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TOPIC HIGHLIGHT

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Helicobacter pylori infection and drugs malabsorption

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Abstract

Drug absorption represents an important factor affecting the efficacy of oral drug treatment. Gastric secretion and motility seem to be critical for drug absorption. A causal relationship between impaired absorption of orally administered drugs and *Helicobacter pylori* (*H. pylori*) infection has been proposed. Associations have been reported between poor bioavailability of l-thyroxine and l-dopa and *H. pylori* infection. According to the Maastricht Florence Consensus Report on the management of *H. pylori* infection, *H. pylori* treatment improves the bioavailability of both these drugs, whereas the direct clinical benefits to patients still await to be established. Less strong seems the association between *H. pylori* infection and other drugs malabsorption, such as delavirdine and ketoconazole. The exact mechanisms forming the basis of the relationship between *H. pylori* infection and impaired drugs absorption and/or bioavailability are not fully elucidated. *H. pylori* infection may trigger a chronic inflammation of the gastric mucosa, and impaired gastric acid secretion often follows. The reduction of acid secretion closely relates with the wideness and the severity of the damage and may affect drug absorption. This minireview focuses on the evidence of *H. pylori* infection associated with impaired drug absorption.

Key words: Drug malabsorption; *Helicobacter pylori* gastritis; Gastric hypoacidity; Thyroxine treatment; Thyroxine malabsorption; Human immunodeficiency virus; Delavirdine; L-dopa; Parkinson's disease; Ketaconazole

Core tip: Drug absorption is a critical factor affecting the efficacy of orally administered therapies. A causal relationship between impaired absorption of orally administered drugs and *Helicobacter pylori* (*H. pylori*) infection has been proposed. Previous studies have observed that *H. pylori* infection and poor bioavailability of l-dopa and l-thyroxine are associated. Less strong seems the association between *H. pylori* infection and delavirdine and ketoconazole malabsorption. The absorption of oral drugs may potentially be influenced by gastric pH. When a treatment with an oral drug fails, this may be due to a *H. pylori*-related gastritis and its associated gastric hypochlorhydria, which may partially or totally be reversible.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a widely distributed patho-

gen of humans infecting about one half of the world population. *H. pylori* infection is associated with divergent outcomes ranging from symptom-free gastritis to peptic ulcer and gastric cancer[1,2]. The chronic inflammatory response to *H. pylori* infection may impair some of the physiological gastric functions, *i.e.*, acid secretion. The severity and distribution of gastritis determine the effect of *H. pylori* infection on gastric acid secretion: when the inflammatory response involves the acid secreting corporal mucosa harbouring the oxyntic glands, hypochlorhydria may occur[3].

Drug absorption is an important factor affecting the efficacy of oral drug treatment. In turn, drug absorption may be affected by gastric secretion and motility[4,5]. A causal relationship between impaired absorption of orally administered drugs and *H. pylori* infection has been proposed. Previous studies linked the poor bioavailability of both thyroxine and l-dopa to *H. pylori* infection[6]. According to the Maastricht Florence Consensus Report on the management of *H. pylori* infection, the bioavailability of both these drugs was improved by *H. pylori* treatment, whereas the direct clinical benefits to patients still await to be established[7]. Less strong seems the association between *H. pylori* infection and other drugs, such as delavirdine and ketoconazole malabsorption[6]. This minireview focuses on the evidence of *H. pylori* infection associated with impaired drug absorption.

H. PYLORI INFECTION, L-DOPA AND PARKINSON'S DISEASE

L-dopa is the mainstream drug in Parkinson's disease treatment[8]. The effect of eradication treatment on the clinical and pharmacokinetic response to L-dopa was investigated in advanced Parkinson's disease patients with high IgG antibody titer against *H. pylori*[9]. From a pilot study (conducted on six patients only) it emerged that eradication treatment increased by 21%; the L-dopa plasma concentration also improving the clinical benefit. A RCT[10] performed on 34 Parkinson's disease patients with active *H. pylori*-gastritis diagnosed by histology, confirmed these results. Patients were randomized to eradication treatment or an antioxidant treatment (allopurinol). In the group of patients treated with eradication therapy, L-dopa absorption increased by 54%, the clinical disability of patients significantly improved and a significant decrease of gastritis scores kept in step with improved L-dopa pharmacokinetics. The positive effect of *H. pylori* eradication treatment on motor fluctuations was confirmed in a more recent study conducted in South Korea in 2008[11]: in 34 *H. pylori*-positive patients with Parkinson's disease, the l-dopa "onset" time and the l-dopa "on-time" significantly decreased by 25.9% and increased by 11.9% after successful cure of infection, while the symptoms score assessed by UPDRS-Ⅲ scale did not differ before and after cure. The authors therefore concluded that *H. pylori* eradication may prevent and improve the clinical status of *H. pylori* infected patients with Parkinson's disease and motor fluctuations (Table 1).

The results of a very recent study[12] showed that, compared to age- and gender-matched *H. pylori*-negative patients, 20 *H. pylori* positive patients with Parkinson's disease had decreased "complications of therapy" with average total UPDRS-IV symptoms score of 4.8 ± 3.0 *vs* 7.7 ± 3.8 ($P < 0.05$), despite no significant difference in l-dopa equivalent dose. Wearing-off and sleep disturbance were significantly less common in the *H. pylori* group. The authors explain the observed decreased occurrence of symptoms fluctuations with a likely altered absorption of l-dopa due to the presence of *H. pylori* infection, but unfortunately they did not assess l-dopa plasma levels neither eradication treatment to support their hypothesis.

H. PYLORI INFECTION, THYROXINE AND THYROID DISEASE

Levothyroxine sodium (T_4) is the drug of choice in the treatment of thyroid failure as well as of differentiated thyroid carcinoma[13]. A proper T_4 treatment requires both the identification of the optimal daily dosage, calculated on the basis of the single patient anthropometric characteristics, and an efficient intestinal absorption of the hormone. It has been proven that both gastric[14-16] and intestinal disorders[17,18] may adversely affect the absorption of the hormone although it actually takes place at the small intestine level[19,20].

In 2006 the first study was published describing that at least three different conditions of impaired gastric acid secretion may affect the daily requirement of thyroxine in patients with multinodular goiter. *H. pylori* infection, gastric atrophy and a chronic PPI treatment were, in fact, all associated with a significant increase of T_4 dose. Gastric atrophy required a stable increase of about one third of daily T_4 dose whereas the effect of *H. pylori* infection on T_4 treatment was reversed upon bacterial eradication; however, in this latter case, the dose had to be increased to reach the therapeutic target[14]. This part of the work was confirmed five years later in a different and less accurate setting[21] and criticized by the same authors in that the potential presence of additional intestinal disorders was not quoted. However, the pleiotropic characteristics of *H. pylori* infection/host interaction account for the different drug absorption impairment as well[22].

Autoimmune disorders affecting the stomach have been also proven to be responsible for T_4 therapy failure. Patients with chronic atrophic gastritis exhibited an increased T_4 requirement and these data have been confirmed in a study from Checchi *et al*[16] who have shown a positive correlation between the increased need for T_4 and the high titre of serum parietal cell antibodies (PCA). These antibodies, directed against H^+/K^+ ATPase, are considered as a marker of gastric autoimmunity and a suspicious flag for the presence of gastric atrophy[23]. However, the increase of T_4 requirement was greater in patients with histologically proven gastric atrophy than in PCA-positive subjects[16], suggesting that the presence

Table 1 Effects of cure of *Helicobacter pylori* infection on l-dopa absorption and/or symptoms scores in patients with Parkinson's disease

Ref.	Study design (level of evidence)[1]	*n*	*Helicobacter pylori* positivity	Intervention	Outcome measure	Effect of eradicaction treatment
Benvenga *et al*[20]	Crossover study (4)	6	Serology	Eradication tx *vs* placebo	AUC of L-dopa	21% increase after eradication treatment No variation after placebo
Pierantozzi *et al*[10]	RCT (1)	34	Serology, stool test, CP-test or culture	Eradication tx *vs* antioxidant tx (allopurinol)	AUC of L-dopa	54% increase after eradication treatment No variation after antioxidant tx
Lee *et al*[11]	Case series (3)	65	Urea breath test	Eradication tx	UPDRS-Ⅲ L-dopa "onset" and "on-time"	No variation 25.9% decrease and 11.9% increase after eradication tx

[1]Levels of evidence based on the Oxford Centre for Evidence-Based Medicine. AUC: Area under the plasma concentration curve; Tx: Treatment.

of PCA does not necessarily imply the presence of atrophic gastritis[23]. More controversial is the interference of proton pump inhibitor (PPI) administration on the levothyroxine sodium treatment[24]. This is relevant in that patients with *H. pylori* infection often use PPI for treatment. A clear-cut effect of chronic PPI treatment on the elevation of TSH and the consequent need to increase thyroxine dose has been reported in two different studies[14,25]. These findings, however, have not been confirmed in the case of short periods of PPI administration: two pharmacokinetic trials in subjects treated at the same time with T_4 and PPI for 1 wk failed to reveal significant differences in peak T_4 levels or in the mean Area Under the Curve (AUC) for T_4 absorption[24]. The discrepancy has been attributed to the different length of PPI treatment as suggested in a minded review by Liwanpo and Hershman[24].

H. PYLORI INFECTION, DELAVIRDINE, KETOCONAZOLE AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Delavirdine, a reverse transcriptase inhibitor, is approved by the Food and Drug Administration as combination therapy with appropriate antiretroviral drugs for human immunodeficiency virus (*HIV*)-*1* infection treatment[26]. So far, in only two studies performed by the same authors[27,28] the role of hypochlorhydria in absorption of delavirdine was evaluated in *H. pylori*-positive patients with concomitant *HIV*-seropositivity. In a case-series of five *HIV*-positive patients with gastric hypoacidity (intragastric pH > 3) and positivity to *H. pylori* serology, it was shown that eradication treatment was able to reverse hypochlorhydria and to significantly increase the absorption of delavirdine[27]. A randomized crossover study on 21 *HIV*-positive with (n = 11) and without (n = 10) gastric hypoacidity, showed that delavirdine absorption is decreased by 47% in hypoacidic subjects and can be increased by the administration of delavirdine together with orange juice (increase by 57%)[28]. These findings suggest that in subjects with *HIV*-infection, absorption of delavirdine can be increased by an acid intragastric pH. In 62% of the investigated patients, positive *H. pylori* serology was reported, but unfortunately eradication treatment was not performed. Despite the similar prevalence of *H. pylori* infection in both *HIV*-positive and -negative patients[29,30], a higher histological score of *H. pylori*-gastritis has been described in *HIV*-positive patients[31].

In *HIV*-positive subjects, ketoconazole absorption also seems to be impaired. In a small case series conducted in 1988 by Lake-Bakaar *et al*[32], the absorption of oral ketoconazole was correlated with gastric acidity in AIDS patients. In this study, the area under the curve of ketoconazole concentration decreased and was normalized by hydrochloric acid in all 7 hypochlorhydric patients, whereas the 3 normochlorhydric patients had normal levels of ketoconazole absorption. This study, however, did not even consider the presence of *H. pylori* infection, but concluded that in AIDS patients ketoconazole tablets given with acid may be more efficacious because of its pH-dependent bioavailability.

POSSIBLE MECHANISMS FOR A LINK BETWEEN *H. PYLORI* INFECTION AND IMPAIRED DRUGS ABSORPTION

The exact mechanisms forming the basis of the relationship between *H. pylori* infection and impaired drugs absorption and/or bioavailability are not yet established. In general, characteristics of the drug, as molecular size and shape, ionization degree, and lipid solubility of its ionized and nonionized forms may affect drug absorption[4,5]. Noticeably, motility of the stomach as well as volume and modifications of gastric juice may influence the pharmacokinetics of a drug[33].

H. pylori infection acts as a trigger to chronic inflammation of gastric mucosa, causing an impairment of gastric physiology[3]: gastric motility may be affected by inducing myoelectrical activity variations which in turn bring about an impaired gastric emptying[34-36]. Also an impaired gastric acid secretion often follows *H. pylori*-induced gastritis, being the degree of impairment closely related with the wideness and the severity of the damage[3]. In fact, when *H. pylori* gastritis involves the corporal mucosa, which contains the oxyntic glands, a diminished acid secretion may ensue. At an early stage of infection, a

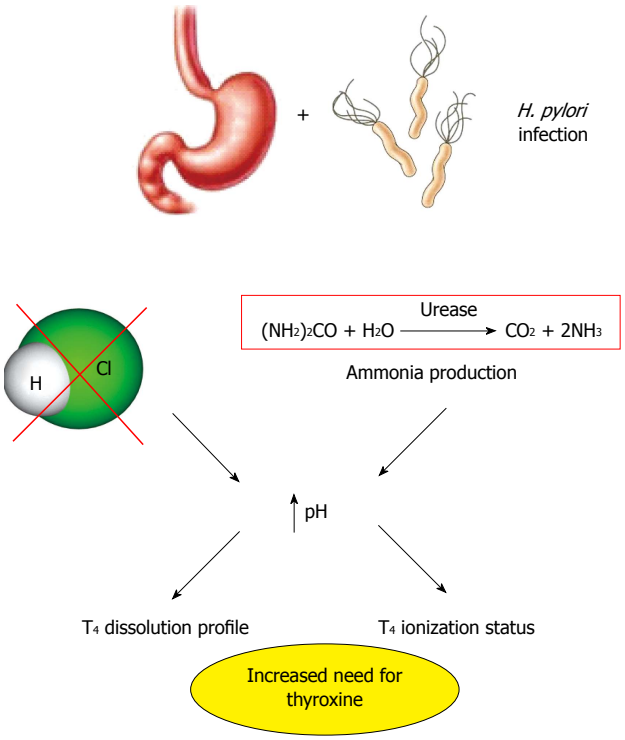

Figure 1 Possible mechanisms involved in the increased need for thyroxine in *Helicobacter pylori* infection.

direct inhibition of the parietal cells secretion may be exerted by products of inflammation[3,37]. Interleukin 1β, a proinflammatory cytokine and a key mediator in *H. pylori*-associated disease, inhibits gastric acid secretion *in vitro* and *in vivo*[38-40]. Gastric hypoaciditiy may be partly or fully reversed upon *H. pylori* eradication, without losing the bulk of parietal cells[41-43]. A massive loss of parietal cells, as a consequence of long-standing *H. pylori* injury, may ensue atrophy of oxyntic glands and, thus, hypoacidity of gastric juice[3,37]. In such a case, whether the cure of infection might reverse the impaired acid secretion is, as yet, controversial[42].

The process of drug absorption may be potentially affected by these pathological changes of the intragastric environment during *H. pylori* infection. The consequences of this infection may explain the proposed link between *H. pylori*-related gastritis and reduced bioavailability of some drugs. In particular, the reduced gastric acid secretion seems to be relevant in the process of impaired drug absorption associated with *H. pylori* infection (Figure 1). In this condition, the process of drug absorption may be affected by the different ionization degree of the molecules as well as by the lesser solubility of many drugs[5].

As far as concern with l-dopa, the hypotheses on the interfering effect of *H. pylori* on its absorption are still debated. The solubility of l-dopa is pH-sensitive[44], and the putative restoration of normal gastric acidity upon eradication may account for the improved absorption of this drug and the related clinical response[3]. Unluckily, gastric acidity was not assessed in the abovementioned studies. In one of them[10], however, the reported scores of inflammation suggest corporal gastritis and, thus, potential hypoacidity in most of the Parkinson's disease patients studied[10]. More recently, an interesting hypothesis was proposed and supported by experimental data by Lyte *et al*[45]: they suggested a direct utilization of l-dopa by *H. pylori* to preserve its ecological *milieu* in the gastric mucosa. Evidence that l-dopa may affect the *in vitro* growth of *H. pylori* in an iron-restricted minimal medium strengthen this hypothesis[45]. In fact, *H. pylori* seems to reduce the amount of available oral l-dopa for the treatment of Parkinson's disease, utilizing l-dopa for its own survival and growth. An association between the incidence of *H. pylori* infection and occurrence of Parkinsons' disease has been observed, and a possible cause/effect relationship has been proposed suggesting that *H. pylori*-induced autoimmunity may act as a trigger for the neuronal damage leading to Parkinsonism[46]. A recent review proposed, through statistical models, a linkage between idiopathic Parkinsonism and infectious/inflammatory status of the gastrointestinal mucosa, mainly due to *H. pylori* infection[47]. This association between defective absorption of l-dopa and *H. pylori*-gastritis may be relevant from an epidemiological point of view, since a high incidence of *H. pylori* infection has been reported in the ten years of highest prevalence of Parkinson's disease[8,48]. On this ground, a specific diagnostic work-up to detect *H. pylori* should be proposed in elderly Parkinson's disease patients, in whom the response to l-dopa treatment is often poor[48].

With regard to T_4 malabsorption in subjects with gastric disease or undergoing therapy with PPI, the exact mechanism is incompletely understood, but the variations of gastric acid secretion are a distinctive feature in this situation. The mechanisms underlying the reduction of gastric acidity are shown in Figure 1. Gastric pH variations may change ionization of thyroxine molecule leading to a different ability of this hormone to cross the lipid bilayer of enterocytes apostrophe plasma membrane. In fact, levothyroxine is a low permeability molecule with three ionizable groups and, depending on the solution pH, it can exist as a cation, zwitterion, anion or dianion[49,50]. Sodium- and pH-sensitivity of the iodothyronines cellular uptake in several tissues has been already shown about 30 years ago[51-53]. The pH-dependent variability may or may not deal with a further clue parameter: the dissolution profile of pharmaceutical thyroxine preparation[54,55]. The water solubility of thyroxine sodium salt is reduced in environmental pH from 1 to 3, remains constant between 3 and 7 and increases in pH of about 7[54]. The dissolution of T_4 is one of most limiting phases for its absorption but it is not needed when using a liquid preparation of thyroxine[54]. A better pH-dependent dissolution profile of glycerol-dissolved preparations (*e.g.*, softgel) has also been demonstrated, as compared with the traditional tablets[55]. These new formulations may help to improve T_4 treatment efficacy in patients with *H. pylori* infections or other causes of altered gastric secretion[56].

A causative role of hypochlorhydria in impaired delavirdine absorption has been proposed, even taking into

account the small sample size and the uncontrolled nature of the study design. In *HIV*-positive subjects, hypochlorhydria has been frequently reported[57-59] and the most significant predictor for increased intragastric pH has been reported to be *H. pylori* infection[29]. Delavirdine is a weakly basic drug, whose solubility is strongly reduced when median pH increases. This underlines the sustainability of a biochemical role of intragastric pH on the absorption of delavirdine[30]. Finally, impaired oral ketoconazole absorption in HIV-positive patients was correlated with reduced gastric acid secretion, corrected by administration of hydrochloric acid[32].

CONCLUSION

The impact of *H. pylori* infection on drug malabsorption has been focused in this review despite the limited number of studies addressing that issue. To date, four drugs used for the treatment of very different diseases have been investigated, l-dopa, thyroxine, delavirdine and ketoconazole. The issue of drug malabsorption may be particularly important when the implicated drug is generally used for long-term treatments as occurs for l-dopa and thyroxine used for the treatment of chronic conditions such as Parkinon's disease and thyroid disease.

The common denominator of the impaired absorption of these very different drugs and *H. pylori* infection seems to be decreased gastric acid secretion.

However, the limit of this review is that the single studies of this issue are very dyshomogeneous and the overall level of evidence is poor. Furthermore, specific pathophysiological studies investigating the probable link between hypochlorhydria and impaired drugs absorption are lacking. Thus, the exact role of *H. pylori* infection in drug malabsorption remains, to date, speculative and further studies are needed. Despite the constrained evidence of available studies, when an oral drug therapy fails, one of the possible reasons may be a *H. pylori*-related gastritis and its associated gastric hypoacidity which may be partially or totally reversible. So far, when a treatment is prescribed in general practice, physicians should be aware of the possibility that changes in gastric mucosa and/or gastric acidity status may impair the kinetics of certain drugs. *H. pylori* infection in this process may be of paramount importance due to its huge prevalence all over the world.

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