REVIEW

Available from: URL: http://www.jgld.ro/2015/1/16.html
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.fio

A Systematic Review on Drugs Absorption Modifications after Eradication in *Helicobacter pylori* Positive Patients undergoing Replacement Therapy

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Received: 14..01.2015
Accepted: 16.02.2015

ABSTRACT

Background & Aims: *Helicobacter pylori* (*H. pylori*) infection has been suggested as a cause of impaired drug absorption. This infection leads to alteration of the gastric acid secretion that may change the conformational characteristics of drugs and their intestinal absorption leading to uncertainties about the dose to administer and the therapeutic results. A systematic review was undertaken to clarify the implications of drug absorption during the administration of replacement therapies.

Methods: Electronic databases such as MEDLINE/Pubmed, EMBASE and The Cochrane Library [which includes Cochrane Database of Systematic Review (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstract of Reviews of Effect (DARE)] were searched. Grey literature databases (e.g. the International clinical trials registry platform, Trials Register, Clinical Trials.gov, Controlled Trials and TrialsCentral), Theses database, Government publication and LILACS database were also searched. No language restriction was applied.

Results: Infection and altered drug absorption were evaluated in patients under replacement therapies with iron, thyroxin and L-dopa. In all, seven studies included an improvement in drug absorption after eradication and an existing inverse correlation between the grade of gastric inflammation and indices of drug absorption were noticed.

Conclusion: This systematic review confirmed the presence of an interaction between infection and drug absorption of orally administered replacement therapies. Gastric acid reduction and subsequent alteration of drug composition seem to lead this mechanism. Clinicians should be aware of this possible interaction when starting a replacement therapy in patients and when evaluating poor clinical response.

Key words: *Helicobacter pylori* – absorption – replacement therapy.

Abbreviations: CBA: controlled before-after; CDSR: Cochrane Database of Systematic Review ; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstract of Reviews of Effect; Hb: haemoglobin; H. pylori: helicobacter pylori; RUT: rapid urease test; RCTs: Randomised Controlled Trials; SAT: stool antigen test; SF: serum ferritin; TF: transferrin saturation;13C-UBT: urea breath test.

INTRODUCTION

Since its discovery in 1982, interest in the role of *Helicobacter pylori* in determining human pathologies has grown and it has been recognised as one of the key factors responsible for many gastric and extra-gastric pathologies. Recently it has been also suggested as a causal agent of drug malabsorption. There is evidence that this infection is one of the principal determinants of altered gastric acid secretion whose severity depends on the extension of the infection in the stomach and on the duration of the disease [1]. Despite the fact that this infection can potentially alter the bioavailability of any drug, those who are part of a therapy designed to compensate for a lack or deficiency arising from inadequate nutrition, dysfunctions or losses (replacement therapies) are more likely to be affected by its presence and are potentially of high clinical interest due to the close relationship between the drug effect and the dose administered. Therefore, the objective of this systematic review is to assess the effect of eradication on drugs absorption in patients undergoing oral replacement therapy.

METHODS

Search methods for study identification

Key electronic databases such as the Cochrane Library [which includes the Cochrane Database of Systematic Review (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effect (DARE)], MEDLINE/Pubmed, EMBASE and LILACS database (Latin American and Caribbean Health Sciences Literature) were screened. To identify additional records these sources were included: International clinical trials registry platform (http://www.who.int/trialsearch); ClinicalTrials.gov (http://www.clinicaltrials.gov), Current Controlled Trials (http://www.controlled-trials.com/) and TrialsCentral (http://www.trialscentral.org), theses database (http://www.theses.com/) and Government publications (http://www.opengrey.eu/). The PICO strategy (Population, Intervention, Comparator and Outcomes) was used to select appropriate terms for the search: helicobacter pylori/H.P./positive/infection were combined with "replacement therapy", "nutrients", "micronutrients", "nutrient replacement", "vitamins", "trace elements" and "absorption" with appropriate Boolean operator (Supplementary material: Appendix 1, available from http://www.jgld.ro/2015/1/16.html). Abstracts and conference proceedings from the United European Gastroenterology Week (published in Gut), Digestive Disease Week (published in Gastroenterology), and European Helicobacter Pylori Study Group (published in Helicobacter) from January 2012 to January 2014 were also hand-searched. Experts in the field were also contacted to supply information about unpublished or ongoing researches and to double check the electronic searches for missing studies identification.

Study inclusion and exclusion criteria

The participants considered were people over 16 years with *H. pylori* infection that had underwent replacement therapy independently from the histological grading of their infection-related gastric inflammation. They were considered positive for *H. pylori* infection if at least one test of the following: histology, rapid urease test (RUT), culture, serology, urea breath test (^{13}C-UBT) and stool antigen test (SAT) was positive. If studies were a mixture of participants with impaired acid production due to *H. pylori* infection and other medical conditions (e.g. autoimmune atrophic gastritis or chronic proton pump inhibitor-PPI therapy), data regarding participants with the infection were extracted and analyzed separately. Oral replacement therapy was referred to any treatment orally administered to "*compensate for a lack or deficiency arising from inadequate nutrition, from certain dysfunctions (glandular hyposecretion), or from losses (hemorrhage)*" [2] whose effectiveness was evaluated in a routine clinical practice to inform a clinical decision (e.g. dosage to administer).

H. pylori eradication treatment was considered effective if administered for at least one week with an achieved eradication rate of at least 70%. Eradication status was considered valid if assessed from 4 to 6 weeks after the end of the treatment by ^{13}C-UBT or SAT. Eleven randomized trials and observational studies (cohort studies, case-control and case-series) were included in the search to explore the impact of the intervention on the primary outcome in routine clinical practice. Meta-analyses and reviews were not included but their references were scanned to find additional primary studies.

No language restrictions were used.

Selection procedure

Relevant studies were analyzed and extracted by two unblinded reviewers (G.F. and V.C.) using a form adapted from The Cochrane Data Extraction and Assessment Form [3]. Data collected included title, first author, year of publication, type of publication (full text/ abstract, published/ unpublished), language, study design, characteristics of the population, disease/condition that needs replacement therapy, type of replacement therapy, type of *H. pylori* infection assessment, histological grading of gastric inflammation, if present, and assessment of hypochlorhydria, type of eradication treatment administered, type of outcome measurement performed, presence of adverse effects due to eradication therapy and drug absorption modification. The quality of studies as Randomised Controlled Trials (RCTs), randomised cluster trials and randomised cross-over trials, non-randomised controlled trials (NRCTs) and controlled before-after (CBA) studies was assessed by an adapted form of the Risk of Bias Criteria for EPOC reviews proposed by the Cochrane Public Health Group [4]. The quality of observational studies was assessed using an adaptation of the chart proposed by Petticrew et al. (2006) [5]. Differences and disagreements were discussed and resolved by consensus.

RESULTS

The database searches were conducted in April 2014 and identified 3,400 potentially relevant findings. No further relevant records were identified through the hand-search of abstracts and conferences. After duplicates had been removed, 3,109 out of 3,400 records were evaluated independently by two unblinded reviewers. A summary of the process is showed in a flow diagram according to the PRISMA Statement [6] (Fig. 1).

A total of seven studies were selected for review of the full paper and data extraction [7-13]. The high clinical heterogeneity detected in primary studies due to different types of intervention administered, different outcomes described and the low number of identified studies did not allow us to pool data together to produce a summary measure and to perform statistical evaluation. However, the systematic approach that was used made it possible to evaluate the effect of the intervention between studies on the same replacement therapy and to speculate about the presence of a common pattern among studies on different drugs [14]. Characteristics of the included studies are shown in Table I.

***H. pylori* eradication and thyroxine**

Two studies explored the effect of *H. pylori* eradication therapy on thyroxine absorption by looking at thyroid function test commonly used to check the effect of thyroxine replacement therapy. They both performed thyroid function tests before and after the administration of eradication treatment and noticed a statistically significant improvement in the results. In particular, in the study by Centanni et al. [7], the

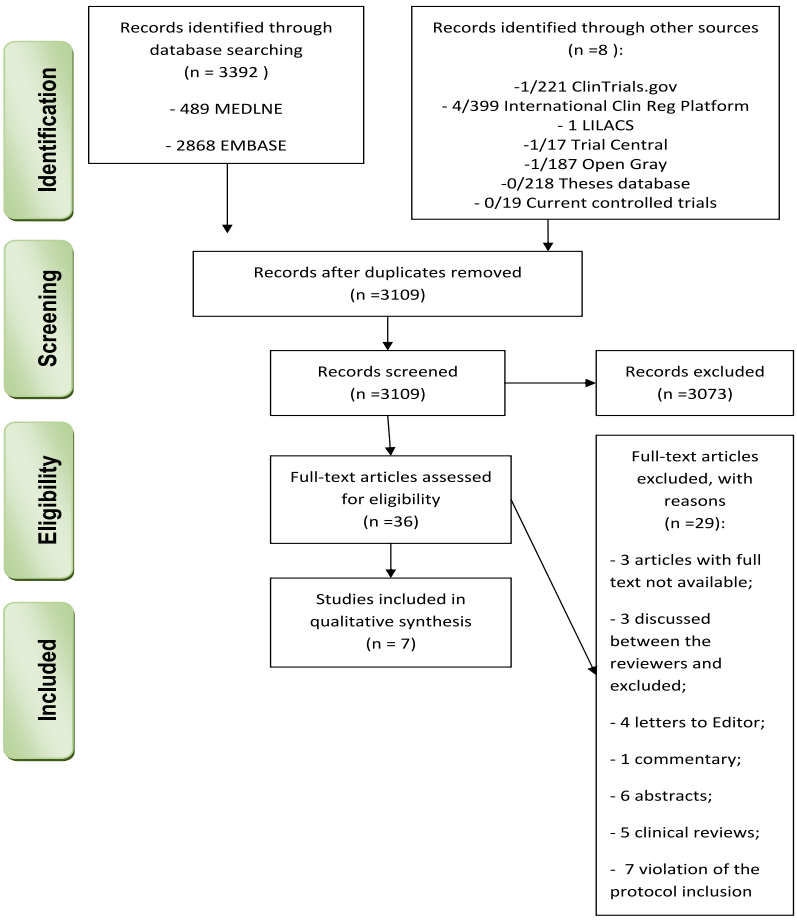

Fig. 1. PRISMA flow diagram

daily need for thyroxine was nearly reversed after eradication treatment and was associated with a decrease in thyrotropin levels that was calculated to be near 94% [15]. Similar results were obtained by Bugdaci et al. (2011) [12], who noticed a statistically significant improvement in thyroid function tests after *H. pylori* eradication in all of the enrolled cases. They also noticed the development of a clinical condition related to an excessive absorption of thyroxine (thyrotoxicosis) in 21% of cases after the cure of the infection.

***H. pylori* eradication and L-Dopa absorption**

Two studies evaluated the effect of *H. pylori* eradication treatment on L-dopa absorption [9, 10]. The effect of the treatment was evaluated on the pharmacokinetic and clinical response to L-dopa in patients with advanced Parkinson's disease and *H. pylori* infection.

The first study was a case series of six patients where the authors demonstrated that the eradication treatment led to a 21% increase in L-dopa plasma concentration and a concomitant clinical benefit. They subsequently confirmed their results in a RCT where patients were randomly divided in two groups and received either eradication therapy or placebo. In this study, the eradication therapy group achieved a 54% increase in L-dopa absorption and showed significant symptom improvement. This positive relationship was reinforced by the absence of L-dopa pharmacokinetics and symptoms improvement in two patients that failed the eradication.

***H. pylori* eradication and iron absorption**

All studies that explored the effect of *H. pylori* eradication on iron absorption concluded that *H. pylori* infection is associated with a poorer response to oral iron therapy, that its treatment can enhance the efficacy of oral iron replacement therapy and that the screening for this infection should be considered in patients with unexplained or refractory iron deficiency anemia [4, 8, 16]. Results of the case series performed by Kotb et al. (2012) [13] showed a statistically significant increase in haematological indices such as haemoglobin (Hb), serum ferritin (SF) and transferrin saturation (TF) achieved after *H. pylori* eradication compared to baseline at 6 and 12 weeks post therapy. They also noticed a significant inverse correlation with the above mentioned parameters and the grade of inflammation detected in the stomach. Their results were supported by the findings of two randomised trials [8, 11] that explored also changes in iron related parameters in blood after *H. pylori* eradication. All three studies considered a slightly different panel of iron related parameters other than haemoglobin, which was a shared surrogate outcome for the evaluation of the effectiveness of iron replacement therapy. Hemoglobin values significantly increased after eradication in all the studies.

Quality assessment of included studies

The quality of included studies was assessed independently by two unblinded reviewers (G.F. and V.C.) and differences were discussed and solved by consensus. Each study was labelled at

Table I. Characteristics of included studies

Drug	Study design	Participants	*H. pylori* diagnosis	Intervention/s	Outcome	
Bugdaci (2011) [12]	Thyroxine	Case series	32 patients with hypothyroidism Age: 39.6 ±11 y (SD) M/F: 84% female	Histology	Eradication with standard triple therapy (Is tine) or quadruple therapy (IInd line) for 14 days	Modifications in thyroid function tests (TSH, fT3, FT4)
Centanni (2012) [7]	Thyroxine	Case series subgroup of a case-control study	269 patients with hypothyroidism: 113 with hypochloridria, 135 with no gastric disorders. 11 patients with infection eradicated Age: 44 y (median) M/F: 100% female	Histology and/or serology for 269 but reassessed with ^{13}C-UBT for the 11 pts in the case series	Eradication with standard triple therapy for 14 days	Modifications in thyroid function test (TSH)
Pierantozzi (2001) [9]	L-Dopa	Case series	6 patients with advanced PD Age: 57.0±9.7y (mean) M/F: not specified.	Serology	*H. pylori* eradication with standard triple therapy for 7 days vs placebo	L-dopa AUC and clinical improvement (UPDRS score)
Pierantozzi (2006) [10]	L-Dopa	RCT double blind, parallel group design	34 patients with PD Age: 65.55 ±7.6y (mean) M/F:53% female	Serology, stool test, histology and RUT	*H. pylori* eradication with standard triple therapy for 7 days vs antioxidant (allopurinol)	L-dopa AUC, Cmax and clinical improvement (UPDRS score)
Valiyaveettil (2005) [11]	Iron	RCT	52 patients Age: 30-49 y (range) M/F: 75% female	Histology, RUT	*H. pylori* eradication with standard triple therapy for 7 days + ferrous sulphate vs oral ferrous sulphate alone + delayed H pylori eradication (during second month) vs ferrous sulphate alone	Improvement in iron indices (Hb, SI and SF)
Chen (2007) [8]	Iron	RCT	86 patients Age: 18-76 y (range) M/F:42% female	^{13}C-UBT	*H. pylori* eradication with standard triple therapy for 14 days + ferrous succinate vs oral ferrous succinate alone	Improvement in iron indices (Hb, SI, SF, MCH and MCV)
Kotb (2012) [13]	Iron	Case series	20 patients Age: 25-55 y (range) M/F: 60% female	Histology	*H. pylori* eradication with sequential therapy +iron sulphate	Improvement in iron indices (Hb, SF and transferrin)

PD: Parkinson's disease; SI: sideremia; SF: serum ferritin; MCH: mean Hb concentration; MCV: mean corpuscular volume; Hb: hemoglobin; RUT: rapid urea test; ^{13}C-UBT: urea breath test

a "Low, "Medium" or "High" risk of bias taking into account the study design and the potential impact of the identified bias. An adapted form of the Risk of Bias Criteria for EPOC reviews proposed by the Cochrane Public Health Group (CPHG, 2011) was used for RCTs and NRCTs, while the quality of Observational Studies was assessed using an adaptation of the chart proposed by Petticrew et al. [5].

Based on the results of the assessment performed, case series on the relationship between *H. pylori* eradication and thyroxine absorption [7, 12] were considered of medium quality. The two studies performed by Pierantozzi et al. [9, 10] on L-dopa absorption after *H. pylori* treated infection were a case series and a randomised trial and were considered of low and high quality, respectively. Finally, studies on *H. pylori* eradication and iron absorption were evaluated as being of low quality [8, 11] and medium quality [13], respectively.

DISCUSSION

This systematic review provides strength to the hypothesis that there is an inverse relationship between *H. pylori* infection and drug absorption. Although this link has been previously evaluated [13], this review focused on a particular category of drugs which are frequently used in routine clinical practice and whose dosage and clinical effectiveness strictly depends on the amount of drug absorbed; with appropriate restrictions and specifications they have been referred to as "replacement therapies" because they are used to compensate for a lack or deficiency arising from inadequate nutrition, dysfunctions or losses. It has been noticed that, independently from the drug considered, there is a positive modification in replacement therapies absorption after *H. pylori* eradication [17]. This modification can be seen both directly by using pharmacokinetics indices (AUC and Cmax) and/or indirectly through the modification of specific parameters in blood tests or through clinical scores.

Those findings suggested a possible mechanism that relates the infection and drug absorption based on alterations in gastric acidity. Previous studies have reported that the intestinal absorption of thyroxine, L-Dopa and iron are pH-dependent [7, 18, 19]. However, only two studies on thyroxine absorption [7, 12] and one study on iron absorption [13] explored the correlation between the grade of *H. pylori* related gastritis in gastric biopsies, its location in the stomach mucosa (e.g.

antrum or corpus), the gastric pH and drug absorption with pre and post eradication changes. Hypochloridria is not the only possible explanation of impaired drug absorption in *H. pylori* positive patients. Past studies on L-dopa showed that *H. pylori* infection can cause a delayed gastric emptying. This may be responsible for modifications in the normal pathway of drug absorption by favouring a bacterial overgrowth that can compete with absorption mechanisms and by increasing the contact time between a substance and gastric enzymes [20]. Alternatively, for iron it has been speculated that *H. pylori* can actively compete with the body for its absorption [21]. Iron also needs to be transformed into an absorbable form and this is achieved both by the presence of an appropriate gastric pH and by the presence of ascorbic acid secreted in gastric juice. *H pylori* infection alters both mechanisms [22].

Chronic blood loss related to *H. pylori* gastritis can be another reasonable cause of iron depletion and poor response to orally administered replacement therapy. However, not all patients with *H. pylori* gastritis develop iron deficiency anemia, suggesting that more than one mechanism can be involved [23].

From these findings it is clear that drugs absorption is a complex mechanism that still needs to be fully understood. This review provided strength to the hypothesis that *H. pylori* infection plays an important role in drug metabolism and that it is one of the leading cause in altering the mechanisms of drug absorption.

The implications of impaired drug absorption in subjects with *H. pylori* infection can be relevant for clinical practice due to the high prevalence of the infection worldwide [24]. At the same time, clinical conditions that need replacement therapies, such as hypothyroidism, iron deficiency anemia and Parkinson's disease, are widespread. It has been estimated that about 4.6% of the United States population has hypothyroidism, increasing with age to more than 10% in adults above 65 years old [15, 16]. Iron deficiency anemia is even more prevalent, with 30% of the world population affected [26]. Finally, an estimated seven to ten million people worldwide are living with Parkinson's disease [27].

The presence of a relationship between drug absorption and *H. pylori* raises further questions regarding the opportunity to change our clinical practice. Ideally, patients that need to start a replacement therapy as well as patients currently under therapy should be screened for *H. pylori* infection. Moreover, the dosage of the administered drugs should be re-evaluated, with a different timing in patients that have been eradicated to avoid overdose and related side effects.

What differentiates this infection from other causes of impaired drug absorption is that alterations related to the presence of *H. pylori* are reversible once the bacteria is eradicated with an antibacterial therapy [28]. However, the administration of an eradication treatment for every person diagnosed with *H. pylori* infection will cost more than $32 billion in the Unites States alone [29]. This underlines that a clear strategy is required to target appropriately people that would benefit from the eradication treatment. This review can contribute to this aim by highlighting specific clinical conditions that improve after *H. pylori* eradication and by targeting subgroups of patients that need to be screened for *H. pylori* positivity before being administered replacement therapies.

Despite the fact that results on the relationship between *H. pylori* and drug absorption that have been obtained in this review are consistent, there are several limitations that need to be highlighted: the paucity of studies available for inclusion, the limitations of the available data and the methodological weaknesses that have been evaluated. These determine the need to consider these results as non-definitive. Moreover, the statistical significance of the results could not fully correspond to a clinical significance that needs to be further explored with better quality studies.

CONCLUSIONS

This systematic review has found a small number of studies that support the hypothesis of an existing interaction between *H. pylori* infection and drug absorption of orally administered replacement therapies. Clinicians should be aware of this possible interaction when initiating a replacement therapy in a new patient and when evaluating poor clinical or laboratory response in patients under chronic treatments. The optimization of the medical therapy to obtain the best result with the lowest number of side effects should be the goal of any correct therapeutic approach. However, the limitations that have been highlighted and the scarcity of good quality studies on this topic underline the necessity of a greater number of studies on this subject and of better quality.

Conflicts of interest and source of funding: all authors declare no conflict of interest. The protocol and the paper received no external funding.

Authors' contribution: G.F. is the submission's guarantor, planned the protocol, interpreted the results and wrote the paper. J.M.B. and E.H. supported the protocol planning and edited the paper. V.C. acted as a second reviewer. D.V. wrote and edited the paper. All authors approved the final version of the manuscript.

Acknowledgment: The authors thank Dr. Rachel Richardson for her support and helpful advice.

Supplementary material (Appendix 1) available from http://www.jgld.ro/2015/1/16.html

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Appendix 1: Literature search strategy

Database: **OvidMEDLINE** (http://ovidsp.ovid.com)

Searched from 1946 to February Week 4 2014

The following search strategy was used in MEDLINE and then adapted

as necessary for other databases:

1 helicobacter pylori.mp. or exp Helicobacter pylori/ (32600)

2 exp Helicobacter Infections/ or h pylori.mp. (29173)

3 helicobacter infection*.tw. (430)

4 (helicobacter adj3 positive).tw. (1017)

5 (h pylori adj3 infect*).tw. (10344)

6 1 or 2 or 3 or 4 or 5 (34132)

7 exp Thyroxine/ or exp Estrogen Replacement Therapy/ or exp Hypothyroidism/ or replacement therapy.mp. (105969)

8 replacement therap*.tw. (34229)

9 drug* replacement therap*.tw. (6)

10 nutrient* replacement*.mp. (14)

11 nutrient* deficien*.tw. (948)

12 micronutrients/ or trace elements/ or vitamins/ (32151)

13 7 or 8 or 9 or 10 or 11 or 12 (139951)

14 exp Absorption/ or exp Intestinal Absorption/ or absorption*.mp. (193293)

15 drug* absorption*.tw. (2787)

16 absorb*.mp. (83454)

17 (impaired adj3 absorption*).tw. (767)

18 (reduced adj3 absorption*).tw. (1960)

19 (altered adj3 absorption*).tw. (337)

20 malabsorption*.mp. (13722)

21 14 or 15 or 16 or 17 or 18 or 19 or 20 (265372)

22 6 and 13 (80)

23 6 and 21 (427)

24 22 or 23 (489)