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Research paper

Mechanistic understanding of time-dependent oral absorption based on gastric motor activity in humans

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Abstract

The relationship of gastric motor activity and gastric emptying of 0.7 mm caffeine pellets with their absorption was investigated in the fed state in healthy human subjects by simultaneous monitoring of antral motility and plasma concentrations. A kinetic model for gastric emptying-dependent absorption yielded multiple phases of gastric emptying and rate constants (k_g) with large inter-individual differences and large variability in onset of gastric emptying (50–175 min). The model suggests that 50% of the dose is emptied in 1–2 h and over 90% emptied by 3.5 h following dosing, in all subjects. The maximum values of k_g (k_g(max)) were much greater than those reported for emptying of liquids in the fasted state and were comparable to k_g values in the late Phase II/III of the migrating motor complex (MMC). The model described the observed irregular absorption rate–time and plasma concentration–time profiles adequately but not in detail. The model was more successful at simulating double-peak phenomena in absorption rate profiles and onset of caffeine absorption. The results suggest that gastric emptying regulates drug absorption of small particles in the fed state. Further, estimates of k_a derived using the time-dependent absorption model were closer to the intrinsic absorption rate constant for caffeine.

Keywords: Time-dependent absorption; Gastric motor activity; Gastric emptying; Fed state; Absorption rate constant; Absorption rate; Plasma concentration–time profile; Caffeine

1. Introduction

Drug absorption kinetics after oral administration can be determined using membrane permeability, drug dissolution and gastrointestinal (GI) motility, although intestinal metabolism and secretion must be considered as factors influencing the drug absorption for some drugs [1–3]. Gastric emptying can be the rate-limiting step in absorption of high permeability-high solubility drugs classified as Class I in the Biopharmaceutics Classification System [2], because the absorption from the stomach is generally very small due to the very small effective surface area of stomach and the 1–1.5-mm thick mucus layer covering the mucosal surface [1]. Acetaminophen orally administered as a liquid solution is known to be regulated by gastric emptying under fasted conditions [4]. Lipka et al. reported that

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fasted-state gastric motility determined the rate and the extent of celiprolol absorption in dogs [5]. The retardation of GI transit, especially that of gastric emptying, is reported to cause the delay of T_{max} for several drugs after oral administration in the fasted state in rats [6]. The increased variability in plasma concentration–time curves of cimetidine has been shown to be related to variability in gastric emptying [7]. The appearance of double peaks in plasma concentration–time curves is a typical example of variability of plasma profiles and has been observed with several drugs [4,5,8–14]. Several hypotheses based on region-dependent variation in absorption [13], enterohepatic recirculation [15,16], variable gastric emptying and intestinal transit rates [4,5,17], and intestinal bacterial reconversion of biliary metabolite [18] have been proposed to account for these observations.

The possible role of gastrointestinal motility as a major determinant of the phenomena of secondary maxima occurring in the fasted state has been previously addressed [16,19]. Gastrointestinal motility in the fasted state is characterized by cyclical fluctuations in contractile activity of the stomach and intestine and is composed of four phases [20]. The initial basal phase, Phase I, is characterized by a complete lack of contractions followed by a 'preburst' activity, also termed Phase II, wherein the contractions increase in number and activity. Phase III is characterized by large-amplitude contractions that occur at the maximum frequency observable and is followed by an intermediate stage, Phase IV, before the cycle repeats itself. Phase IV is sometimes absent and is a transition period between the intense activity in Phase III and the basal quiescent Phase I. This cyclical pattern of contractile activity is termed the migrating motility complex (MMC). The regulation of MMC has been reported to be under both humoral and neural control. Thus, gastric motor activity in MMC regulates gastric emptying in the fasted state [21,22]. Gastric emptying in the fed and fasted state is governed by antral motility in conjunction with pyloric resistance and duodenal feedback mechanisms [21,23]. In the fed state, the MMC is largely abolished; however, low amplitude contractions facilitate gastric emptying of small solid particles through the pylorus.

It has been suggested that beyond a certain size (2–7 mm) [24,25], gastric emptying occurs predominantly during Phase II and III of the fasted-state MMC. In a previous study we demonstrated that gastric emptying of 0.7 mm caffeine pellets occurred in the fed state whereas 3.6 mm acetaminophen pellets emptied following onset of Phase II contractions in the fasted state, corroborating size-dependent gastric emptying [26]. Although gastric motor activity has often been monitored [23] and its qualitative relationship with drug absorption described in several reports [19,23,26,27], quantitative models correlating drug absorption kinetics to gastric motor activity data have yet to be published. In the present report we utilized the gastric motility and plasma concentration–time data that were simultaneously determined in the previous study [26], and developed a kinetic model to describe absorption rate–time and plasma concentration–time profiles in terms of the measured gastric motor activity in each subject.

2. Materials and methods

2.1. Materials

Spherical enteric-coated caffeine pellets, 0.7 mm in diameter, were manufactured under cGMP guidelines in collaboration with Pharmacia Upjohn Co. (now Pfizer) (Kalamazoo, MI) and have been described in detail earlier [26]. The diameter of the pellets was measured using a direct digital micrometer (Mitutoyo; Tokyo, Japan) [26]. Hydroxypropylmethylcellulose (HPMC) was obtained from The Dow Chemical Co. (Midland, MI). All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO) and were of analytical grade or better. HPLC grade solvents were used in all the assays.

2.2. Caffeine pellet dose and viscous caloric meal

The caffeine dose consisted entirely of single pellets, as all fused pellets were manually removed prior to weighing. The *in vitro* characterization of the pellet and drug release in various media have been described earlier [26]. Thus, it was determined that no drug marker was released at pH 2.0 for 2 h and that 80–100% of caffeine was released within 20 min at pH 6.0 [26]. The viscous caloric meal consisted of HPMC, glucose, and water. The target viscosity of 4000 cP was achieved with K15MP HPMC using the hot/cold dispersion method [28]. Each 200-ml viscous meal contained 100 kcal of glucose by incorporation of a glucose tolerance beverage (General Medical Corp., Richmond, VA). The viscosity level of each meal was assessed at 37 °C with a Rheo-Tech Visco-Elastic Rheometer (Rheo-Tech International Ltd.) and was considered acceptable if it was within ±200 cP of the target viscosity. The 4000-cP viscosity meal was chosen since the most significant relationship between the onset of absorption and gastric motility was observed with a 4000-cP viscous caloric meal compared to either the 6000- or 8000-cP viscosity meal [26]. It was also noted that neither gastric motility patterns nor plasma pharmacokinetic parameters such as AUC, C_{max}, and T_{max} were affected in the range of viscosities examined [26].

2.3. Human study protocol

Twelve healthy subjects (10 males and 2 females) gave informed written consent to participate in the study. This investigation complied with tenets of the Declaration of Helsinki promulgated in 1964 and was approved by the University of Michigan Institutional Review Board. The subjects were 22–39 years of age and were within 20% of their ideal body weight. Subjects were deemed healthy based on medical history, physical examination, complete blood count and serum chemistries. Persons with a history