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ScienceDirect
International Journal of Pharmaceutics 349 (2008) 101–107
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Formulation and evaluation of ondansetron nasal delivery systems

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Received 15 March 2007; received in revised form 23 May 2007; accepted 22 July 2007
Available online 27 July 2007

Abstract

This study aimed to formulate and evaluate nasal delivery systems containing ondansetron hydrochloride. In the *in vitro* study, the permeation rate with the addition of 10% polyethylene glycol 300 (PEG 300) to aqueous solution containing 0.01% benzalkonium chloride (BC) and 10% sulfobutylether ß-cyclodextrin sodium salt (SBCD) was somewhat more rapid up to 1.5 h compared to the addition of 10% PG. The permeation flux increased as the drug concentration increased regardless of the vehicles used. The addition of nicotinamide or chitosan to aqueous drug solution (40 mg/ml) with 10% PEG 300 and 0.01% BC rather decreased permeation rate and delayed lag time. Even though cyclodextrins including SBCD or dimethyl-ß-cyclodextrin failed to show permeation enhancing effects of ondansetron hydrochloride, the addition of 10% SBCD to aqueous solution containing 10% PEG 300 and 0.01% BC could be a good candidate for ondansetron nasal delivery systems because of its safety profile, stable storage in refrigerator and solubilizing effect. With the above formulation, the nasal delivery system increased $AUC_{0-2\,h}$ and C_{max} by 2.1 and 1.7 times compared to those of oral delivery, respectively while there was no difference found in $AUC_{0-2\,h}$ with intravenous administration. Therefore, the nasal delivery system of ondansetron hydrochloride formulated in this study was feasible for nasal administration.

Keywords: Ondansetron hydrochloride; Vehicles; Permeation rate; Lag time; Pharmacokinetic parameters

1. Introduction

Ondansetron is a serotonin (5-hydroxytryptamine) subtype 3 (5-HT_3) receptor antagonist used in the management of nausea and vomiting (Butcher, 1993; McKenzie et al., 1993; Scuderi et al., 1993). 5-HT_3 receptors, located centrally in the chemoreceptor trigger zone of the area postrema as well as peripherally on vagal nerve terminals, are key receptors in the nausea and vomiting response (Hesketh and Gandara, 1991). Ondansetron has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery (Butcher, 1993; Hesketh and Gandara, 1991; McKenzie et al., 1993; Scuderi et al., 1993). Unlike metoclopramide, ondansetron is known not to block dopamine subtype-2 receptors, and therefore not to induce the undesirable side effect such as extrapyramidal reactions. The most commonly reported adverse events with ondansetron are headache, constipation and diarrhea, which are mild to moderate in severity and rarely necessitate treatment withdrawal (Blackwell and Harding, 1989).

Ondansetron hydrochloride has been used by oral and injectable administration. Ondansetron hydrochloride is rapidly absorbed orally, but extensively metabolized by the liver (Figg et al., 1996). It should be administered 30 min before chemotherapy, and the orally administered antiemetic drug tends to be discharged by vomiting (Rolia and Del Favero, 1995). On the contrary, intravenous administration renders rapid effects to a patient, but the onset of effects is too rapid to cause undesirable effects. In addition, it gives a local pain, and may cause an unexpected accident when it is not perfectly prepared.

Nasal delivery has been paid attention as an alternative dosage form. The advantages of nasal route have been suggested as follows: rapid absorption, higher bioavailability allowing lower doses, fast onset of therapeutic action, avoidance of liver or gastrointestinal metabolism, avoidance of irritation of the gastrointestinal membrane, reduced risk of overdose, non-invasive administration, ease of convenience and self-medication, improved patient compliance, feasibility of beneficial adjunct product to an existing product and reduced risk

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doi:10.1016/j.ijpharm.2007.07.028

of infectious disease transmission (Behl et al., 1998). Although transdermal ondansetron formulation has been reported (Gwak et al., 2003, 2004), the lag time for transdermal permeation is long and the flux is low. Considering that the dose of ondansetron hydrochloride is low (4–24 mg) and rapid onset of action is required, however, it is valuable to develop ondansetron nasal delivery system.

Although the nasal administration has such many advantages, in the case of solution formulation, it should not form precipitates even during longer period of storage. In addition, the higher permeation across the nasal mucosa can be easily achieved when the concentration of active ingredient is relatively high. However, it is difficult to meet the above two requirements at the same time.

This study aimed to formulate the most suitable nasal delivery system of ondansetron hydrochloride and evaluate it. For this, the effects of vehicles and penetration enhancers on the permeation of ondansetron across excised rabbit nasal mucosa were examined. Based on the *in vitro* results, the most suitable formulation was constructed and administered to the rat by nasal route, and pharmacokinetic parameters were compared with those by oral and intravenous route.

2. Materials and methods

2.1. Materials and animals

Ondansetron hydrochloride was purchased from Zunan Commerce & Industrial Co., Ltd. (China). Isopropyl myristate and benzalkonium chloride (BC) were purchased from Sigma Chemical Co. (USA). Dimethyl-ß-cyclodextrin (DMCD, Sigma Chem. Co. Ltd., USA), sulfobutyl ether ß-cyclodextrin sodium salt (SBCD, CyDex Inc., USA), 2-hydroxypropyl-ß-cyclodextrin (2-HPßCD, Cargill Inc., USA) and ß-cyclodextrin (Kimura Sangyo co., Japan) were used. Nicotinamide (Janssen Chimica, Belgium) and chitosan (M.W. = 300,000, Jakwang, Korea) were purchased. Polyethylene glycol 300 (PEG 300), polyethylene glycol 400 (PEG 400, Hayashi Pure Chemical Ind., Japan), *n*-octanol, propylene glycol (PG, Daejung Chemicals Co., Korea) and povidone K 30 (Kollidon 30, BASF Corp., USA) were used. Acetonitrile and methanol used were of HPLC grade. Other reagents were of analytical grade.

Male New Zealand white rabbits weighing 3.0 kg and Sprague-Dawley female rats weighing 250–300 g were purchased from Samtako Bio Korea Co., Ltd. (Korea).

2.2. Analysis

Samples from permeation and stability studies were analyzed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (Series 410, Perkin-Elmer, USA) with a detector (Model LC 90 UV, Perkin-Elmer, USA) set at 302 nm and an integrator (Model 4290, Varian, USA). An ODS column (μBondapak C18, 3.9 mm × 300 mm, 10 μm, Waters, USA) equipped with a C18 Radial Pak insert was used. The mobile phase was composed of acetonitrile, methanol, water and triethylamine (25:10:65:0.1, v/v), whose pH was adjusted to 4.0 by phosphoric acid, and delivered at a flow rate of 1.2 ml/min. The injection volume was 20 μl. The internal standard (IS) used was terazosin hydrochloride (30 μg/ml). A calibration curve was constructed based on peak area ratio measurements.

2.3. Partition coefficient determination

Water and oil solutions including isopropyl myristate and *n*-octanol were saturated with each other before the experiment. Ondansetron hydrochloride solution (100 μg/ml) was prepared with water saturated with oil phase. One milliliter of this solution was then transferred to 10 ml centrifuge tube containing 1 ml of oil phase saturated with water. The tube was vortex-mixed for 3 min and centrifuged at 3000 × *g* for 5 min. After centrifugation, 100 μl was withdrawn from water phase and oil phase, respectively, and the intrinsic partition coefficient was determined by HPLC.

2.4. Solubility determination

An excess amount of ondansetron hydrochloride was added to various vehicles and shaken in a water bath set at 37 °C for more than 48 h. The solutions were centrifuged at 3000 × *g* for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

2.5. Observation of precipitation of ondansetron hydrochloride in vehicles

Ondansetron hydrochloride solutions of 10, 20, 30 and 40 mg/ml were prepared using various vehicles with or without additives, and stored at refrigerator for 3 weeks. Precipitate formation was observed by naked eyes.

2.6. Stability test of ondansetron hydrochloride in nasal mucosa extracts of rabbits

Freshly excised nasal mucosa was mounted to a side-by-side permeation system, and 3.5 ml of normal saline was filled in both sides of cells. After 4 h extraction while stirring, extract solutions were collected respectively, from the both sides. Ondansetron hydrochloride was then added at the concentration of 200 μg/ml to the nasal mucosa extract, and incubated at 37 °C up to 4 h. The amount remaining at predetermined time interval (1, 2, 3 and 4 h) was analyzed by HPLC.

2.7. Procedure for mucosa permeation in vitro

After sacrificing rabbit by injecting air into the marginal ear vein, the nasal, duodenal, colonic and rectal mucosae were carefully excised and mounted onto the cell opening (0.64 cm^2) of a side-by-side permeation system. The mucosal side of excised mucosa was faced to donor compartment and its serosal side was faced to receptor compartment. Donor half-cell was filled with 3.5 ml of ondansetron hydrochloride solution in normal saline and the receptor half-cell was filled with 3.5 ml of 40% PEG 400