]
F_{buccal} (% dose)	70.6 ± 22.1 [d]	71.1 ± 11.5 [c]

[a] Naloxone-HCl 25 mg/kg oral, 2.2 mg/kg buccal.
[b] Naltrexone HCl 20 mg/kg oral, 2.2 mg/kg buccal.
[c] $n = 5$.
[d] $n = 6$.

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