Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Chapter 7

Use of acid suppressant drugs in patients with chronic functional dyspepsia or GERD before and after H. pylori eradication.

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Submitted
Background
We investigated, whether the use of maintenance doses of acid suppressant drugs (ASD) is influenced by \textit{H. pylori} eradication in General Practice in patients with chronic functional dyspepsia or mild gastro esophageal reflux disease (GERD).

Methods
After gastrointestinal endoscopy, \textit{H. pylori} positive dyspeptic patients using maintenance ASD were randomised double blind to receive \textit{H. pylori} eradication treatment (group I) or placebo (group II). After treatment and a subsequent 3 weeks period of titrating the dose of ASD to zero, patients were prospectively followed 24 weeks during which antacids or ASD in low dose only were taken when required. Endoscopy was done 4-6 weeks after treatment. The endpoints were: Proportion of patients ASD free at 24 weeks, ASD free interval (median, % ASD free); mean daily ASD and antacid intake.

Results
Of 131 eligible patients, 115 patients completed the protocol. No significant differences in endpoints were observed between group I (n=56) and group II (n=59). Of 61 patients with functional dyspepsia, 57% (16/28) in group I and 52% (17/33) in group II (n.s.) abstained from ASD use during 24 weeks. The reduction in the mean daily dosage of ASD per patient was 85% in group I and 83% in group II (ns). Of patients with GERD (n=54), 21% (6/28) in group I and 50% (13/26) of group II (p<0.05) abstained from ASD use. In GERD patients the mean daily ASD dosage per patient decreased 62% in group I and 82% in group II (p<0.05). Rescue antacid intake was low.

Conclusions
\textit{H. pylori} eradication does not facilitate reduction of ASD dosage in chronic dyspeptic patients. Strikingly it impedes the reduction of ASD use in patients with GERD.
Introduction

In General Practice, patients presenting with dyspeptic symptoms are often given acid suppressant drugs (ASD), such as proton pump inhibitors (PPI) or H₂-receptor-antagonists (H₂RA) as initial short-term empirical treatment. Due to the relapsing character of dyspeptic symptoms, long-term ASD prescription for control of these symptoms is common in primary care. The frequency of long-term prescription of ASD varies from 2 to 5% in the total population.¹² Most ASD prescriptions are repeat prescriptions.³ The costs of long-term use of ASD are considerable. In patients with ulcer diathesis, *H. pylori* eradication might lead to reduction in ASD use, since the ulcer will not relapse after successful eradication⁴. The role of *H. pylori* in gastro-esophageal reflux disease (GERD) is uncertain⁵ and the effect of eradication of *H. pylori* on symptoms in functional dyspepsia is also unclear.⁶–¹⁰ Despite the uncertainties on the outcome, it is recommended to eradicate *H. pylori* in all chronic ASD using dyspeptic patients.¹¹ We feel that there may be overtreatment and we doubt whether it is useful to propagate a test and treat strategy, because definitive concluding data are lacking. The presence or absence of *H. pylori* infection might influence the requirement of ASD, since the presence of *H. pylori* seems to be linked to acid regulation in functional dyspepsia¹² and intra-gastric buffering.³

General Practitioners (GPs) experience that in dyspeptic patients, once started on long-term ASD, dyspeptic symptoms frequently recur rapidly when ASD are discontinued. Therefore, a period of gradual reduction of the dose might be beneficial before discontinuing ASD medication in this group of patients.

In our prospective, randomised, double-blind, placebo controlled, general practice-based intervention study, we investigated the effect of *H. pylori* eradication on the use of ASD in chronic dyspeptic patients on long-term ASD therapy, and the relation to the diagnosis of functional dyspepsia or GERD on the medication use.

Materials and Methods

Patient population

During the period April 1997-October 1999 fifty-four general practitioners (GPs) in the Amsterdam area participated in this study. We selected chronic dyspeptic patients on ASD in the age range 18-85 years. Chronic dyspepsia was defined as chronic upper abdominal pain/discomfort or gastro esophageal reflux disease (symptomatic or oesophagitis grade one (Savary Miller)) thought to require maintenance ASD during at least the 8 weeks immediately before entry into the study. Patients were identified by computerised reviews of medication by pharmacists co-operating with the GPs. Exclusion criteria included: history of documented peptic ulcer disease, history of documented gastroesophageal reflux disease grade II, III or IV (Savary-Miller) at endoscopy; gastroduodenoscopy in the previous four months; clinically significant cardiovascular, pulmonary, renal, hepatobiliary or pancreatic
disease or malignancy; bleeding and weight loss; abdominal surgery; pregnant or lactating women; insufficient knowledge of the Dutch language; ingestion of antibiotics or bismuth-containing compounds during the previous month, ingestion of NSAIDs; any condition associated with poor compliance. Data results of upper GI-endoscopy or radiology and previous medication, were obtained by the principal GP-investigator (GH) from the patient’s GP. A meeting between the principal GP-investigator and the patient’s GP was arranged to verify and complete the data of each patient.

All eligible patients were invited to participate in a letter from their own GP. Participating patients were asked to stop ingestion of their ASD at least one week before upper GI-endoscopy. Two weeks after endoscopy patients attended the clinic for randomisation. During the two weeks between the upper GI-endoscopy and randomisation patients were allowed to continue to take their maintenance doses of ASD. Follow-up endoscopy took place 4-6 weeks after \textit{H. pylori} eradication or placebo treatment.

Demographic and dyspepsia questionnaires were filled out in hospital.

The study was approved by the Institutional Ethics Committee of the Academic Medical Center and written informed consent was obtained from the patient before the initial endoscopy.

\textbf{Endoscopy and assessment of} \textit{H. pylori} \textbf{infection}

Patients with previous documented oesophagitis grade 1 (Savary-Miller) or oesophagitis grade 1 at entry endoscopy or with predominant typical reflux symptoms (heartburn, acid regurgitations) were regarded as suffering from reflux disease.\textsuperscript{13}

During upper GI-endoscopy before and 4-6 weeks after \textit{H. pylori} eradication or placebo treatment, 3 antral and 3 corpus mucosal biopsy specimens were obtained for histological and bacteriological assessment and were routinely processed.\textsuperscript{14} Patients were defined as positive for \textit{H. pylori} if one of the biopsy specimens was positive for \textit{H. pylori}. \textit{H. pylori} infection was considered to absent if all bacterial cultures and histopathology data were negative for \textit{H. pylori}. The histopathologist and microbiologist were blinded to each other’s results.

Seven patients, who refused endoscopy after \textit{H. pylori} eradication treatment, were assessed for \textit{H. pylori} infection by \textsuperscript{13}C Urea Breath Test\textsuperscript{15} (C-UBT) using a Laser-Assisted-Ratio-Analyser (Alimenterics B.V., Hoofddorp, Netherlands). The LARA \textsuperscript{13}C-UBT has a sensitivity of 93\% and specificity of 96\% in the detection of \textit{H. pylori} infection.\textsuperscript{15}

\textbf{Randomisation, treatment and follow-up}

The \textit{H. pylori} positive patients with functional dyspepsia or GERD were double-blind randomised to receive omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg bid for 7 days or omeprazole 20 mg and placebo bid for 7 days. Randomisation and packaging was carried out by researchers not selecting and evaluating the participants in order to maintain concealment. The active and placebo tablets of antibiotics were equal in
amount and identical in appearance. Neither the participants nor the investigator were aware of the H. pylori status during follow-up.

Patients were asked to taper the dose of ASD within 3 weeks after the H. pylori eradication treatment by reducing the daily dose gradually. After this 3 weeks period patients had to stop the ASD completely and started a 6 months period of reporting symptoms and medication use. If in this 6 months period dyspeptic symptoms were not controlled by on demand antacids (calcium carbonate 680 mg/magnesium carbonate 80 mg; Roche Nicholas, Netherlands) omeprazole 10 mg could be taken as required, or a higher dose could be taken if necessary. H2RA-users at study entry, who preferred to take H2RA as required, were allowed to do so. Every patient was provided with antacids at the hospital and could obtain a new supply of antacids and prescriptions for ASD at his/her GP’s office.

Patients reported the predominant dyspeptic symptom(s) and the amount of antacids or ASD ingested per week in a diary throughout a 24 weeks period. At the 6 month visit, questionnaires were filled out again. ASD use, as reported by the patients was compared to prescription data in the GP’s office and at the pharmacy.

Endpoints.
The intake of ASD during the follow-up period in both groups was compared.
The ASD intake free interval (in weeks) after the 3 weeks period of tapering the dose, the proportion of patients ASD free at 24 weeks and the total amount of antacids, omeprazole 10 mg or its equivalent used in the follow-up period of 24 weeks were recorded in both groups.

Analysis and statistics.
Per-protocol (n=115) and intention-to-treat analysis (n=131) were performed. Analysis was performed using SPSS for Windows (version 7.5.3). The Chi-square test was used for comparison of proportions. The Mann Whitney-U test was used for comparison of the mean use of ASD. Wilcoxon Matched-Pairs Signed-Rank Test was used for comparison of the mean use of ASD at entry and during follow-up of each patient. Significance was set at α = 0.05 (two-sided).

Results
Patients
1083 chronic dyspeptic patients met eligibility criteria; 434 (40%) of these volunteered to participate for endoscopy. Of the volunteers 227 (52%) patients were H. pylori positive: 78 with and 149 without PUD. Of the 149 non-ulcer patients 18 were excluded for the following reasons: refusal to participate further (9), esophagitis grade 3 (2), Barrett's esophagus (7). The remaining 131 patients were randomised to receive treatment for H. pylori eradication (n=65) or placebo (n=66) (figure 1).
General characteristics of the patients (n=131) were: mean age 52 years (range 18-79); male 41.2%; one or more documented prior investigations by barium meal and/or upper GI endoscopy 52%; H2-receptor-antagonist use at entry 64.9%; protonpump inhibitor use at entry 35.1%. No significant difference between the two randomisation groups was found with respect to these variables.

Five patients in the treatment group and six patients in the placebo group refused follow-up, declining either endoscopy or 13C Urea Breath Test. One hundred and thirteen patients underwent follow-up endoscopy and an additional seven patients had the 13C Urea Breath Test (3 in the placebo- and 4 in the treatment group). H. pylori eradication treatment was successful in 86.2% (56/65) of patients in intention-to-treat and in 93.3% (56/60) in per-protocol analysis. One patient in the placebo group had received H. pylori eradication therapy elsewhere during the follow-up period. In 91.6% (120/131) of patients ASD measurement could be analysed according to protocol. Per-protocol analysis was performed for 115 patients (Hp eradicated: n=56 and placebo: n=59).

Figure 1. Flow of patients

![Flow of patients diagram]

Diagnosis

The diagnoses of patients with treatment according to protocol (n=115) are presented in table 1.

There was a prior or current diagnosis of hiatal hernia in 36% of patients (41/115); 21 of these patients had esophagitis grade 1.

After H. pylori eradication “de novo” development of GERD was not diagnosed. Two patients, both in the placebo group, had reflux esophagitis grade 1 at the follow-up endoscopy: one had a previous diagnosis of reflux esophagitis, the other not.
**ASD use before and after H. pylori eradication in functional dyspepsia or GERD**

Table 1. *Diagnosis of patients in H. pylori eradication treatment and placebo group.*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment N=56 (100%)</th>
<th>Placebo N=59 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>functional dyspepsia</td>
<td>28 (50)</td>
<td>33 (56)</td>
</tr>
<tr>
<td>gastro esophageal reflux disease</td>
<td>28 (50)</td>
<td>26 (44)</td>
</tr>
<tr>
<td>endoscopic negative reflux</td>
<td>10 (18)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>reflux esophagitis grade 1</td>
<td>18 (32)</td>
<td>15 (25)</td>
</tr>
</tbody>
</table>

*Acid suppressant drugs free period during follow-up*

The median ASD free interval in the *H. pylori* eradication and in the placebo groups were 11 and 24 weeks, respectively (ns, table 2). Of 63 patients who restarted ASD use 49 (78%) had taken ASD within the first weeks 8 weeks of follow-up. During the follow-up period 45% of patients (52/115) stopped ASD therapy completely. More patients in the placebo group than in the *H. pylori* eradication group were able to discontinue the use of ASD, 51% (30/59) and 39% (22/56), respectively. However, this difference did not reach statistical significance. At 24 weeks the proportions of ASD free patients in the *H. pylori* eradication group and the placebo group were equal.

Table 2. *Use of acid suppressant drugs (ASD)* at entry and during 24 weeks of follow-up after *H. pylori* eradication treatment or placebo.

<table>
<thead>
<tr>
<th></th>
<th>All patients n=115</th>
<th>treatment n=56</th>
<th>placebo n=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>median interval free of ASD use (weeks)</td>
<td>14</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>% of patients ASD free at 24 weeks</td>
<td>67</td>
<td>64</td>
<td>69</td>
</tr>
<tr>
<td>% of patients with no ASD use during 24 weeks</td>
<td>45</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>% of patients with mean 0-1 unit ASD/day</td>
<td>39</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>% of patients with mean &gt;1 unit ASD/day</td>
<td>16</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>mean ASD units/day at entry</td>
<td>1.92†</td>
<td>1.88‡</td>
<td>1.97‡</td>
</tr>
<tr>
<td>mean ASD units/day during follow-up</td>
<td>0.42†</td>
<td>0.49‡</td>
<td>0.34‡</td>
</tr>
<tr>
<td>% reduction in ASD units/day</td>
<td>78</td>
<td>74</td>
<td>83</td>
</tr>
</tbody>
</table>

* One unit Acid suppressant drug = 10 mg omeprazole or its equivalent ASD
†, ‡, § p<0.001 by Wilcoxon Matched-Pairs Signed-Ranks Test
Chapter 7

Use of ASD during follow-up and escape antacids

In all patients (n=115) the mean daily units of ASD use per patient was reduced by 78% from 1.92 at entry to 0.42 during follow-up (p<0.001). The mean daily dosage ASD during follow-up in both study groups was similar. No differences in ASD use were observed in patients in the *H. pylori* eradication group and in the placebo group.

Patients who stopped ASD intake were not always asymptomatic. To keep dyspeptic symptoms under control antacids were used by 75% of ASD free patients (39/52). However, in general the mean dosage was low: 0-1 tablet antacid/day in 92% of these patients (48/52).

**ASD use related to diagnosis**

The aforementioned data about the mean ASD free interval suggested a trend towards a longer ASD free interval in the placebo group than in the *H. pylori* eradication group. Therefore, a subanalysis among patients with functional dyspepsia and patients with GERD was performed.

Patients in the *H. pylori* eradication group with the diagnosis of GERD had a significantly shorter median ASD free interval than those in the placebo group (table 3). In GERD patients, the *H. pylori* eradication group restarted ASD significantly more frequently and used a significantly higher daily dose of ASD than did the placebo group (p<0.01, table 3).

**intention to treat**

Analyses for all randomised patients (with filling in missing data) (n=131) were performed. Reasons for failing to complete the protocol (n=11) were: too busy (2), revisiting the hospital and recording is too much a burden (6), use of an alternative medication (1), admission to a psychiatric hospital (1), unknown (1). The ASD data of these 11 patients were reconstructed from the computerized prescription data of the patient’s GP and information provided by the the pharmacy and the patient by telephone.

The intention to treat analyses revealed no significant differences between intervention groups with respect to general characteristics of patients, diagnosis, ASD intake free interval and medication use at entry and during follow-up. The proportions of patients that were able to stop ASD use in the two main groups and in the specified subgroups of patients were similar as compared to the per protocol analyses.
Table 3. Use of acid suppressant drugs (ASD)* at entry and during 24 weeks of follow-up after H. pylori eradication treatment or placebo - stratified for diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>treatment</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>functional dyspepsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median interval free of ASD use (weeks)</td>
<td>n=28</td>
<td>n=33</td>
</tr>
<tr>
<td>% of patients with no ASD use during 24 weeks</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>% of patients with no ASD use at 24 weeks</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>mean ASD units/day at entry</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>mean ASD units/day during follow-up</td>
<td>1.89^t</td>
<td>1.97''</td>
</tr>
<tr>
<td>% of reduction of mean ASD units/day</td>
<td>0.29^t</td>
<td>0.33''</td>
</tr>
<tr>
<td>mean ASD units/day</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>% of reduction of mean ASD units/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gastro esophageal reflux disease</td>
<td>n=28</td>
<td>n=26</td>
</tr>
<tr>
<td>median interval free of ASD use (weeks)</td>
<td>4^t</td>
<td>21^t</td>
</tr>
<tr>
<td>% of patients with no ASD use during 24 weeks</td>
<td>21^t</td>
<td>50^t</td>
</tr>
<tr>
<td>% of patients with no ASD use at 24 weeks</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>mean ASD units/day at entry</td>
<td>1.86</td>
<td></td>
</tr>
<tr>
<td>mean ASD units/day during follow-up</td>
<td>0.70^l^3</td>
<td>0.36**^4</td>
</tr>
<tr>
<td>% of reduction of mean ASD units/day</td>
<td>62</td>
<td>82</td>
</tr>
</tbody>
</table>

* One unit Acid suppressant drug = 10 mg omeprazole or its equivalent ASD

^t,"t,"||,"** p<0.001 by Wilcoxon Matched-Pairs Signed-Ranks Test

^t p<0.01 by Chi-square

^t p<0.01 by Mann-Whitney U

^t p=0.046 by Mann-Whitney U

Discussion

This study differs from many other studies on dyspepsia with respect to the setting where patients were recruited and treatment goals. A common critique on trials of treatment of patients with dyspepsia is, that patients are generally recruited from hospital clinics, whereas most dyspeptic patients are treated in General Practice.\(^6\) Our study was conducted in the setting of general practice.
In previous studies improvement of dyspepsia complaints was defined as study endpoint. However, until now it remained uncertain whether this subjective scoring is valuable since it may be influenced by ASD use in the period before the measurement. Therefore, in this study the use of ASD during follow-up was used as an endpoint. Decisions to taper, to discontinue, to restart or to change the dosage of ASD were left to the patient, according to the severity of symptoms.

Rebound acid hypersecretion after ASD withdrawal particularly in *H. pylori* negative patients, the acid buffering capacity of *H. pylori* and underlying diagnosis are factors that may relate to the feasibility of ASD withdrawal. Rebound acid hypersecretion in healthy subjects is a well documented phenomenon after treatment with H$_2$-receptor antagonists or PPIs and may lead to relapse of dyspeptic symptoms.\textsuperscript{17,20} Despite this risk, 39% of *H. pylori* negative patients and 51% of *H. pylori* positive patients stopped ASD intake. Those who did not stop were able to reduce the maintenance ASD dosage. These findings indicate that the efficacy of ASD medication in relieving functional dyspepsia is doubtful because of the variable, but generally high, response to placebo.\textsuperscript{21,22} In addition, in another study in the primary care setting in which patients with reflux disease without erosive esophagitis, after initial symptom control, were treated with 10 mg omeprazole daily or placebo during 24 weeks, adequate symptom relief occurred in 73% and 46% of the patients, respectively.\textsuperscript{23} These findings imply that even in patients with reflux disease (without erosive esophagitis) placebo treatment is associated with adequate relief of symptoms in nearly half of the patients. Placebo effect of the upper GI endoscopy itself, may be a potential confounding factor. In our study population this factor cannot be of importance since the follow-up was 6 months and restart of ASD took place mainly in the first 8 weeks of follow-up. The most important factors that contributed to reduction of the use of ASD in patients with chronic dyspepsia are the advice to the patient to gradually reduce ASD intake (in our study during three weeks prior to follow-up) and the offer of alternative medication such as antacids or low dose ASD. Antacids in very low dosage could be a substitute for ASD in controlling dyspeptic symptoms.

An important finding in our study was that successful *H. pylori* eradication did not facilitate the use of ASD intake in dyspeptic patients with functional dyspepsia. This observation is in accordance with results from studies of the effect of *H. pylori* eradication on symptom relief in patients with functional dyspepsia, showing no or only a limited benefit on symptom improvement.\textsuperscript{6-10} In this report we show that *H. pylori* eradication also impedes the reduction of ASD use in patients with (mild) GERD. This observation might be indicative for increased esophageal gastric acid exposure after *H. pylori* eradication in patients with GERD.\textsuperscript{24}
ASD use before and after H. pylori eradication in functional dyspepsia or GERD

In general, reduction of ASD use is feasible in chronic dyspeptic patients who do not have PUD and are on maintenance ASD. An H. pylori test and treat approach does not result in reduction of the use of ASD in patients with functional dyspepsia, while it impedes the reduction of the dose of ASD in patients with GERD. In conclusion, if the physician leaves the decision whether to take ASD for symptoms of functional dyspepsia or GERD to the patient the use of ASD might be reduced considerably.

References