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Research paper

Selection of drug candidates for gastroretentive dosage forms: Pharmacokinetics following continuous intragastric mode of administration in a rat model

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Abstract

The purpose of the study was to evaluate the pharmacokinetic effects obtained by gastroretentive dosage form (GRDF) for drugs absorbed by passive paracellular diffusion (atenolol, acyclovir) or active transport (valacyclovir). Model drugs were delivered as gastric infusion (GInf) through an implanted catheter (resembling GRDF), intravenous, oral (PO), and colonic administration to rats. For atenolol (highly soluble drug), GInf resulted in a prolonged T_{max} and reduced C_{max} in comparison to PO, whereas bioavailability was similar. Bioavailability after colonic bolus was significantly lower. Results were also simulated by a pharmacokinetic model. For acyclovir, GInf and PO demonstrated almost the same pharmacokinetic profile with low bioavailability, most probably due to the solubility-limited absorption. Valacyclovir demonstrated the significant change in the shape of pharmacokinetic profile as a function of the rate of gastric delivery, without variation in bioavailability. Valacyclovir was not absorbed from colon. Experimental and theoretical methodologies to assess the pharmacokinetic influences of GRDF mode of administration were developed, avoiding the need to compound the drug in a dosage form. GRDF provides a mean for controlled release of compounds that are absorbed by active transport in the upper intestine. It also enables controlled delivery for paracellularly absorbed drugs without a decrease in bioavailability.

Keywords: Pharmacokinetic model; Controlled release; Absorption mechanism; Intestinal transit; Absorption window

1. Introduction

The gastro-intestinal (GI) tract is composed of several regions differing in anatomy, biochemical environment, microbial flora, expression of transporters, and absorption characteristics. There are several processes that may occur simultaneously following drug release from a dosage form (DF) in the GI tract, including: chemical/enzymatic/bacterial degradation, absorption (passive and/or active), precipitation, efflux by P-glycoprotein pump, and metabolism by Cyp450 enzymes. As a consequence the pharmacokinetic profile of a drug may be influenced by its delivery site.

Many clinically used drugs could benefit from controlled release dosage forms (CR). A common property of conventional CR technologies is that a large part of the drug load is released in the colon, where the DF stays for a relatively long time period. This delivery approach, while suitable for many molecules, was found to be inappropriate for drugs that are poorly absorbed from the lower part of the GI tract [1].

The concept of controlled release gastroretentive dosage form (GRDF) was introduced in order to enable continuous delivery to the upper part of the GI tract, while minimizing the limitation of poor absorption from the colon. These DFs are designed to be retained in the stomach for

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a prolonged time period while releasing their content in a continuous and controlled manner. The gastric retention is attained by preventing the DF from passing through the pyloric sphincter. Detailed discussion regarding the different technological approaches to achieve gastric retention can be found elsewhere [2–6]. A number of alterations in pharmacokinetic and pharmacodynamic profiles of drugs have been reported following drug administration in GRDFs [7–11]. However, while much effort has been invested by research laboratories in the technological development of different types of GRDFs, systematic research on appropriate drug candidates as presented in this work has not been performed, yet.

The GI tracts of rats and humans were found to be similar in their absorption properties [12–15]. In the present study we developed experimental and theoretical methodologies for evaluation of pharmacokinetic effects of GRDF in the rat model. The effects of this delivery mode on pharmacokinetics of three model molecules differing in their molecular and absorption characteristics (acyclovir (ACV), atenolol (AT), and valacyclovir (VACV)) were investigated.

2. Materials and methods

2.1. Chemicals

Atenolol, acyclovir, and metoprolol tartarate were purchased from Sigma–Aldrich, Rehovot, Israel. Acyclovir suspension (Zovirax®) was purchased in the local pharmacy. Valacyclovir was purchased from Eurotrade World Commerce, Madrid. All other chemicals were of analytical reagent grade, and solvents were of HPLC grade.

2.2. Animals

All surgical and experimental procedures were reviewed and approved by the Animal Experimentation Ethics Committee of The Hebrew University Hadassah Medical School, Jerusalem. Male Wistar rats (Harlan, Israel), weighing 280–400 g, were used for all surgical procedures. The anesthesia of animals for the period of surgery was initiated with 1 mL/kg solution of ketamine 20 mg/mL: xylazine 100 mg/mL (90:10, v/v) by intra-peritoneal injection and maintained by pure ketamine as needed. In all rats the right jugular vein was cannulated with a cannula made up of polyethylene tubing (PE50, Intramedic® Polyethylene Tubing, Becton–Dickinson, MD) to allow blood sampling. Furthermore, in groups that received gastric continuous infusion or colonic administration, an additional PE50 cannula was inserted into the appropriate part of the GI tract (stomach or colon) to allow drug administration. After the surgery, animals were transferred to metabolic cages and stabilized overnight (12–16 h), during which the animals were fasted, and water was available *ad libitum*.

2.3. Experimental procedure

In the present study the drugs were administered by several routes. Intravenous bolus (IV) dose was delivered through the jugular vein cannula and followed by 0.2 mL of heparinized saline (50 IU/mL) to ensure the delivery of the whole dose. Oral bolus dose was delivered by a gavage needle. Delivery to the stomach or colon (caecum) was conducted through the cannula in the corresponding region of the GI tract.

The following doses and dosing formulations were used in the study. Acyclovir: IV dosing – 5 mg/kg (2.5 mg/mL solution in water, at 37 °C); oral bolus – 120 mg/kg (suspension 40 mg/mL); gastric infusion – 120 mg/kg over 4 h (10 mg/mL solution in water, with pH adjusted to 1.2 with HCl). Valacyclovir: oral bolus – 20 and 40 mg/kg (20 or 40 mg/mL solution in water, respectively); gastric infusion – 20 mg/kg over 4 or 8 h (2 or 1 mg/mL solution in water, respectively); colon infusion – 20 mg/kg over 4 h (2 mg/mL solution in water). Atenolol: IV dosing – 2 mg/kg (2 mg/mL solution in water); oral bolus, gastric infusion, and caecum bolus – 10 mg/kg (5, 1, and 15 mg/mL solution in water, respectively). Sequential blood samples were collected into heparin-containing test tubes at predetermined time intervals. Plasma was separated by centrifugation for 8 min at 1000*g* and stored at −20 °C until analysis.

2.4. Analytical procedure

All tested compounds were analyzed using Waters 2695 Separation Module HPLC system with Waters 2475 Fluorescence Detector and Waters 2996 Photodiode Array Detector (Waters Corporation, Milford, MA).

The assay procedure for acyclovir in plasma samples was based on a method previously described by Mascher et al. [16]. In brief, plasma (120 μL) was mixed for 20 s with 35 μL of perchloric acid (3 N) and then centrifuged for 8 min at 10,000*g*. The supernatant was injected directly into the HPLC system. The volume of injection was 50 μL. The separation was achieved by Phenomenex Gemini C18 column (5 μm, 4.6× 250 mm) at ambient temperature. The mobile phase consisted of methanol (15%) and water (85%, adjusted to pH 1.2 with perchloric acid). The flow was set to 1 mL/min. Acyclovir was detected with a $\lambda_{excitation}$ of 260 nm and $\lambda_{emission}$ of 375 nm. Retention time of acyclovir was about 3.7 min. The method was linear between 20 and 20,000 ng/mL.

Analysis of atenolol was based on previously reported methods [17,18] that were modified to meet our requirements. Plasma samples (150 μL) were mixed with 150 μL NaOH (1 M) and 15 μL of internal standard (metoprolol tartarate, 1 μg/mL). Both materials were extracted with 4 mL of ethyl acetate, evaporated to dryness and reconstituted with 140 μL of water. The volume of injection was 90 μL. The separation was achieved by XTerra RP-18 (3.5 μm, 4.6× 100 mm, Waters). The mobile phase consisted