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SHORT COMMUNICATION

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Nasal absorption of ondansetron in rats: an alternative route of drug delivery

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Abstract *Purpose*: Ondansetron (OND) is a 5-HT_3 receptor antagonist that is used therapeutically for the prevention of nausea and vomiting associated with emetogenic cancer therapy. There is a need for nasal drug delivery in specific patient populations where the use of commercially available intravenous and oral dosage forms may be inconvenient and/or unfeasible. *Methods*: OND (Zofran Injection, 2 mg/ml) was administered at a dose of 1 mg/kg to male Sprague-Dawley rats intravenously or intranasally ($n = 3$ in each group). A special surgical procedure was performed to ensure that the drug solution was held in the nasal cavity. OND was injected into the femoral vein for the intravenous group. Blood samples were collected at appropriate times for 60 min. An HPLC method was employed to determine OND in the plasma. *Results*: The results clearly showed that OND was readily and rapidly absorbed through the nasal mucosa of the rat. The peak plasma level was attained within 10 min. OND was also completely absorbed as the plasma concentration-time profiles for the two routes were comparable. The terminal elimination half-lives were also similar. *Conclusions*: The nasal administration route for OND is apparently as effective as the intravenous route. If one considers the limitations of delivering OND orally or intravenously to patients undergoing emetogenic cancer therapy, it becomes obvious that the intranasal route is a potential alternative modality to prevent nausea and vomiting associated with such therapy.

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Introduction

Ondansetron is a novel antiemetic agent that acts by antagonizing a subtype of the 5-hydroxytryptamine (5-HT, serotonin) receptor, i.e. the 5-HT_3 receptor. It is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. Although intravenous and oral dosage forms of the drug are commercially available (film-coated tablets, orally disintegrating tablets, and solution), there is a need for alternative formulations for utilization in specific patient populations where a more convenient route of drug delivery might be advantageous. Patients who are either vomiting or, for some reason, cannot absorb orally administered drugs effectively are potential candidates for the use of alternative formulations.

Hsyu et al. have shown that rectally administered ondansetron, using a retention enema, is well absorbed with an absolute bioavailability of 58%. Based on this finding, they suggested that a suppository formulation is feasible [8]. However, rectal administration is often either impractical for or unacceptable by patients. A less invasive route of administration is clearly needed especially where a rapid response is desired therapeutically.

Previous studies in our laboratories and elsewhere have shown that many drugs with a wide variety of chemical structures and pharmacological activities (such as buprenorphine, propranolol, albuterol, and steroids) are readily absorbed from the nasal cavities of animals and humans [1–7]. Very often, absorption through the nasal membrane occurs so rapidly and completely that the resulting blood concentration versus time profiles resemble those observed following intravenous injection. Because of these attributes, butorphanol tartrate, for example, is marketed as a nasal spray (Stadol NS) for the management of pain, including migraine headache

pain [9]. Furthermore, the nasal absorption profiles of many drugs, except peptides, are almost the same in rats and in humans [1]. We report here the results of a comparative investigation of the blood levels of ondansetron delivered intravenously and intranasally.

Materials and methods

Surgical procedure

Male Sprague-Dawley rats, each weighing approximately 320 g, were anesthetized with pentobarbital sodium (Nembural sodium solution, 50 mg/ml; Abbott Laboratories) using a dose of 50 mg/kg. The surgical procedure and method of administration have been previously described [4]. A diagram of this procedure is shown in Fig. 1. An incision was made in the neck of the rat, and the trachea was cannulated with a polyethylene tube. A closed-end tube was inserted through an incision in the esophagus and secured against the posterior part of the nasal cavity to prevent any loss of the dose. The nasopalatine passage was also blocked with an adhesive agent to ensure that the drug did not drain into the mouth. A dose of 1 mg/kg ondansetron (2 mg/ml; Zofran Injection, Glaxo) was administered into the nasal cavity by means of a microsyringe. For intravenous administration, the same dose was injected into a cannulated jugular vein. Blood samples (200 µl) were collected from the femoral artery at 0, 5, 10, 20, 30, 40, and 60 min.

Analysis of ondansetron in plasma

An isocratic reverse-phase high-performance liquid chromatography (HPLC) method was used to determine the ondansetron concentration in the plasma. A calibration curve obtained by analyzing plasma samples spiked with ondansetron in the concentration range of 0.067 to 1 µg/ml was subjected to regression analysis. The assay was linear ($r^2 = 0.999$) over the concentration range investigated. Acetonitrile (0.2 ml) was added to plasma (0.1 ml) and the mixture was vortex-mixed for 1 min and then placed in an Eppendorf microcentrifuge at 10,000 rpm for another minute. An aliquot of the supernatant was injected onto the HPLC column. The chromatographic conditions were as follows: column, TosoHass TSKgel ODS-120 T, 5 µm, with C_{18} guard column; injection volume, 50 µl; mobile phase, 0.05% acetic acid/acetonitrile (75:25); flow rate, 1 ml/min; detection at 305 nm; retention time, 10 min: detection limit, 0.01 µg/ml.

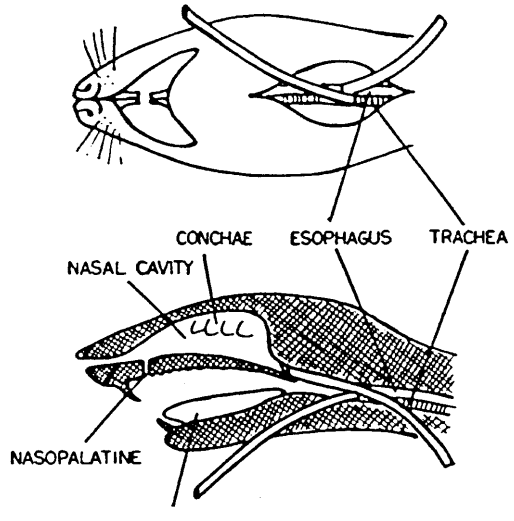

Fig. 1 Diagram of the surgical procedure used for intranasal administration of drugs to rats

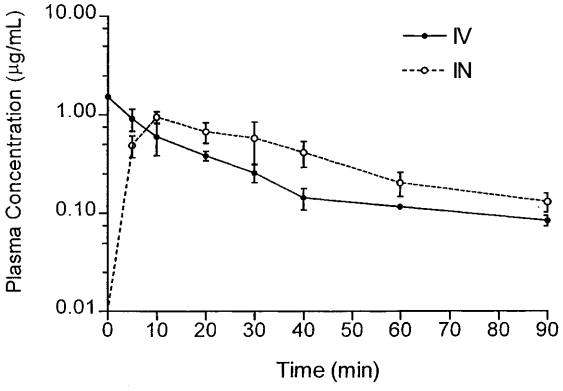

Fig. 2 Plasma ondansetron concentration following intranasal (○) and intravenous (●) administration of 1 mg/kg to rats ($n = 3$). The points represent means ± SD

Results

Figure 2 shows the plasma ondansetron concentrations versus time for the intranasal and intravenous routes of administration. The plasma drug levels for these two routes following a dose of 1 mg/kg ondansetron appeared to be comparable. Furthermore, the results clearly reveal that the drug was readily and rapidly absorbed through the nasal mucosa of the rat. The peak plasma level was attained within 10 min of delivering the dose into the nasal cavity. The terminal elimination half-lives of the two routes were also similar.

Discussion

Since hepatic first-pass metabolism is avoided with nasal administration of drugs, the systemic bioavailability is expected to increase. The oral bioavailability of ondansetron in humans is known to be relatively low, i.e. young, 57%, aged, 61%, elderly, 69% [10]. In contrast, our data show that nasal ondansetron was completely absorbed.

The nasal route for ondansetron administration is apparently as effective as the intravenous route. In healthy individuals, the time to reach peak concentration is 1.0 to 2.1 h after oral administration; thus, oral formulations should be given to patients at least 30 min prior to chemotherapy [11]. The rapid absorption that occurs intranasally allows the drug into the systemic circulation almost instantly. In conclusion, if one considers the limitations of delivering ondansetron orally to patients undergoing emetogenic cancer chemotherapy, it becomes obvious that the intranasal route of administration in the case of this drug is an attractive alternative modality to prevent nausea and vomiting associated with such therapy.

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