Pharmacoeconomic analysis of proton pump inhibitor therapy and interventions to control Helicobacter pylori infection
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 6

Gastrointestinal drug use after Helicobacter pylori eradication in chronic users; studies in pharmacy data and General Practitioners’ data

Based on:
Abstract

Introduction: Eradication of *Helicobacter pylori* has been proven to prevent recurrence of peptic ulcer, potentially resulting in increased quality-of-life and less money spent on gastrointestinal drugs. Pharmacoeconomic analyses of *Helicobacter pylori* eradication often presume this favourable monetary effect on drug costs. We investigated the presumed beneficial effect of *Helicobacter pylori* eradication on the use of gastrointestinal drugs before and after *Helicobacter pylori* eradication in two separate databases. The first database consists of pharmacy data on dispensed gastrointestinal drugs, whereas the second database consists of general practitioners (GP) data on prescribed gastrointestinal drugs.

Methods: For pharmacy data, the drug dispensing data were extracted from the InterActie-database. This database comprises prescription information of approximately 150,000 patients. These patients are registered with more than 20 pharmacies in the north and east of the Netherlands. Data on *Helicobacter pylori* eradactions from 1995 to 1998 were used in this study. To enable inclusion of prior and post eradication periods additional information was also taken from 1994 and 1999. For GP data, the drug prescribing data was extracted from the RNG-database. This database comprises prescription information of approximately 30,000 patients. These patients are registered with 17 GPs in the north of the Netherlands. Data on *Helicobacter pylori* eradactions from 1997 to 2000 were used in this study. To enable inclusion of prior and post eradication periods additional information was also taken from 1996 and 2001. We identified patients with a *Helicobacter pylori* eradication as patients with a prescription for a gastrointestinal drug (ATC=A02*) and at least two prescriptions for antibiotics (ATC=J*) on the same day. For clarity, only patients with an eradication regimen that was not preceded or followed by another eradication regimen within one year of eradication were analysed. Gastrointestinal drug costs were based on acquisition prices for Dutch public pharmacies (excluding value added tax) set by the Royal Dutch Association for the Advancement of Pharmacy for May 2002. Drug
Gastrointestinal drug utilization prior and post *Helicobacter pylori* eradication

utilisation and costs were calculated for 4-monthly periods prior to eradication (months 4-0 before) and one year later (9-12 months post eradication). For comparison costs in all periods were expressed per patient per month. For statistical analysis the STUDENT’s t-test was used.

**Results:** *Pharmacy data;* Generally the percentage of patients on gastrointestinal drugs after eradication decreases with time elapsed since eradication. In 40% of the cases, persons became non-users post eradication. Costs for gastrointestinal drugs are €34 per patient per month prior to eradication. A significant decline in this variable is observed post eradication, one year later. Costs for PPIs show an opposite trend: costs per patient per month are 25% higher post eradication compared to prior. Also, more than half of the gastrointestinal drug costs in the pre-eradication period relate to non-PPIs whereas post eradication 83% of the drug costs is for PPIs.

*GP data;* Generally the percentage of patients on gastrointestinal drugs decreased with time elapsed after eradication. The costs per patient per period for all gastrointestinal drugs decrease after eradication. However, the costs for PPIs do not differ significantly. Post eradication 40% of the patients continued using gastrointestinal drugs, of which 60% used a PPI. Before eradication 29% on gastrointestinal drugs used a PPI. In the non-ulcer group the percentage of people on PPIs after *Helicobacter pylori* eradication is higher compared to the ulcer group. The cost in non-ulcer group is also higher compared to the ulcer group. This is the case prior and post eradication. The difference in PPI cost before and after eradication is non-significant in both groups, indicating no difference in PPI costs before and after eradication.

**Conclusion:** In practice continued use and costs of PPIs exist after *Helicobacter pylori* eradication. Costs post eradication are mainly due to PPIs. There may be a great pharmacoeconomical advantage when it is possible to predict which patients are more likely to ‘fail’ eradication therapy.
6.1 Introduction

Eradication of Helicobacter pylori has been proven to prevent recurrence of peptic ulcer, potentially resulting in increased quality-of-life and less money spent on gastrointestinal drugs [1]. Pharmacoeconomic analyses of Helicobacter pylori eradication often presume this favourable monetary effect on drug costs [2-4].

Helicobacter pylori eradication regimens comprise combinations of proton pump inhibitors (PPIs) and two antibiotics. Effectiveness in eradicating Helicobacter pylori may exceed 80% [5]. The currently preferred regimen internationally and in the Netherlands is triple therapy with a PPI, clarithromycin and amoxicillin twice daily during 7-10 days [6].

We investigated the presumed beneficial effect of Helicobacter pylori eradication on the use of gastrointestinal drugs before and after Helicobacter pylori eradication in two separate databases. The first database consists of pharmacy data on dispensed gastrointestinal drugs, whereas the second database consists of general practitioners (GP) data on prescribed gastrointestinal drugs.

6.2 Pharmacy data

Data and Methods

Drug dispensing data were extracted from the InterAction-database [7]. This database comprises prescription information of approximately 150,000 patients. These patients are registered with more than 20 pharmacies in the north and east of the Netherlands. In the Netherlands all pharmacies have computer systems in which patient history with dispensing records are stored. Data on Helicobacter pylori eradictions from 1995 to 1998 were used in this study. To enable inclusion of prior and post eradication periods additional information was also taken from 1994 and 1999.

We identified patients with a Helicobacter pylori eradication as patients with a prescription for a gastrointestinal drug (ATC=A02*) and at least two
prescriptions for antibiotics (ATC=J*) on the same day. For clarity, only patients with an eradication regimen that was not preceded or followed by another eradication regimen within one year of eradication were analysed.

Chronic utilisation of gastrointestinal drugs was defined as more than 0.5 DDD per day on average during the 4 months prior to eradication of Helicobacter pylori. To exclude NSAID-induced gastrointestinal drug utilisation, patients with an NSAID-prescription during at least one month in the year prior to or in the year after eradication were excluded (N=11).

Gastrointestinal drug costs were based on acquisition prices for Dutch public pharmacies (excluding value added tax) set by the Royal Dutch Association for the Advancement of Pharmacy for May 2002 [8]. Drug utilisation and costs were calculated for 4-monthly periods prior to eradication (months 4-0 before) and one year later (9-12 months post eradication).

For comparison costs in all periods were expressed per patient per month. For statistical analysis the STUDENT’s t-test was used.

Results
We identified 161 Helicobacter pylori eradications, all used the preferred regimen. Of the eradications 58% were among men. The comprised age range was 24-85 years (average of 56 years). Over the years analysed there was a shift in prescriber of the eradication regimen, in 1995 40% of the eradication regimens was prescribed by the GP, whereas in 1998 this was almost 60%, the remainder was prescribed by the gastroenterologists (FIGURE 1).

Generally the percentage of patients on gastrointestinal drugs after eradication decreases with time elapsed since eradication (TABLE 1). In 40% of the cases, persons became non-users post eradication.
Costs for gastrointestinal drugs are €34 per patient per month prior to eradication. A significant decline in this variable is observed post eradication, one year later. Costs for PPIs show an opposite trend: costs per patient per month are 25% higher post eradication compared to prior. Also, more than half of the gastrointestinal drug costs in the pre-eradication period relate to non-PPIs whereas post eradication 83% of the drug costs is for PPIs.

Of the persons on PPIs prior to eradication only 30% became a non-user of gastrointestinal drugs one year later. Users of gastrointestinal drugs are primarily PPI-users: 83% of the users and 90% of the costs post eradication. Of those persons without PPIs 60% became PPI-user post eradication and PPIs account for 75% of their gastrointestinal drug costs in this period.
### 6.3 GP data

**Data and Methods**

Drug prescribing data was extracted from the RNG-database [9,10]. This database comprises prescription information of approximately 30,000 patients. These patients are registered with 17 GPs in the north of the Netherlands. GPs in the Netherlands have a constant population registered within their practice for which they provide care. GPs account for more than 90% of the referrals to specialists. Approximately 80% of the population of the GPs participating in the RNG-database stay with the same GP over a 4 year time period. The other 20% disappears or appears through movement, birth or dead. The participating GPs have meetings to discuss diagnostic classifications. As guidance the Dutch General Practitioners guideline is used [11]. The guideline concerning stomach complaints advises not to treat stomach complaints with ‘blind’ eradication therapy without gastroscopy. All the participating GPs had free access to gastroscopy. Data on *Helicobacter pylori* eradications from 1997 to 2000 were used in this study. To

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**Table 1.** Cost of gastrointestinal (GI) drugs per person per month prior to and post *Helicobacter pylori* eradication therapy for chronic GI-drug users (N=161) in € (cost level 1999) and percentages on GI-drugs; based on pharmacy data.

<table>
<thead>
<tr>
<th>Users</th>
<th>Period</th>
<th>Prior</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI-drug costs</td>
<td>€ 34</td>
<td>€ 24 (p=0.002)</td>
</tr>
<tr>
<td></td>
<td>PPI-costs</td>
<td>€ 16</td>
<td>€ 20 (p=0.17)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100 (42)</td>
<td>60 (71)</td>
</tr>
<tr>
<td>PPI</td>
<td>GI-drug costs</td>
<td>€ 44</td>
<td>€ 24 (p=0.008)</td>
</tr>
<tr>
<td></td>
<td>PPI-costs</td>
<td>€ 38</td>
<td>€ 20 (p=0.06)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100 (100)</td>
<td>70 (83)</td>
</tr>
<tr>
<td>Non-PPI</td>
<td>GI-drug costs</td>
<td>€ 26</td>
<td>€ 20 (p=0.003)</td>
</tr>
<tr>
<td></td>
<td>PPI-costs</td>
<td>€ 0</td>
<td>€ 15 (p=0.0001)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100 (0)</td>
<td>53 (60)</td>
</tr>
</tbody>
</table>

Periods are: prior; 4 months prior to eradication, post; 9-12 months post eradication. Between brackets percentages for users of proton pump inhibitors (PPI) of those still on GI-drugs. For statistical inference the paired t-test was used, between brackets p-values for the t-test on the difference with Prior are shown for costs. Results are specified for all chronic users, those on PPI prior to eradication and those without a PPI (non-PPI) prior to eradication.
enable inclusion of prior and post eradication periods additional information was also taken from 1996 and 2001.

We identified patients with a *Helicobacter pylori* eradication as patients with a prescription for a gastrointestinal drug (ATC=A02*) and at least two prescriptions for antibiotics (ATC=J*) on the same day. For clarity, only patients with an eradication regimen that was not preceded or followed by another eradication regimen within one year of eradication were analysed. Patients with eradication within one year of eradication were therefore excluded. Patients with incomplete data post or prior eradication were excluded.

Further selection was done using the registered diagnosis for the *Helicobacter pylori* eradication. Diagnose was registered using the internationally accepted ICPC-code [12]. Patients were assigned either to a group with diagnosed ulcers (ICPC D85 and D86) or a group without diagnosed ulcers (ICPC D02, D03, D84 and D87). Chronic utilisation of gastrointestinal drugs was defined as utilization of a gastrointestinal drug during the 4 months prior to eradication of *Helicobacter pylori*.

Gastrointestinal drug costs were based on acquisition prices for Dutch public pharmacies (excluding value added tax) set by the Royal Dutch Association for the Advancement of Pharmacy for may 2002 [8]. Drug utilisation and costs were calculated for 4-monthly periods prior to eradication (months 4-0 before) and one year later (9-12 months post eradication).

For comparison costs in both periods were expressed per patient per month. For statistical analyses a paired t-test was used.

**Results**

We identified 110 patients with a prescription for a *Helicobacter pylori* eradication. Of these patients 2 had an eradication within one year of the first eradication and 6 patients were excluded because of incomplete data prior or post
Gastrointestinal drug utilization prior and post *Helicobacter pylori* eradication eradication, which leaves 102 patients for evaluation. Of these 102 patients 63 (62%) were identified as chronic GI-drug users. Of these 63 patients who were prescribed a *Helicobacter pylori* eradication regime, 19 (30%) were diagnosed with peptic ulcer disease and 44 (70%) had not.

Generally the percentage of patients on gastrointestinal drugs decreased with time elapsed after eradication (TABLE 2). The costs per patient per period for all gastrointestinal drugs decrease after eradication. However, the costs for PPIs do not differ significantly. Post eradication 40% of the patients continued using gastrointestinal drugs, of which 60% used a PPI. Before eradication 29% on gastrointestinal drugs used a PPI.

In the non-ulcer group the percentage of people on PPIs after *Helicobacter pylori* eradication is higher compared to the ulcer group. The cost in non-ulcer group is also higher compared to the ulcer group. This is the case prior and post eradication. The difference in PPI cost before and after eradication is non-significant in both groups, indicating no difference in PPI costs before and after eradication.

6.4 Discussion & Conclusion

Overall the triple therapy for eradication of *Helicobacter pylori* is prescribed primarily by the GP. However, in the beginning of the study period gastroenterologists were the primary prescriber of the triple therapy. Reason for this shift is probably the fact that triple therapy was relatively new in 1995 and GPs generally follow specialists (in this case the gastroenterologists) in new strategies.

Both the pharmacy data and the GP data show a decrease in total gastrointestinal drug costs. In both groups this is significant for all patients. However in both databases continued use and costs of PPIs after *Helicobacter pylori* eradication is shown. This is contrary to the assumption in most
Table 2. Cost of all gastrointestinal (GI) drugs and proton pump inhibitors (PPIs) per patient per 4-monthly period prior and post Helicobacter pylori eradication in € (price year: 2002) and percentages on GI-drugs for 63 Helicobacter pylori eradication; based on GP data

<table>
<thead>
<tr>
<th>Group</th>
<th>Period</th>
<th>Prior</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer chronic (n=19)</td>
<td>GI-drug costs</td>
<td>€ 42</td>
<td>€ 18 (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>PPI costs</td>
<td>€ 11</td>
<td>€ 12 (p=0.84)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100% (21%)</td>
<td>37% (43%)</td>
</tr>
<tr>
<td>Non-Ulcer chronic (n=44)</td>
<td>GI-drug costs</td>
<td>€ 58</td>
<td>€ 29 (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>PPI costs</td>
<td>€ 27</td>
<td>€ 23 (p=0.58)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100% (32%)</td>
<td>41% (67%)</td>
</tr>
<tr>
<td>All chronic (n=63)</td>
<td>GI-drug costs</td>
<td>€ 53</td>
<td>€ 26 (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>PPI costs</td>
<td>€ 22</td>
<td>€ 20 (p=0.62)</td>
</tr>
<tr>
<td></td>
<td>% on GI-drugs (PPI)</td>
<td>100% (29%)</td>
<td>40% (60%)</td>
</tr>
</tbody>
</table>

Periods are: prior; 4 months prior to eradication, post; 9-12 months post eradication. Between brackets percentages for users of proton pump inhibitors (PPI) of those (still) using GI-drugs are shown. Distinguished groups refer to all ulcer patients (ICPC D85 and D86) and to all non-ulcer patients (ICPC D02, D03, D84 and D87) which were chronic GI-drug users. For statistical inference the paired t-test was used.

pharmacoeconomic models that Helicobacter pylori eradication results in lower PPI use and costs.

Several explanations present themselves for gastrointestinal drug use after eradication. Firstly, eradication therapy was successful but the Helicobacter pylori infection was not responsible for the gastrointestinal problems. This could also explain the PPI use and costs, as Helicobacter pylori infection potenates the inhibition of acid secretion by omeprazole [13]. When Helicobacter pylori is eradicated a higher dose of PPIs would be necessary to reach the same acid inhibitory effect. This could explain part of the users in the ulcer group, as Helicobacter pylori may not be responsible for all ulcers found. In a meta-analysis concerning the situation in the US, Laine et al. [14] found that 20% of ulcer recurrence was neither NSAID nor Helicobacter pylori induced. The findings of Laine et al. are not necessarily true for the Netherlands; nevertheless it could explain some of the post eradication users. For the non-ulcer group this could be the case for a majority of the users. Moayyedi et al. [15] found that 15 patients had
to be treated to cure 1 patient of non-ulcer dyspepsia, which indicates that Helicobacter pylori eradication is not an effective treatment in a majority of patients with non-ulcer dyspepsia. Both these arguments are also applicable to the pharmacy data used in this study.

Furthermore NSAID-use was not considered in the selection of the patients in the GP-data used in this study. It is possible that post eradication GI-drug use is caused by NSAID related ulcers and not Helicobacter pylori related ulcers. In the group identified by pharmacy data we found similar figures, with exclusion of NSAID users. As we had no information concerning over the counter NSAID use, there is not a complete overview of NSAID use prior and post Helicobacter pylori eradication. The NSAID use prescribed by the GPs, in the RNG database, was constant over the study period.

It can also be that eradication therapy has failed. Factors associated with an adverse treatment outcome are high intragastric bacterial load before treatment, bacterial genotype and host genetic polymorphisms of the cytochrome-P450 isoenzymes that are involved in the metabolisms of PPIs [16]. Another reason for failure of an eradication regime is antibiotic resistance [17,18]. In this study the main eradication regimen used consisted of amoxicillin and clarithromycin for which the antibiotic resistance in the Netherlands is low [19]. Next to these arguments, accordance to therapy may influence success of eradication. We excluded patients who had another Helicobacter pylori eradication within one year of the studied eradication, this makes the possibility of failed Helicobacter pylori therapy unlikely. Another possibility is that patients are re-infected with Helicobacter pylori; this is however also unlikely because the rate of re-infection is considered to be low [20,21].

Although we have information on the diagnosis made by the GP in the GP database, we do not have any information on Helicobacter pylori testing. Therefore we can not be sure that Helicobacter pylori is present prior to the prescribed eradication regimen. When Helicobacter pylori is not present an eradication
therapy is unlikely to benefit the patient. In a recent survey, Weijnen et al. [22] found that not all GPs test for Helicobacter pylori infection before prescribing an eradication regimen. Therefore with the decreasing prevalence of Helicobacter pylori in the Netherlands [23] there is an increasing possibility that patients with gastrointestinal problems have no Helicobacter pylori infection. In a study concerning the adherence to formulary guidelines by the participating GPs. It was found that the GPs had a global adherence which varied from 76-89% [10]. In the Dutch General Practitioners guidelines, ‘blind’ Helicobacter pylori therapy is only recommended in case of proven ulcus duodeni [10]. In case of a ulcus ventriculi Helicobacter pylori diagnostics is necessary. For the eradication therapies prescribed by the GPs in the GP database it is therefore likely that Helicobacter pylori testing is done prior to eradication.

It is argued that after eradication therapy patients have a higher risk of developing gastroesophageal reflux disease (GERD) [24]. Development of GERD could potentially lead to an increase in the use of PPIs. In the GP-database we did not find any indications that patients developed GERD after eradication therapy. Only 2 patients were prescribed PPIs because of GERD after eradication therapy.

Another argument for the use of PPIs is rebound hypersecretion which occurs when gastric acid inhibition therapy is stopped [25,26]. When rebound hypersecretion occurs gastrointestinal problems will reappear and the need for PPIs will return. It is unclear to what extend this is the case in both populations studied.

There was no suggestion in our data that the diagnosis by the general practitioner for which the Helicobacter pylori eradication was prescribed had any influence on the success of the eradication in terms of costs and use of gastrointestinal drugs. The costs of gastrointestinal drugs appear to be higher in the non-ulcer group but the use and costs of gastrointestinal drugs follow the same trend.

As is shown the results of Helicobacter pylori eradication in terms of utilization and cost for PPIs and all gastrointestinal drugs is comparable in both
Gastrointestinal drug utilization prior and post *Helicobacter pylori* eradication databases used. Both databases used have their own specific advantages. For the pharmacy database it is certain that the prescriptions are delivered to the patients, for the GP database this is not the case. However, the information on receiving the medication does not guarantee that the medication is used properly. For the GP database the advantage is that there is an indication why medications are prescribed. However in this study the indication for why *Helicobacter pylori* eradication was prescribed did not make a difference for the final conclusions. Another advantage of the pharmacy data is that next to GP prescriptions also prescriptions by specialists are included.

In practice continued use and costs of PPIs exist after *Helicobacter pylori* eradication. Costs post eradication are mainly due to PPIs. There may be a great pharmacoeconomical advantage when it is possible to predict which patients are more likely to ‘fail’ eradication therapy in terms of continued gastrointestinal drug use.


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