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REVIEW

Effects of Proton Pump Inhibitors on Gastric Emptying: A Systematic Review

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Abstract The proton pump inhibitor (PPI) is widely used for the treatment of gastroesophageal reflux disease, peptic ulcer diseases, and functional dyspepsia. The pathogenesis of these acid-related and/or functional upper gastrointestinal disorders is potentially associated with abnormal gastric emptying. To date, variable effects of PPIs on gastric emptying have been reported. Therefore, it is relevant to gather and analyze published information on this topic. A systematic literature search has been performed, showing that the delaying effect of PPIs on gastric emptying of solid meals is consistent, whereas the effect of PPIs on the emptying of liquids is inconsistent. The underlying mechanisms whereby PPIs may affect gastric emptying have been discussed, most of which still remain hypothetic. Gastric emptying of solids involves a process of peptic hydrolysis. PPIs impair the hydrolytic digestion by inhibiting acid-dependent peptic activity, thereby delaying the solid emptying. Gastric emptying of liquids largely depends on volume and energy density of intragastric contents. PPIs variably modify the volume and the energy density by reducing gastric fluid secretion, thereby modifying the liquid emptying in an unpredictable manner. Hypergastrinemia has been considered to delay gastric emptying, but it seems of minor importance in the regulation of gastric emptying during PPI use. The delayed emptying of solids due to PPI therapy may have clinical implications in the management of gastroesophageal reflux disease, functional dyspepsia, as well as diabetes.

Keywords Gastric secretion · Gastric acid · Gastric emptying · Proton pump inhibitor

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Introduction

Gastroesophageal reflux disease, peptic ulcer diseases, and functional dyspepsia are very prevalent in outpatient settings. These acid-related and/or functional disorders of the upper gastrointestinal tract are currently treated with antisecretory compounds, including a histamine H_2-receptor antagonist (H_2RA) and a proton pump inhibitor (PPI) [1, 2]. PPIs are more potent in reducing gastric acid than H_2RAs, therefore they are the most important drugs in practices.

The stomach is functionally characterized by motor and secretory functions, and these two functions are closely interrelated [3, 4]. Motor function is generally represented by gastric emptying. Orderly gastric emptying plays an important role in establishing nutritional homeostasis, without evoking unpleasant abdominal sensations [5]. On the other hand, disordered emptying may be associated with the pathophysiology of gastroesophageal reflux disease [1], peptic ulcer diseases [6], and functional dyspepsia [7]. The secretory function is essential for effective digestion and absorption of nutrients. The stomach secretes a large volume of gastric juice to properly adjust acidity, osmolality, caloric density, and viscosity of intragastric contents [8]. PPIs drastically change gastroduodenal luminal environments by suppressing gastric secretion. Taking the close motor-secretory interaction into account, PPIs are necessarily expected to modulate gastric emptying. To date, variable effects of PPIs on gastric emptying have been reported [3].

In the present review we analyze published information about the effects of PPIs on gastric emptying, discuss the underlying mechanisms by which PPIs may affect gastric emptying, and provide clinical implications of PPI-related alterations in gastric emptying. To our knowledge, no review article addressing this subject has yet been published.

Review of Articles Concerning the Effects of PPIs on Gastric Emptying

This section summarizes published information as to whether PPIs affect gastric emptying.

The English language articles reporting the effects of PPIs on gastric emptying in human adults were searched via PUBMED (from 1979 to September 2009), using the international nonproprietary names of currently used PPIs ("omeprazole," "lansoprazole," "rabeprazole," "esomeprazole," and "pantoprazole") in combination with the key term "gastric emptying." An additional manual search was performed for references listed in each of the articles. As a result, a total of 25 relevant publications were identified [9–33], consisting of 23 full papers and two conference abstracts [10, 25]. There was only one study on esomeprazole [21], and no studies were found on pantoprazole.

Results

The effects of PPIs on gastric emptying were highly variable. Several confounding factors would contribute to the variability, including test meals, sample size of subjects, methods for measuring gastric emptying, and pretreatment regimen of PPIs. Of these confounding factors, the test meals would be the most influential [12, 17]. Thus, the results have been separately summarized according to the test meals (inert liquid vs. caloric liquid vs. solid). Of the 25 articles collected, eight were on the gastric emptying of inert liquids (Table 1), seven were on that of caloric liquids (Table 2), and 14 were on that of solids (Table 3). With the exception of Horowitz's study, which enrolled duodenal ulcer patients [24], all the studies were carried out on healthy individuals.

The summary for gastric emptying of inert liquids shows entirely inconsistent results (Table 1). Five of the eight studies might not represent a pure effect of PPIs on the inert-liquid emptying. In the studies of Rasmussen et al. [9, 12, 13] and the study of Jian et al. [10], gastric emptying of water was evaluated following ingestion of a solid/liquid mixed meal. When solid/liquid mixed meals are consumed, the solid component may alter gastric emptying of the liquid component, or vice versa [8, 34, 35]. In the study of van Wyk et al. [11], gastric emptying was assessed as an absorption rate of paracetamol given orally in the form of a tablet. This method would not accurately reflect gastric emptying because absorption processes of a paracetamol tablet involve not only gastric emptying but also tablet dissolution [36]. The remaining three studies appear to be relevant for the pure effect of PPIs [14–16]. From the results of the only three studies, however, we cannot refer to any definitive conclusion at all.

The summary for gastric emptying of caloric liquids suggests that PPIs are unlikely to affect the emptying (Table 2). Only two of the eight studies showed a delaying effect of rabeprazole, but statistical significance for the effect was marginal [22, 23].

Table 1 Effects of proton pump inhibitors on gastric emptying of inert liquids

Effect	Authors (year of publication)	Drug	Number of subjects	Dosage	Test meal (calorie of solid component)	Method	Reference
No effect	Rasmussen et al. (1991)	Omeprazole	$n = 10$	40 mg daily for 10 days	150 ml water omelet (334 kcal)	Scintigraphy	[9]
	Jian et al. (1989)	Lansoprazole	$n = 18$	30 mg daily for 2 days	500 ml water solid meal (calorie, not stated)	Scintigraphy	[10]
Delaying	van Wyk et al. (1994)	Omeprazole	$n = 6$	240 mg divided three times within a day	250 ml water	Paracetamol absorption	[11]
	Rasmussen et al. (1997)	Omeprazole	$n = 10$	40 mg daily for 10 days	150 ml water omelet (334 kcal)	Scintigraphy	[12]
	Rasmussen et al. (1999)	Omeprazole	$n = 10$	40 mg daily for 10 days	150 ml water omelet (334 kcal)	Scintigraphy	[13]
	Sanaka et al. (2009)	Rabeprazole	$n = 9$	20 mg daily for 3 days	1,000 ml water	^{13}C breath test	[14]
Accelerating	Chang et al. (2001)	Omeprazole	$n = 15$	Single 20 mg before meal	500 ml water	Applied potential tomography	[15]
	Sanaka et al. (1999)	Lansoprazole	$n = 6$	30 mg daily for 3 days	200 ml water	Paracetamol absorption	[16]

Table 2 Effects of proton pump inhibitors on gastric emptying of calorie-containing liquids

Effect	Authors (year of publication)	Drug	Number of subjects	Dosage	Test meal (calorie/volume)	Method	Reference
No effect	Cecil et al. (2004)	Omeprazole	$n = 8$	Single 80 mg before meal	Soup (400 kcal/425 ml)	Scintigraphy	[17]
	Vidon et al. (1993)	Lansoprazole	$n = 6$	30 mg daily for 7 days	Commercialized semi-solid meal (500 kcal/400 ml)	Aspiration technique	[18]
	Renou et al. (2001)	Lansoprazole	$n = 6$	30 mg daily for 7 days	Commercialized liquid meal (375 kcal/375 ml)	Aspiration technique	[19]
	Takahashi et al. (2006)	Rabeprazole	$n = 20$	10 mg daily for 7 days	Commercialized liquid meal (200 kcal/200 ml)	^{13}C breath test	[20]
	Franke et al. (2008)	Esomeprazole	$n = 16$	20 mg daily for 7 days	Beer (500 ml)	Ultrasound	[21]
Delaying	Sanaka et al. (2006)	Rabeprazole	$n = 13$	20 mg daily for 3 days	Commercialized liquid meal (300 kcal/300 ml)	^{13}C breath test	[22]
	Yamamoto et al. (2008)	Ransoprazole	$n = 12$	20 mg daily for 3 days	Commercialized liquid meal (300 kcal/300 ml)	^{13}C breath test	[23]

The summary for gastric emptying of solids demonstrates a fairly consistent trend that PPIs delay the emptying of solids (Table 3). It should be pointed out that in most of the studies, the test meal was relatively soft, such as an egg-derived food. Since hard meals are emptied from the stomach more slowly than soft ones [5, 8], studies with harder test meals, such as chicken liver, may provide more consistent results of delayed gastric emptying of solids after PPIs.

Potential Confounding Factors

Small sample size is responsible for a statistical type II error (false negative). The sample size was small ($n < 10$) in eight of the 25 studies: three of the eight studies were about gastric emptying of inert liquids [11, 14, 16], three were about that of caloric liquids [17–19], and two about that of solids [24, 25]. The three studies with inert liquids yielded statistically significant results. In contrast, the other five studies with caloric liquids and solids showed insignificant results ("No effect"), which might be of the type II error.

A variety of methods are used to measure gastric emptying (Tables 1, 2, 3). The accuracy of the measurements might influence the results of studies [37, 38]. Of the methods for gastric emptying, scintigraphy is regarded as the most accurate, but its use is highly limited because of substantial irradiation posed by the technique. Non-radioactive modalities in widespread use include ultrasonography and indirect tracer methods (paracetamol absorption and breath testing). However, these methods are less sensitive than the scintigraphy, and use of them can cause the type II error. The aspiration technique is essentially accurate for evaluating gastric emptying of liquids, but the technique requires gastric and duodenal intubation [37], which themselves interfere with gastric motility [39]. The other methods, such as applied potential tomography, need further validation regarding their accuracy.

PPIs require a multiple-dosing regimen to achieve sufficient suppression of gastric secretion [40]. Insufficient suppression due to single dosing can be responsible for the type II error, because the delaying effect of PPIs on solid emptying seems to be dose-dependent [41]. The three studies employed the single-dosing regimen [15, 17, 24], only one of which provided a significant result [15].

Basic Physiology of Gastric Motor-Secretory Functions

Knowledge of the basic physiology of gastric functions is essential for a full understanding of how PPIs modulate gastric emptying. Thus, before discussing mechanisms by which PPIs may affect gastric emptying, this section

Table 3 Effects of proton pump inhibitors on gastric emptying of solids

Effect	Authors (year of publication)	Drug	Number of subjects	Dosage	Test meal (calorie)	Method	Reference
No effect	Horowitz et al. (1984)	Omeprazole	$n = 8$	Single 90 mg before meal	Ground beef hamburger (not stated) 150 ml 10% dextrose solution	Scintigraphy	[24]
	Hongo et al. (1989)	Omeprazole	$n = 6$	20 mg daily for 5 days	Scrambled egg (not stated)	Scintigraphy	[25]
	Jones et al. (2003)	Rabeprazole	$n = 17$	20 mg daily for 7 days	Rye roll, cream cheese (total 250 kcal) grape juice (80 kcal)	^{13}C breath test	[26]
	Grudell et al. (2006)	Rabeprazole	$n = 13$	40 mg daily for 3 days	Egg meal (300 kcal) 250 ml water	Single photon emission computed tomography	[27]
Delaying	Rasmussen et al. (1991)	Omeprazole	$n = 10$	40 mg daily for 10 days	Omelet (334 kcal) 150 ml water	Scintigraphy	[9]
	Atherton et al. (1994)	Omeprazole	$n = 12$	40 mg daily for 5 days	Beefburger (not stated) 50 ml water	Scintigraphy	[28]
	Benini et al. (1996)	Omeprazole	$n = 21$	40 mg daily for 5 days	Macaroni alla bolognese (800 kcal) 250 ml water	Ultrasound	[29]
	Rasmussen et al. (1997)	Omeprazole	$n = 10$	40 mg daily for 10 days	Omelet (334 kcal) 150 ml water	Scintigraphy	[12]
	Parkman et al. (1998)	Omeprazole	$n = 15$	20 mg daily for 7 days	Egg sandwich (not stated) 300 ml water	Scintigraphy	[30]
	Rasmussen et al. (1999)	Omeprazole	$n = 10$	40 mg daily for 10 days	Omelet (334 kcal) 150 ml water	Scintigraphy	[13]
	Togus et al. (2005)	Omeprazole	$n = 40$	40 mg daily for 14 days	Scrambled egg + white bread, strawberry jam (Total 255 kcal) 120 ml water	Scintigraphy	[31]
	Jian et al. (1989)	Lansoprazole	$n = 18$	30 mg daily for 2 days	Solid meal (not detailed) (500 kcal) 500 ml water	Scintigraphy	[10]
	Anjiki et al. (2005)	Ransoprazole	$n = 24$	20 mg daily for 3 days	Muffin (320 kcal) 200 ml water	^{13}C breath test	[32]
	Terai et al. (2009)	Ransoprazole	$n = 15$	10 mg daily for 7 days	Muffin (400 kcal) 100 ml water	^{13}C breath test	[33]

provides an overview of the physiological basis of gastric motor-secretory functions [5, 7, 8, 34, 42].

Gastric Motility

The stomach consists of three functionally different regions: the proximal stomach (cardia, fundus, and proximal body), the distal stomach (distal body and antrum), and the pylorus. The proximal stomach reserves a meal bolus and generates endoluminal pressure forcing intragastric contents forward. The distal stomach grinds, mixes, and evacuates solid materials. The pylorus regulates duodenal entry of ingesta. Integration of these region-specific motor actions enables intragastric contents to move in order.

The proximal reservoir function is accomplished by fundic relaxation that is vagally mediated in response to meal ingestion. The reflexive relaxation allows the proximal stomach to expand its volume without a significant elevation in intraluminal pressure. The relaxatory reflex involves the sequential two phases: a transient receptive relaxation occurs with the act of swallowing, and then a more prolonged relaxation, known as the gastric accommodation, is evoked by gastric filling with meals (distension) and duodenal exposure to nutrients [7]. Once the accommodation fully responds to meals, fundic wall tension eventually elevates. Subsequently, the proximal stomach exhibits tonic and sustained contractions, which yield a stable luminal pressure force. In contrast to the proximal stomach, the distal stomach exhibits rhythmic and synchronized contractions. Active antral contractions are required to fragment solid materials and to mix them with gastric juice and enzymes. The antral grinding produces a multiphase slurry of nutrients in various physical states (liquid, globular, pasty, or particulate), called gastric chyme. Duodenal delivery of the chyme is regulated by antropyloric outflow resistance. The pylorus exhibits a complex motor pattern of prolonged periods of outlet closure interrupted by brief interval, during which antral contents can traverse a patent pylorus. Only small-sized particles (usually <1–2 mm in diameter) are permitted to enter the duodenum [5].

Gastric emptying is a series of highly coordinated processes that control gastric efflux. The emptying rate depends on a balance between contractive driving force and occlusive outlet resistance. The balance is tightly controlled by neural and hormonal signals that are released by stimulation of physicochemical receptors in the duodenum. This neurohumoral feedback loop keeps the rate of stomach emptying optimal for efficient digestion and absorption of nutrients in the small gut.

The stomach handles liquids and solids in quite different manners [5, 8, 34]. Inert liquids, such as water and isotonic saline, do not activate the feedback regulatory pathways. Thus, the emptying of inert liquids is simply governed by the luminal pressure force, which originates from high wall tension due to gastric volume and proximal tonic contractions. Liquid meals containing macronutrients (carbohydrates, proteins, and fats) evoke the doudenogastric feedback regulation. Initially, a substantial amount of nutritive liquids is rushed into the duodenum according to the intragastric pressure. Upon the arrival of the nutrients in the duodenum, the feedback system is immediately activated to slow down the subsequent emptying, and then it maintains a stable emptying rate. As a consequence, kinetics of the nutritive-liquid emptying exhibits dual phases of the initial rapid and the subsequent slower, constant emptying. Gastric emptying of solids is fundamentally distinct from the emptying of liquids in that the solid emptying requires the trituration process and is independent of intragastric volume [5, 34]. Dynamics of the solid emptying exhibits dual features of an initial lag phase followed by a constant emptying. The lag phase is regarded as the time interval necessary for the antral trituration, which accounts for the time difference in emptying between solids and caloric liquids. The rate of post-lag emptying is kept stable under the enterogastric feedback.

Gastric Secretion

Gastric juice is typically a viscous fluid containing hydrochloric acid, digestive enzymes (e.g., pepsinogens), mucus, and water. In the fasted state, residual volume of the stomach is as low as 25 ml and the rate of fluid secretion is 1 ml/min. Following meal ingestion, the secretion rate is markedly increased up to 10–50 ml/min, and cumulative fluid volume reaches as much as 2–3 l/day [8]. Postprandial output of gastric acid produces a satisfactory acidic state for enzyme-dependent digestion. Acid potentiates conversion of pepsinogens to activated pepsin. The peptic activity is maximized at gastric pH 2 while it is almost absent at pH > 5.5 [43]. Gastric fluid dilutes the liquid-component and solubilizes the solid-component of meals, consequently decreasing consistency, viscosity, caloric density, and osmolality of ingesta. Solid meals trigger secretory responses more intensively than do liquid meals [5], because solids need a larger fluid volume to be properly hydrated compared to liquids.

Possible Mechanisms by Which PPIs May Affect Gastric Emptying

The literature review has suggested that PPIs have a delaying effect on gastric emptying of solid meals, whereas the agents have variable influences on the liquid emptying (Tables 1–3). In this section, candidate mechanisms whereby PPIs may affect gastric motility and emptying have thoroughly been discussed, although most of them still remain hypothetic.

Alterations in Gastric Motility

Gastric acid delivered into the duodenum evokes a feedback regulatory system to slow gastric emptying, thereby preventing excess duodenal entry of acid and maintaining a neutral pH environment for effective digestion in the small gut. The acid-induced slowing is achieved by relaxation of the proximal stomach, suppression of propulsive contractions in the distal stomach, and enhancement of occlusive contractions at the pyloroduodenal region [4, 5, 7, 8, 34]. Removal of acid by PPIs, in turn, would attenuate the acid-induced alterations in gastric motor functions: PPIs are expected to make the proximal stomach tense, promote the distal contractility, and loosen the pyloric ring. Interactions between these regional alterations in the motility determine gastric emptying. If the acid-sensitive feedback regulation is totally attenuated after PPIs, gastric emptying would be accelerated. However, the accelerated emptying with PPIs has been shown only in the two studies about the emptying of water [15, 16].

The effects of acid suppression by PPIs on the proximal motility have not well been investigated. Mearadji et al. [44] provided clear evidence that omeprazole abolished the relaxation of proximal stomach induced by acid in the fasting state. On the other hand, clear evidence is lacking in the fed state. Lee et al. [45] demonstrated that duodenal perfusion of hydrochloric acid induced the fundic relaxation in the preprandial state while it blunted the further relaxation in the postprandial state, suggesting that acid impairs the gastric accommodation to meals. This observation leads to a hypothesis that removal of acid by PPIs would restore or even enhance the gastric accommodation. In their preliminary report, Sanaka et al. [14] addressed an enhancing effect of PPIs on the accommodation. They demonstrated that rabeprazole delayed gastric emptying of a large volume (1,000 ml) of water. The acute loading of 1,000 ml water would fully distend the stomach, thereby stimulating the mechanical tension receptors on the stomach wall enough to trigger the distension-induced gastric accommodation. As gastric emptying of water depends only on the intragastric pressure force, the delayed emptying after rabeprazole is considered to result from decreased endoluminal pressure. Accordingly, the authors speculated that rabaprazole would enhance the distension-induced accommodation and would consequently attenuate a postprandial increment of luminal pressure. On the other hand, Parkman et al. [30] showed that omeprazole did not prolong the time for retention of solid meals in the proximal stomach. Their results indicate that omeprazole does not decrease the proximal luminal pressure because it does not enhance the nutrition-induced gastric accommodation. Since defective gastric accommodation is involved in the pathogenesis of functional dyspepsia, the impact of PPIs on the gastric accommodation should deserve much more concern.

Effects of acid removal by PPIs on the distal motility have been elucidated. Simrén et al. [46] showed that intraduodenal instillation of exogenous acid suppressed the antral contractive activity. Parkman et al. [30] demonstrated that acid suppression by omeprazole augmented the postprandial antral contractions. The augmented antral contractility is considered to paradoxically retard gastric emptying of solids as a result of failed harmonization of antral contraction with pyloric opening [30].

Impaired Peptic Digestion

Solid meals need to be fragmented into fine particulate suspension by the antral milling: connective tissue proteins are broken down by denaturalization and hydrolysis with the assistance of acid and pepsin. Reduced gastric acidity deactivates pepsin and impedes the hydrolytic process, thereby prolonging the time for persistence of indigested large particles in the stomach. This scenario is the long-held model for explaining why PPIs hamper gastric emptying of solids, namely the "acid-pepsin maldigestion hypothesis." The relevance of the hypothesis is supported by the finding that omeprazole prolongs the scintigraphically determined lag-phase [31]. Here, it should be noted that whether the acid-pepsin hypothesis is true or not, the fragmentation of solid meals could also be impaired by decreased volume of gastric fluid that is available for penetrating and solubilizing solid particles [12, 42].

The acid-pepsin hypothesis is apparently relevant, but there are three issues that may conflict with the hypothesis. The first conflicting issue is that omeprazole [30] and rabeprazole [32] do not necessarily delay the initial phase of solid emptying. If PPIs really inhibit the peptic hydrolysis and then the antral milling, the initial emptying involving the lag period would be delayed [29]. However, this conflicting issue could be refuted by the unconventional opinion that the peptic digestion is a continuous process occurring in parallel with gastric emptying, and thus the peptic maldigestion delays the solid emptying independently of the lag phase [30, 47]. The second conflicting issue is that rabeprazole delays gastric emptying of a calorie-containing liquid, which is unrelated to peptic digestion [22, 23]. This finding suggests that PPIs delay gastric emptying independently of the peptic maldigestion [22]. However, the delaying effect of rabeprazole is not in line with the observations that neither omeprazole nor lansoprazole decelerates the emptying of nutritive liquids [17–19]. Anyway, the possibility remains that the peptic maldigestion is not the sole mechanism for the delayed emptying induced by PPIs. The last conflicting issue is that intragastric pH becomes high after meals even without

PPIs, because a buffering effect of meals is substantial [27]. This fact suggests that the postprandial pH environment for the peptic activity may be the same whether PPIs are given or not. A refutation against this conflicting issue is that the luminal pH after PPIs is kept high throughout the postprandial period while the physiological increase in luminal pH is only temporal following meal ingestion. Physiologically, the luminal pH immediately rises up from a 1.3 to 2.5 range in the fasted state to a 4.5 to 5.8 range after meals, but it falls to less than 3.1 within 1 h postprandially [8]. With PPIs, on the other hand, the postprandial elevation in gastric pH is long-lasting [13, 19].

Hypergastrinemia

Gastrin is known as the main stimulant of acid secretion and as a possible modulator of gastric motility. Early human experiments revealed that gastrin administered intravenously relaxed the proximal stomach and stimulated the antral contraction [44, 48–50]. Via these functional modulations, gastrin decreases the proximal pressure force and increases the distal occlusive resistance, thereby delaying gastric emptying.

Pharmacologically induced hypochlorhydria causes a compensatory, slight to mild increase in serum concentrations of gastrin [51]. As the PPI-induced hypergastrinemia casually accompanies delayed gastric emptying [12, 21, 32], the two phenomena have often been linked together. However, the cause-and-effect linkage between the increased gastrin and the delayed emptying is not straightforward at all, being more conjectural as follows. Firstly, the gastrin plasma concentrations are only slightly increased during PPI use [12, 21, 23, 32, 51]. Secondly, PPIs do not always delay gastric emptying in the presence of hypergastrinemia [21]. Lastly, there is no correlation between patterns of postprandial secretion of gastrin and gastric emptying rates [12]. These observations mean that the hypergastrinemia is unlikely responsible for the PPI-induced delay in gastric emptying [17, 21, 32]. Mabayo et al. [52] confirmed that a delay in gastric emptying after omeprazole pretreatment was mediated not via increased gastrin but via the blockade of acid secretion. This observation suggests that the slowing of gastric emptying under the hypergastrinemic state is directly related to the hyperacidity induced by gastrin. Gastrin seems to be merely a "bystander" rather than a "player."

Changes of Physical and Chemical Properties of Ingesta

Gastric fluid influences physical and chemical characters of liquids more directly than those of solids. PPIs hamper processes of dilution and solubilization of ingested meals by suppressing the postprandial gastric secretion, consequently modifying volume, energy density, osmolality, and viscosity of ingesta. An inverse relationship exists between the rate of gastric emptying and each of the volume, the energy density, the osmolality, and the viscosity of intragastric contents [5, 8, 34, 53]. The extent to which these physicochemical properties contributes independently to the emptying rate remains unclear, but the volume and the caloric density are considered to have greater impacts on gastric emptying of liquids than the osmolality and the viscosity [53–57]. To simplify the discussions below, the volume, the caloric density, and gastric emptying of liquids are focused on.

Hunt and Stubbs [53] attempted to relate a rate of liquid emptying to volume and caloric density of original meals. They derived a mathematical equation based on enormous experimental data, expressed as: $t_{1/2} = V \cdot (0.1797 - 0.1670\ e^{-K})$, where $t_{1/2}$ (min) is half emptying time, V(ml) is meal volume ($V > 100$ ml), and K (kcal/ml) is meal caloric density. This equation implies that the rate of gastric emptying ($t_{1/2}$) is made more prolonged as original test meals are larger in the volume (V) and higher in the caloric density (K). This mathematical relationship would be true for the volume and energy density of intragastric contents. The gastric contents under pretreatment with PPIs are smaller in the volume (decreased V) and higher in the caloric density (increased K) than those in the physiological status. The decreased V is an accelerating factor for the emptying rate whereas the increased K is a decelerating one. Thus, the net balance between the two factors determines gastric emptying, but it seems difficult to predict.

Although the potency of PPIs to suppress gastric acid is beyond all doubt, their potency to reduce fluid secretion may be relatively minor. Grudell et al. [27] showed that rabeprazole did not significantly change pre and postprandial gastric volume. Vidon et al. [18] demonstrated that lansoprazole only slightly decreased gastric fluid volume in the fasted state while it moderately suppressed a postprandial increment of the fluid volume: the mean difference in postprandial gastric volume between placebo and lansoprazole was about 100 ml at every sampling time during a 3-h study period. It is questionable whether such a mild suppression of gastric fluid secretion with PPIs causes a substantial change in gastric emptying [47]. PPIs may be less effective in reducing gastric fluid secretion than H_2RAs [58].

Clinical Implications

In this section, clinical implications of the PPI-induced delay in solid emptying have been discussed.

The delayed emptying caused by PPIs may have negative clinical impacts. The magnitude of the delay seems small [31], but clinicians should be aware that PPIs potentially

cause a sizable delay in patients whose baseline gastric emptying is slow, such as those with diabetes mellitus, Parkinson's disease, and functional dyspepsia. Lack of the awareness may lead to inappropriate and ineffective therapies. If diabetic patients on insulin therapy receive PPIs, they may suffer from frequent hypoglycemic attacks, because the delayed emptying would produce a time lag between release of nutrients into the small intestine and onset of insulin action [59]. If patients with Parkinson's disease on levodopa therapy are given PPIs, they may notice insufficient or fluctuated symptomatic improvements [60], because the delayed emptying could inhibit the delivery of levodopa into the small gut where the drug is exclusively absorbed. Although slow gastric emptying is of relatively minor importance in the pathophysiology of functional dyspepsia [7], it is possible that if patients with dysmotility-like dyspeptic symptoms take PPIs, they may feel their symptoms deteriorated.

On the other hand, the PPI-induced delay in solid emptying may have positive clinical impacts. In a subset of patients with functional dyspepsia, abnormally rapid emptying is assumed to produce dumping-like dyspeptic symptoms [7]. Thus, dyspepsia patients with an accelerated emptying may favorably respond to PPIs not because of their suppressing effect on acid secretion but because of their braking effect on gastric emptying [27]. A substantial portion of patients with type II diabetes have a rapid emptying [59], which exacerbates postprandial hyperglycemia. It is therefore probable that the delay in solid emptying with PPIs blunts a postprandial increase in blood glucose. A recent study showed that type II diabetic patients taking PPIs had better glycemic control than those not taking the agents [61], although the actual reason for this observation remains to be clarified.

Prolonged gastric emptying is considered to cause failure of PPI therapy in patients with gastroesophageal reflux disease [1]. For such refractory cases, an additional prescription of prokinetic drugs is a therapeutic option [1]. Frequently used prokinetics include a dopamine antagonist (metoclopramide, domperidone) and a serotonin (5-HT_4) receptor agonist (tegaserod, mosapride). The 5-HT_4 receptor agonists are reported to normalize the delayed solid emptying caused by PPIs [31, 41]. However, a preventive effect of dopamine antagonists on the PPI-induced delay has never been addressed.

As PPIs are unstable under acidic conditions, prolonged gastric residence of the drugs due to the delayed emptying may lead to a loss of their pharmacological activities [62]. A recent study showed that promotion of gastric emptying with prokinetic agents increased the bioavailability of PPIs, which is related to their efficacy [63]. From these pharmacokinetic aspects, a question arises whether the delayed emptying during long-term PPI therapy may lower their therapeutic efficacy. However, this question is considered unreal, because the acid-reducing effect of PPIs is reported to be stable over a long period [64].

Conclusions

The present review has shown that (1) PPIs delay gastric emptying of solid meals, probably because the drugs impair intragastric peptic digestion, (2) the effects of PPIs on the liquid emptying are unpredictable, because the agents variably modify the volume and energy density of intragastric contents, which are major determinants of gastric emptying of liquids, and (3) the PPI-induced hypergastrinemia is unlikely to contribute to the regulation of gastric emptying during PPI use. The delayed emptying of solids after PPIs may have clinical implications in the management of gastroesophageal reflux disease, functional dyspepsia, and diabetes.

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