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Nasal drug delivery of sumatriptan succinate

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Received May 5, 2004, accepted July 9, 2004

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Pharmazie 60: 347–349 (2005)

The purpose of this work was to increase the nasal absorption of sumatriptan succinate by using bile salts. A rat *in situ* nasal perfusion technique was used to examine the rate and extent of absorption of sumatriptan succinate. *In vitro* enzymatic drug degradation studies were carried out with rat nasal washings. Various experimental conditions such as nasal perfusion rate, pH of the perfusion medium and concentrations of absorption enhancers such as sodium deoxycholate, sodium caprate, sodium tauroglycocholate and EDTA were optimized. *In vivo* studies were carried out for the optimized formulation in rabbits and the pharmacokinetics parameters of nasal solution were compared with marketed nasal solutions. Nasal absorption of sumatriptan succinate was pH dependent. It was found maximum at pH 5.5 and decreased at higher pH values. In *in vitro* enzymatic degradation studies, no measurable degradation was observed during the first week. The extent of drug absorption was increased by absorption enhancers. Sodium deoxycholate appeared to be more effective for enhancing the nasal absorption of sumatriptan succinate than the other absorption enhancers. The order of increasing absorption of sumatriptan succinate caused by the enhancers was sodium deoxycholate $>$ sodium caprate $>$ sodium tauroglycocholate $>$ EDTA.

1. Introduction

Sumatriptan succinate (SMT) is a selective serotonin (5-HT1) agonist given orally or subcutaneously as succinate for the treatment of migraine. Absorption of orally administered SMT is slow, variable and incomplete with a bioavailability of about 14%. Therefore, this compound serves as a good model drug to study nasal absorption enhancement via absorption enhancers.

In this study, the effect of absorption enhancers such as sodium deoxycholate, sodium caprate, sodium tauroglycocholate and EDTA on nasal absorption of SMT was studied. A rat *in situ* nasal perfusion technique (Hirai 1981; Huang 1985) was used to examine the nasal uptake of the drug and their chemical stability and enzymatic hydrolysis of drug.

2. Investigations, results and discussion

In control experiments performed without animals, drug loss by adsorption onto or absorption into the tubes of the perfusion system was found to be insignificant. Consequently, this loss was not taken into account for data processing.

Nasal absorption of SMT was found to be pH dependent as shown in Fig. 1. Nasal absorption of SMT after 120 min at pH 5.5 showed 21.5% whereas at pH 7.2 showed 17.5%. Because drug is of low molecular weight and freely soluble in water, it is expected that the drug will pass mainly by passive diffusion through aqueous pores i.e. tight junctions (Martin et al. 1964). The existence of aqueous pores in the nasal mucosa through which water-soluble drugs permeate has been suggested by several authors (Hirai et al. 1978; Hayashi et al. 1983). In rats, used as a model here the estimated range of the pore size of nasal mucosa is 0.4–0.8 nm and the number of pores is four times higher than that in the jejunum (Yang et al. 2001). The fact indicates that the nasal epithelium barrier is less tight than the intestinal barrier. It is thus clear that those zwitterions, small in molecular size and weight and with significant water solubility will be better

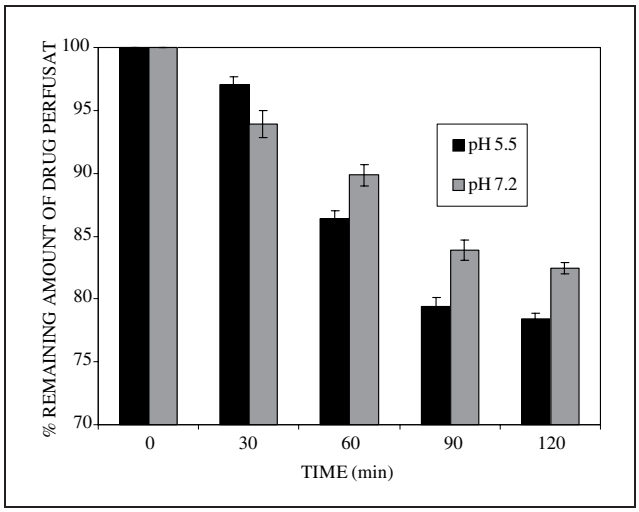

Fig. 1: Effect of pH on nasal absorption of sumatriptan succinate (n = 6)

absorbed from the nasal than from the gastrointestinal mucosa.

Input rates of 1, 2 and 4 ml/min seemed to have no effect on the SMT nasal absorption phase, which was confirmed by the non-significant difference between percent remaining amounts of drug in perfusate after 2 h.

In enzymatic drug degradation studies, no measurable enzymatic drug degradation occurred during the first week. The drug was found to be resistant to the enzymatic activity of rat nasal mucosa.

The effects of various bile salts such as sodium deoxycholate, sodium caprate, sodium tauroglycocholate and a chelating agent such as EDTA on nasal absorption of SMT were studied. Sodium caprate (0.5%w/v) and to a less extent sodium tauroglycocholate (0.5%w/v) are able to improve the nasal absorption of SMT as shown in Fig. 2. Sodium caprate showed 29.7% nasal absorption of SMT whereas sodium tauroglycocholate showed 25.7% nasal absorption of SMT after 120 min. To further improve nasal absorption of SMT, sodium deoxycholate (1% w/v) and EDTA (0.5%w/v) were tried. Sodium deoxycholate showed 37.5% of nasal absorption of SMT whereas EDTA showed 24.8% of nasal absorption of SMT after 120 min as shown in Fig. 3.

Additionally, the effect of different concentrations of bile salts on nasal absorption of SMT was studied. The effect of sodium deoxycholate on nasal absorption of SMT was concentration dependent as shown in Fig. 4. The order of increasing absorption of SMT caused by the enhancers was sodium deoxycholate > sodium caprate > sodium tauroglycocholate > EDTA.

Our data demonstrate that absorption enhancers, especially sodium deoxycholate, were effective in enhancing the nasal absorption of SMT. It was reported that bile salts interact with cell membranes to form reverse micells, which act as channels to increase permeation. It was also reported that bile salts enhance the permeation by removing epithelial cells, which constitute a major permeability barrier (Hersey and Jackson 1987; Zhang et al. 2001; Mikov et al. 2003).

Na-caprate is reported to enhance the transcellular permeability by causing membrane perturbation by interacting with the protein region in the membrane and to enhance the paracellular permeability by some structural changes

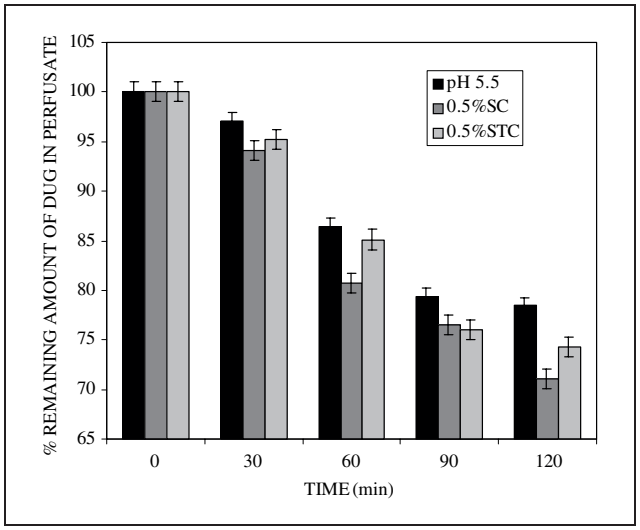

Fig. 2: Effect of sodium tauroglycocholate (STC) and sodium caprate (SC) on nasal absorption of sumatriptan succinate (n = 6)

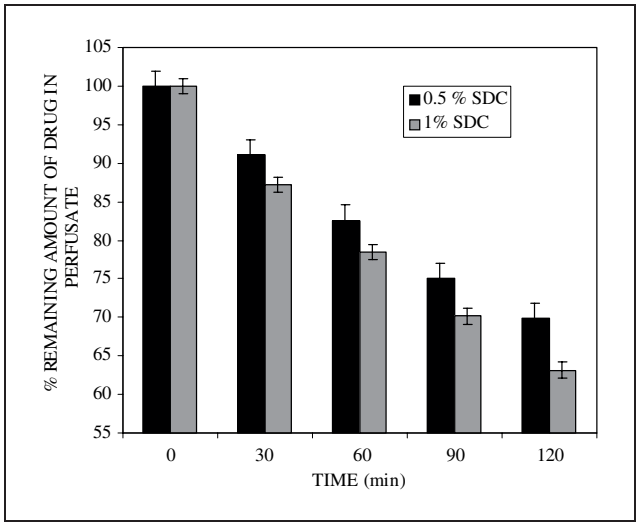

Fig. 4: Effect of various concentrations of SDC on nasal absorption of sumatriptan succinate (n = 6)

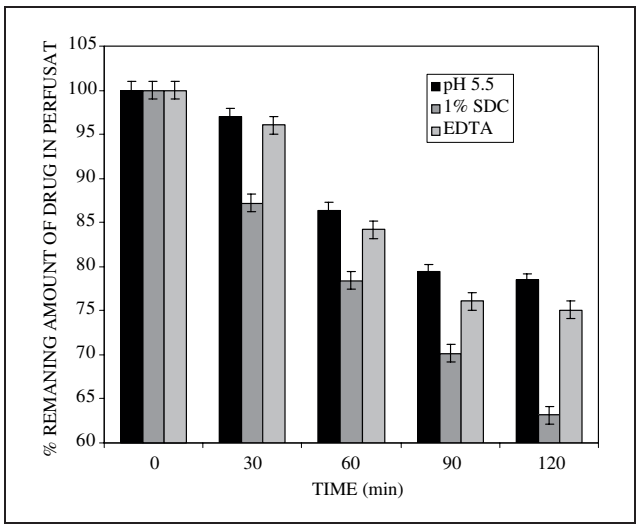

Fig. 3: Effect of EDTA and sodium deoxycholate (SDC) on nasal absorption of umatriptan succinate (n = 6)

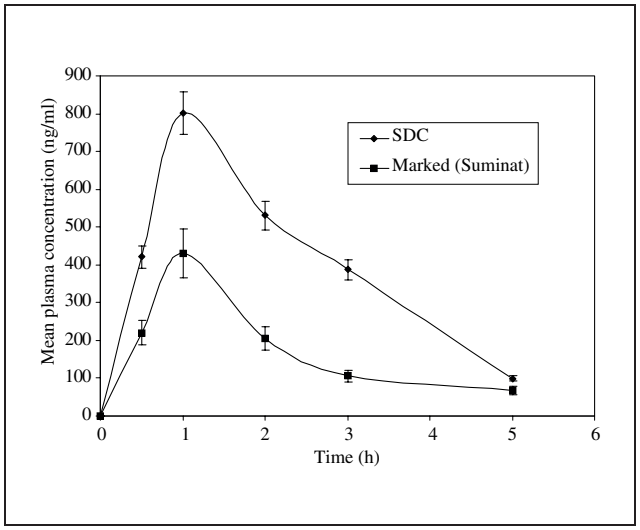

Fig. 5: Mean plasma concentration of SMT from the marketed (Suminat) and 1% SDC containing nasal solutions (n = 6)

in the tight junctions (Tomita et al. 1988). EDTA is known to form a chelating compound with calcium ions existing at the tight junctions in the membrane, resulting in increased permeability of the paracellular route (Gwak et al. 2003).

In vivo studies were carried out for the 1% SDC formulation in rabbits. After administration of nasal solutions, the drug was observed to achieve plasma level rapidly. C_{max} values for marketed nasal and 1% SDC containg nasal solutions were 430 and 802 ng/ml respectively. t_{max} for marketed nasal and 1% SDC containing nasal solutions was 1 h as shown in Fig. 5. K_{el} was 0.36 h^{-1} for the marketed nasal solution and 0.7 h^{-1} for the nasal solution. Plasma half lives for marketed and 1% SDC containing nasal solution were 1.9 and 1.8 h respectively. AUC values for marketed and 1% SDC contain nasal solution were 869 and 2004 h · μg/ml. A significant difference between the products was found for all the pharmacokinetic parameters. However, between the subjects the difference was non-significant indicating that there was little subject-to-subject variation.

The nasal *in situ* perfusion technique can be used to study the nasal absorption of SMT. We conclude that sodium deoxycholate appears to be more effective for enhancing the nasal absorption of sumatriptan succinate than other bile salts. In addition, sodium caprate, sodium taurocholate and EDTA are suitable adjuvants for improving the nasal absorption of SMT.

3. Experimental

3.1. Materials

Sumatriptan succinate (SMT) was a gift sample from Wyeth laboratories Ltd., India. HPLC grade methanol and disodium hydrogen orthophosphate were obtained from s.d. Fine chemicals, India. Sodium deoxycholate (SDC), sodium caprate (SC), sodium tauroglycocholate (STC) and EDTA were obtained from High Media Ltd., India.

3.2. Methods

3.2.1. Preparation of nasal solutions

Absorption enhancers were dissolved in phosphate buffer saline solution to obtain the desired concentration. Drug was dissolved in the above solution (0.45 μg/ml) and pH of the solution was adjusted as necessary with 4M HCL or NaOH. Osmolarity of the solution was adjusted using sodium chloride solution.

3.2.2. Animal studies

The rat *in situ* nasal perfusion technique developed by Hirai et al. (1981) and Huang et al. (1985) was used. Male albino rats, weighing 250–350 g, were anesthetized with an intraperitoneal injection of thiopental sodium (0.1 ml/100 gm body weight). After an incision was made in the neck, the trachea was cannulated with a polyethylene (PE-200) tube to maintain respiration. Another PE-200 tube was inserted through the esophagus towards the posterior part of the nasal cavity to the mouth. The cannula served to deliver the solution to the nasal cavity. The nasopalantine tract was sealed with cyanoacrylate adhesive. The perfusion medium, which was prepared with isotonic phosphate buffer saline solution, pH 5.5, was circulated by means of a peristaltic pump at a flow rate of 1, 2 and 4 ml/min. The perfusate was recollected into a reservoir, which was maintained at a temperature of 37±0.5 °C throughout the course of an experiment. A constant perfusate volume of 5 ml was maintained throughout the experiment with constant stirring and an aliquot (100 μL) was sampled at 0, 30, 60, 90 and 120 min time interval. This was replaced with fresh buffer (100 μL).

Separate experiments were conducted to measure the loss of analyte from the solution due to absorption and/or adsorption to system components (tubing, pump or glasswares) or due to volatilization. Each perfusion solution was circulated for 2 h through the system without the rat included. The reservoirs were sampled at 30 min intervals to measure disappearance of analyte with time.

3.2.3. In Vitro enzymatic degradation study with rat nasal washing

Isotonic phosphate buffer saline solution, pH 5.5, was perfused through the rat nasal cavity for 2 h. The perfusate at the end of the experiment was collected and stored at −70 °C until further use. One volume of drug stock solution was mixed with nine volumes of prewarmed nasal washing solution (37 °C) and vortexed (Yang et al. 2001). A zero time sample (100 μL) was taken and mixed with 10 μL of perchloric acid and vortexed for 30 s to precipitate proteins. The mixture was incubated at 37 °C, and 100 μL samples were withdrawn at predetermined time intervals and subjected to the same treatment.

3.2.4. Analytical procedure

The concentration of SMT was determined by reversed phase HPLC. The HPLC method was validated for linearity, accuracy, precision and extraction efficiency. Prior to analysis, all the samples were treated with perchloric acid (70% solution) to precipitate the proteins. After centrifugation at 10000×g for 15 min, the supernatant was injected onto the HPLC column (Waters C_{18} spherisorb, 5 μm, 250 mm). The signal was monitored at 254 nm. Mobile phase was prepared with methanol and phosphate buffer (pH 7.0) (70 : 30 v/v). The final pH of the mobile phase was adjusted to 3.10 ± 0.01 with orthophosphoric acid. The flow rate was maintained at 1 ml/min.

3.2.5. In vivo studies

Bioavailability studies were conducted in a group of six rabbits divided into two subgroups of three animals each. Each group was administered individually the nasal solution and marketed nasal solution (Suminat) (25 mg/0.1 ml) for comparative studies. The nasal solutions were instilled in the nares of rabbits with the help of a nasal spray (nasal spray contains VP3 valve and CB18AW).

Blood (1.5 ml) was collected from the marginal vein at 0.5, 1, 2, 3 and 5 h following administration of the drug. The samples were centrifuged immediately and plasma was stored at −20 °C till the time of analysis. The drug was extracted from plasma by a suitable extraction procedure. To 1 ml of plasma, 2 ml of acetonitrile were added in a stopper test tube. This was vortexed for 5 min and centrifuged at 5000 rpm for 10 min. The organic phase was collected separately. It was evaporated under nitrogen gas and reconstituted with 0.5 ml of water. This was analysed using HPLC with UV detection. The mobile phase consisted of methanol : phosphate buffer (20 : 80 v/v). pH of the solution was adjusted to 7.30 with orthophosphoric acid. Tetrabutyl ammonium hydroxide (0.1%) was added as an ion-pairing reagent. The analysis was done at a wavelength of 254 nm. Various parameters such as C_{max}, t_{max}, AUC and other parameters such as K_{el} and $t_{1/2}$ were calculated from the observed plasma concentration against time profile.

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