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Nasal absorption of naloxone and buprenorphine in rats

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Summary

The nasal administration of naloxone (30 μg/rat) and buprenorphine (135 μg/rat) was studied in male rats following single doses and compared with intravenous and intraduodenal administration of the two drugs. The nasal bioavailabilities calculated from the ratio of the AUC (nasal/intravenous × 100) was 101% for naloxone and 95% for buprenorphine. The intraduodenal bioavailability for naloxone was only 1.5% of the intravenous bioavailability. These studies showed that the nasal route for the administration of these two drugs can be considered as effective as the parenteral route.

Introduction

Naloxone, a narcotic antagonist, and buprenorphine, an opiate analgesic, have very low bioavailability in both rats and humans from oral dosage forms because of their extensive metabolism in the liver (Fishman et al., 1973; Ngai et al., 1976; Barlett et al., 1980; Bullingham et al., 1980; Brewster et al., 1981). The systemic bioavailability of buprenorphine following intrarectal, sublingual and intraduodenal administration in rats was studied and found to be 54%, 13% and 9.7%, respectively (Brewster et al., 1981). Naloxone is absorbed after oral administration, but it is metabolized so rapidly in its first passage through the liver that it is only one-fiftieth as potent by this route as when given parenterally (Jaffe and Martin, 1980).

Recent studies in our laboratories have shown that for compounds such as the

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beta-blocker, propranolol, and the female contraceptive hormone, progesterone, which are extensively metabolized following oral administration, nasal administration in man and animals resulted in drug blood levels similar to those observed following intravenous administration (Hussain et al., 1979; 1980a and b; 1981). This report presents results on the nasal absorption of naloxone and buprenorphine in rats.

Materials and Methods

[N-ally-2,3-^{3}H]Naloxone (23.6 Ci/mmol) and [15-16(n)-^{3}H]buprenorphine (38 Ci/mmol) were obtained from Endo Dupont and Research Triangle Institute, respectively. All drug solutions were prepared in 0.9% sodium chloride (saline) and volumes of 0.1 ml were administered nasally, intravenously and intraduodenally. A dose of 30 μg/rat (40 μCi/rat) and 135 μg/rat (4.2 μCi/rat) were used for naloxone and buprenorphine, respectively.

Animal studies

Male Sprague–Dawley rats, each weighing approximately 270 g, were used. The surgical procedures and the method of administration of the drugs by the various routes were those described by Hussain et al. (1980). The animals were anesthetized with pentobarbital (50 mg/kg). For the nasal administration, an incision was made in the neck, and the trachea was cannulated with a polyethylene tube. A closed tube was inserted through the esophagus to the posterior part of the nasal cavity. The nasopalatine was closed with an adhesive agent (Super Glue, Woodhill Permetex) to prevent drainage of the drug from the nasal cavity to the mouth. The drug was administered to the nasal cavity by means of a micropipet and the nostrils were then closed with an adhesive agent. For the intravenous administration, the drug was injected through the femoral vein. For the intraduodenal administration, the abdomen was opened by means of midline incision and the drug was injected directly through the duodenum.

Sample collection and assay

Blood samples (0.2 ml) were periodically collected from the femoral artery of the rats. The unchanged radiolabelled naloxone in the plasma was analyzed according to the procedure previously described (Fishman et al., 1973). The method involved centrifugation of the whole blood followed by the addition of 50 μl of a solution containing 5 mg/ml of non-radiolabelled naloxone to 0.1 ml of the plasma sample. Each sample was then diluted with 1 ml of 0.1 M phosphate buffer at pH 7.5 and naloxone was extracted with ethyl acetate (2 × 3 ml). The ethyl acetate layer was evaporated to dryness and the residue was redissolved in 50 μl of ethyl acetate. Forty μl was spotted on TLC plates and the spot corresponding to free naloxone (as visualized by ultraviolet absorption) was scraped off the plates and suspended in scintillation cocktail for a radioactivity count. The recovery of naloxone was calculated to be $52.5 \pm 4\%$ ($n = 6$), as determined by extracting control blood samples, each containing an added quantity of labelled drug. Concentrations of

naloxone in blood were obtained from the counts of radioactivity and corrected for the percent recovery.

In the case of buprenorphine, 0.6 ml of blood was periodically withdrawn and immediately centrifuged. The level of the drug in the plasma was determined by mixing 0.2 ml of the plasma with 10 ml of scintillation cocktail for radioactivity count. It was previously shown that the unmetabolized fraction of buprenorphine was the major component in the blood samples after the administration of the drug regardless of sampling time and route of administration (Brewster et al., 1981).

Results and Discussion

Naloxone was found to be rapidly and completely absorbed from the nasal cavity of rats. Fig. 1 shows the mean naloxone plasma levels following nasal, intravenous

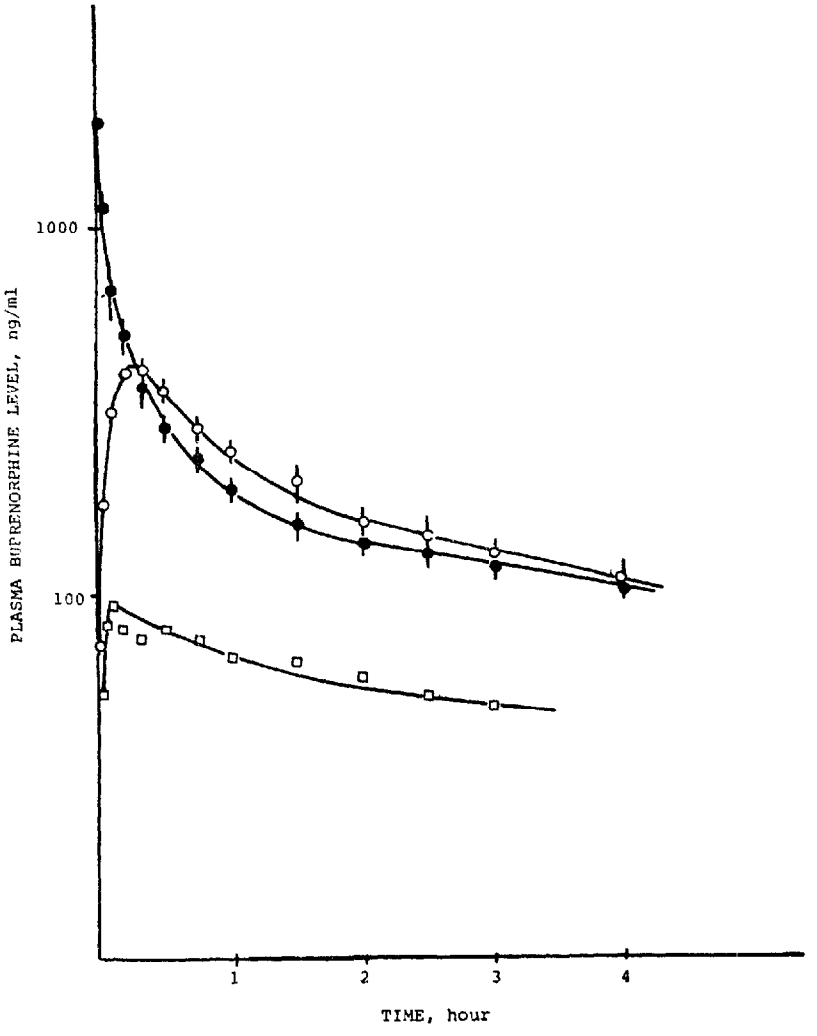

Fig. 1. Mean plasma naloxone levels after nasal (○), intravenous (●), and intraduodenal (□) administration of 30 μg of naloxone. Points represent mean values of 3 animals ± S.E.M.

TABLE 1

AREA UNDER THE PLASMA CONCENTRATION–TIME CURVE OF NALOXONE FOLLOWING INTRAVENOUS, NASAL AND INTRADUODENAL ADMINISTRATION

Route	Area under plasma concentration–time curve ($AUC_{0\rightarrow\infty}$) ($ng \cdot ml^{-1} \cdot min$)	Relative systemic availability (%)
Intravenous	1498.7 ± 121.9	100
Nasal	1517.5 ± 193.5	101
Intraduodenal	22.0 ± 7.1	1.5

Values represent the mean of 3 animals ± S.E.M.

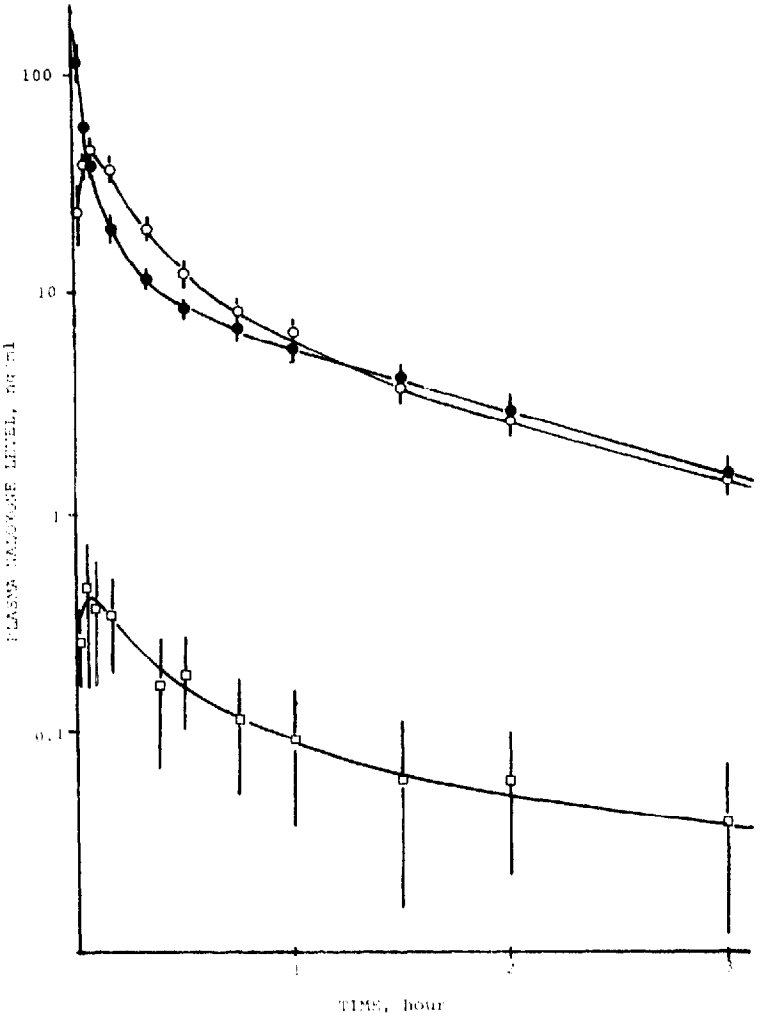

Fig. 2. Mean plasma buprenorphine levels in male rats following nasal (○), intravenous (●), and intraduodenal (□) administration of 135 μg of buprenorphine. Points represent mean values of 4 animals ± S.E.M.

and intraduodenal administration. The plasma drug levels after nasal administration increased rapidly and attained peak levels within the first 3 min. Areas under the curve (AUC) from 0–3 h were calculated by the trapezoidal rule. The remaining AUC (from 3 h to ∞) was estimated by the concentration at 3 h divided by β, the elimination rate constant. Table 1 summarizes the area under the blood level curve ($AUC_{0-\infty}$) for the 3 routes of administration. The nasal bioavailability calculated from the ratio of AUC (nasal/intravenous × 100) was 100%, whereas the intraduodenal bioavailability was only 1.5% that of the intravenous. The half-life calculated from the terminal slope of the blood level–time curves following intravenous and nasal administration was found to be 40–45 min. This data is in agreement with that previously reported by Ngai et al. (1976) for rats (half-life = 30 min) and humans (half-life = 64 min).

In the case of buprenorphine, previous studies in female rats have shown that the intraduodenal bioavailability was only 9.8% of that of the intravenous route. Nasal administration of the drug, however, resulted in drug blood levels similar to those observed following intravenous administration (Fig. 2). Fig. 2 also shows data obtained in one rat following intraduodenal administration and is in accord with the previously reported low bioavailability of the drug from this route of administration. The nasal bioavailability of buprenorphine calculated from the AUC (nasal/intravenous × 100) was 95%.

The above data thus indicate that the nasal route of administration of naloxone and buprenorphine appears to be superior to the oral route and as effective as the intravenous route.

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