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Report

Pharmacokinetics and Bioavailability of Hydromorphone: Effect of Various Routes of Administration

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The pharmacokinetics and bioavailability of hydromorphone following various routes of administration, *i.e.*, intravenous, oral, intranasal, and transdermal, were investigated in rabbits. Hydromorphone plasma concentrations were determined by reverse-phase high-performance liquid chromatography (HLPC). Comparison of area under the concentration versus time curve (AUC) between intravenous and oral administrations showed a low bioavailability of hydromorphone after oral administration. The nasal absorption of hydromorphone was studied by the *in situ* nasal recirculation technique, and the results showed that hydromorphone is well absorbed from the nasal mucosa. The transdermal permeation of hydromorphone was also evaluated for 24 hr and a steady-state plasma concentration (0.135 μg/ml) was achieved during the 6- to 24-hr periods following the application of a transdermal patch on the inner pinna of the rabbit's ear.

KEY WORDS: hydromorphone; intranasal; transdermal; pharmacokinetics; bioavailability.

INTRODUCTION

Narcotic drugs are characterized by important pharmacological differences that are derived from their complex interactions with multiple opiate receptors in the central nervous system (1,2).

Hydromorphone (Fig. 1), a semisynthetic analgesic, chemically and pharmacologically similar to morphine, is efficacious for the relief of postoperative pain or severe chronic pain associated with some terminal illnesses, such as cancer (3–6). Narcotic agonists, such as morphine, hydromorphone, and oxymorphone have shown a low systemic bioavailability (10–20%) by oral administration, which could be the result of extensive hepatic first-pass metabolism (7).

The intranasal and transdermal routes of administration have been reported to be suitable for the systemic administration of drugs since these routes of administration provide the possibility of bypassing gastrointestinal degradation and hepatic first-pass metabolism and afford ease of administration (8–10). The systemic bioavailability following the intranasal administration of buprenorphine (narcotic partial agonist/antagonist) and naloxone (narcotic antagonist) was reported to be 95 and 100%, respectively, following intravenous administration (11).

The objective of this study is to investigate the pharmacokinetics and bioavailability of hydromorphone in the rabbit following various routes of administration, i.e., intravenous, oral, intranasal, and transdermal.

MATERIALS AND METHODS

Animals

New Zealand white male rabbits (6–7 lb) (Davidson Mill Farm, Jamesbury, N.J.) were used. Animals were fasted overnight prior to absorption experiments, but water was given *ad libitum*.

Intravenous and Oral Administration

Hydromorphone was administered intravenously (5 mg/kg) or orally (20 mg/kg) as a concentration of 30 mg/ml in saline solution to conscious animals.

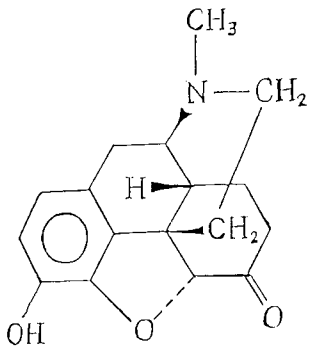

Fig. 1. Structure of hydromorphone

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In Situ Nasal Recirculation Studies

The surgical operation used was similar to that described by Hirai *et al.* in rats. (12). The rabbits were anesthetized with parenteral urethane–acepromazine prior to surgery (13). After shaving the neck, a midline incision was made in the neck and the trachea was cannulated with a polyethylene neonatal endotracheal tube (3.0-mm i.d.) (Mallinckrodt, Inc., Argyle, N.Y.). The esophagus was isolated and ligated. The distal end of the esophagus was closed with suture and flexible Tygon tubing was inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract, which connects the nasal cavity to the mouth, was closed with an adhesive agent to prevent the drainage of drug solution from the nasal cavity. Twenty milliliters of isotonic phosphate buffer solution (37°C) containing 5 mg/kg of hydromorphone HCl was recirculated, using a peristaltic pump (Haake Buchler Instrument) at a rate of 2.2 ml/min. The kinetics of drug absorption was monitored by simultaneously studying the disappearance of the drug from the recirculation solution and the appearance of the drug in the systemic circulation. The rabbit was ventilated during the procedure with a rate of 30 breaths/min and a tidal volume of approximately 50 cm^3.

Transdermal Administration

A transdermal delivery system (3 × 7 cm) was developed for hydromorphone and applied to the inner pinna of the rabbit's left ear. The drug load and the residual drug load in the transdermal patch following application were estimated by extracting the patch three times with methanol and quantitating by high-performance liquid chromatography (HPLC). The actual amount of hydromorphone absorbed was the difference between the drug load and the residual drug load in the transdermal patch.

Determination of the Drug Concentration in the Recirculation Cell

Fifty-microliter samples were withdrawn at specific time intervals and immediately replaced with equal volumes of isotonic phosphate buffer solution (pH 7.2) during the *in situ* nasal recirculation studies. After proper dilution and addition of internal standard, the samples were assayed for hydromorphone concentration by HPLC.

Blood Sampling

Blood samples (1 ml) were taken at specific time intervals from the marginal artery of the rabbits' ears. After centrifugation, the plasma samples were collected and frozen until further analyses were performed.

Determination of Hydromorphone in Plasma

Plasma hydromorphone concentrations were determined by ion-pair reverse-phase high performance liquid chromatography using the following conditions.

Column: μBondapak C18 column (3.9-mm i.d. × 15 cm).

Mobile Phase: 70% phosphate buffer (0.05 *M*) solution, 30% acetonitrile, and 5 m*M* sodium dodecyl sulfate (final pH 4.0).

UV wavelength: 210 nm.

Standard curve: Constructed from 0.02–2.0 μg/ml of hydromorphone HCl solution. Naloxone HCl (200 ng/ml) was added as an internal standard.

Extraction Procedure

Four-tenths milliliter of naloxone HCl solution (200 ng/ml) was added to a plasma sample in a 1.5-ml microcentrifuge tube, to which 0.8 ml of 0.25 *M* perchloric acid solution was added. After vortex and centrifugation at 15,000*g*, the supernatant was transferred to a second sample vial and alkanized with 10% ammonia water. The samples were extracted first with 2 ml of chloroform:isopropanol (9:1) and this organic extract was added with 2 ml of 0.5 *N* HCl solution to convert the drug salt to its free base. The acidic extract was then extracted again with 3 ml of chloroform:isopropanol (9:1). This organic extract was evaporated under

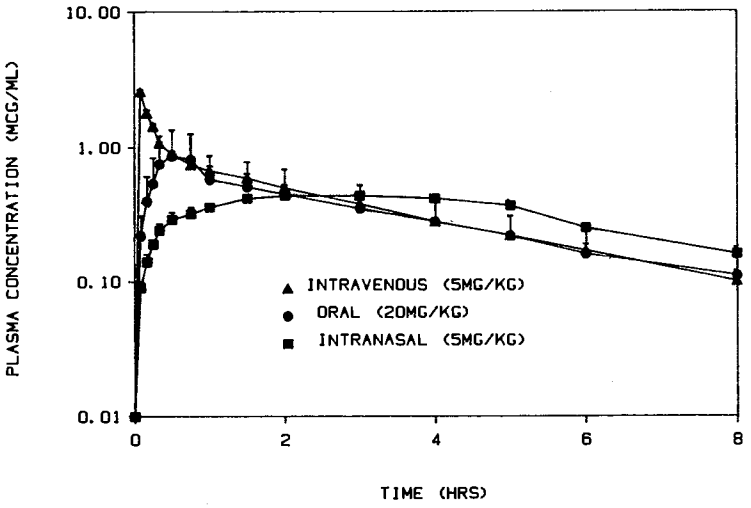

Fig. 2. Mean plasma hydromorphone concentration versus time data in three rabbits following intravenous (5 mg/kg), oral (20 mg/ml), and intranasal (5 mg/kg) administration. The bar represents the SD of three trials.

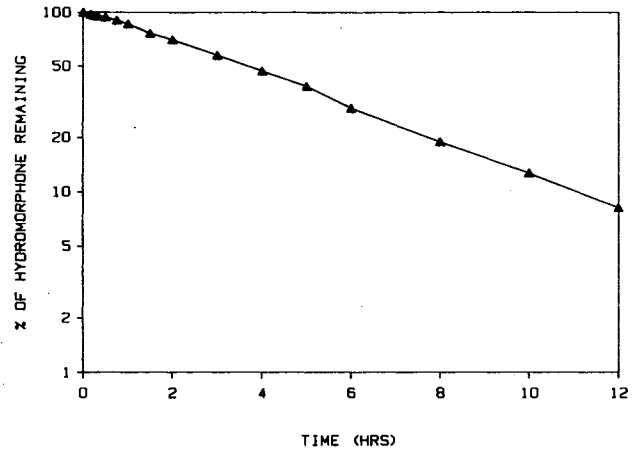

Fig. 3. Mean percentage of hydromorphone remaining in the recirculation solution in *in situ* nasal recirculation studies

nitrogen gas, reconstituted with 0.25 ml of mobile phase, and then filtered through a nylon-66 membrane filter. Five to forty microliters of reconstituted solution was injected into the HPLC.

RESULTS AND DISCUSSION

Intranasal and transdermal administration have recently gained great attention for their potential advantage of bypassing the hepatic circulation. New Zealand male rabbits were chosen as the animal model. Intravenous administration of hydromorphone was also conducted to serve as the reference for the determination of bioavailability of hydromorphone followed by oral, intranasal, and transdermal routes of administration. The therapeutic dose range of hydromorphone for rabbits has not yet been documented and the drug dose used for animals usually is larger than that for humans. The drug dose used in this study is for its easy determination of its blood level by HPLC and therefore for the interpretation of its pharmacokinetics and bioavailability characteristics. Thus, in this study, a 5-mg/kg dose of hydromorphone was used for intravenous or intranasal administration and a 20-mg/kg dose of hydromorphone was used for oral or transdermal administration. Hydromorphone plasma concentrations were determined by reverse-phase high-performance liquid chromatography following several steps of extraction procedures. The standard curve for hydromorphone concentration ranged from 0.02 to 2.0 μg/ml in rabbit plasma and was linear with a correlation coefficient of 0.999 between the peak height ratio (hydromorphone/naloxone) and the hydromorphone concentration.

Figure 2 shows the mean plasma hydromorphone concentration versus time curve for three rabbits following intravenous (5 mg/kg), oral (20 mg/kg), and intranasal (5 mg/kg) administration. After intravenous administration, hydromorphone is rapidly absorbed, disposed, and eliminated in a biphasic fashion. The peak plasma concentration after oral dose administration (four times the intravenous dose) was obtained within 30 min and was only about one-third that of the intravenous administration. The peak plasma concentration after the intranasal dose (one-fourth of the oral dose) was about one-half that of the oral administration and the plasma hydromorphone concentration was maintained at 0.36–0.44 μg/ml during the 1- to 5-h period. The elimination rate constant for intravenous and oral hydromorphone administration is 0.29 ± 0.03 and 0.24 ± 0.09 (± SD), respectively. By comparing the AUC (i.v., 3.63 ± 0.20 μg·hr/ml; oral, 2.96 ± 1.18 μg·hr/ml) and the dose (i.v., 5 mg/kg; oral, 20 mg/ml) administered to those of intravenous administration, the oral bioavailability calculated was only 20.41 ± 9.59%, which could be the result of extensive hepatic first-pass metabolism.

The rabbit has a large nasal accessory sinus with a large surface area of olfactory mucosa, which is comparable to that of humans. The *in situ* nasal recirculation method was used in this study to evaluate the nasal absorption potential of hydromorphone. This method will assure the total penetration of hydromorphone through the nasal mucosa and avoid the drainage of drug solution from the nose which was usually seen in the use of nasal spray. The concentration of hydromorphone in the recirculation solution decreases in a

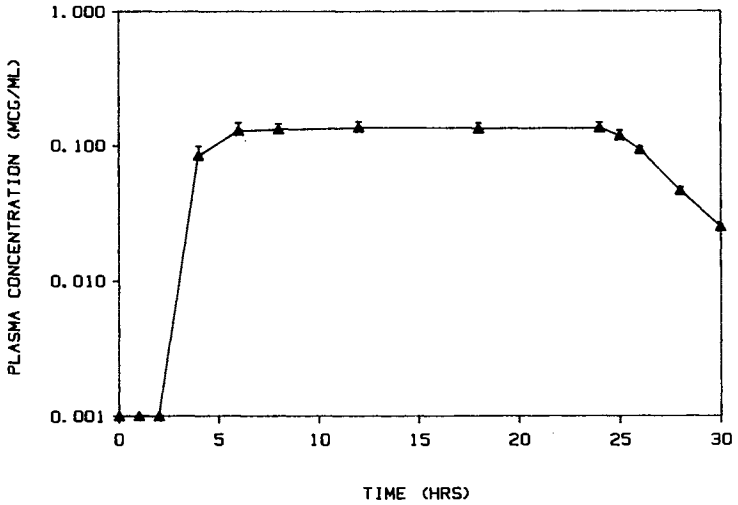

Fig. 4. Mean hydromorphone plasma concentration versus time data following transdermal application in three rabbits. The bar represents the SD of three trials.

first-order manner (Fig. 3). The rate of disappearance for hydromorphone was calculated to be 0.988 hr^{-1} for the first 0.75 hr and 0.2176 hr^{-1} for the period of 0.75–8 hr. The plasma hydromorphone concentration following intranasal administration was found to be maintained at 0.36–0.44 μg/ml during the 1 to 5 hr periods. The bioavailability of hydromorphone for intranasal administration was calculated by comparing its AUC and the dose administered to those of intravenous administration and a systemic bioavailability of 103.62 ± 4.79% was achieved.

It has been well documented that the stratum corneum is the main diffusion barrier for the transdermal drug delivery (10,14). Figure 4 shows that the undetectable hydromorphone concentration was observed during the first 2- to 3-h period following the application of the transdermal patch. This first 2- to 3-hr period was the lag time for the absorption of hydromorphone molecule through the stratum corneum, viable epidermis, and dermis and into the microcirculation. A steady-state plasma concentration (0.135 μg/ml) of hydromorphone was achieved beginning at 6 hr following the application of the transdermal patch and maintained a fairly constant plateau level throughout the 24-hr application. The plasma hydromorphone concentration was decreased after the removal of the trandermal patch. The actual amount of hydromorphone absorbed by the inner pinna of the ear was 18.23 ± 0.68 mg, which was the difference of the drug load and the residual drug load in the patch after its application. By comparing the AUC and the actual dose administered of transdermal application (AUC, 3.38 ± 0.28 μg*hr/ml; dose, 18.23 ± 0.68 mg) to those of intravenous administration (AUC, 3.63 ± 0.20 μg*hr/ml; dose, 16.75 ± 1.23 mg), the mean bioavailability for transdermal administration was calculated to be 85.51 ± 5.87%. This transdermal bioavailability of 85.51 ± 5.87% and the intranasal bioavailability of 103.62 ± 4.79% are much greater than that of 20.41 ± 9.59% obtained after oral administration.

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