Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Chapter 8

Tapering the use of acid suppressant drugs in \textit{H. pylori} negative chronic dyspeptic patients on maintenance therapy: an intervention strategy

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Submitted
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Background
Use of maintenance acid suppressant drugs (ASD) is common. We studied the feasibility of tapering the use of maintenance ASD in H. pylori negative dyspeptic patients in relation to supportive care by the general practitioner (GP), to the endoscopic diagnosis and to type of ASD used at study entry. From 48 general practices, H. pylori negative patients on maintenance ASD therapy with endoscopy-negative dyspepsia or at the most mild gastro esophageal reflux disease (GERD) were included.

Methods
Patients were randomised in two groups: tapering ASD combined with supportive GP care (GP+) and tapering of ASD without GP support (GP-). Endpoints were: ASD free interval (median, % ASD free); mean daily rescue ASD and rescue antacid use during 24 weeks.

Results
The mean daily ASD dosage per patient (n=174) at entry decreased 71% from 2.24 to 0.64 units ASD (p<0.05) during follow-up, while no or small amounts of antacids were used. Support of GP resulted in ASD discontinuation during the entire 24 weeks in 44% of patients (39/89) compared to 35% in GP- (30/85) (ns). Patients in GP+ used less ASD medication than in GP- (p<0.05). More patients with endoscopy negative dyspepsia than patients with GERD stopped ASD, 58%(45/77) and 25%(24/97), respectively (p<0.05). Overall, of the H$_2$RA users 57%(45/79) was able to stop ASD versus 25%(24/95) of the proton pump inhibitor (PPI) users (p<0.05).

Conclusions
The advice to gradually withdraw ASD supported by antacids may be sufficient to facilitate a long-term tapering of ASD in Hp-negative patients on maintenance therapy. Tapering is more successful in H$_2$RA users versus PPI users.
tapering ASD use in H. pylori negative chronic dyspeptic patients

Introduction

Patients presenting with dyspeptic symptoms in general practice are often given acid suppressant drugs (ASD), such as H₂-receptor-antagonists (H₂RA) and proton pump inhibitors (PPI) as initial short-term empirical treatment unless there are ‘sinister’ symptoms such as bleeding or weight loss. After one or more symptom relapses and before patients are prescribed maintenance ASD, primary care physicians usually refer patients for upper-gastrointestinal endoscopy. Due to the relapsing character of dyspeptic symptoms, long-term ASD prescription for control of these symptoms is common in general practice. In the Netherlands 2% of the entire population uses long-term ASD. Of the ASD prescriptions, 82% is issued by continued repeat prescriptions, often for uncomplicated gastroesophageal reflux disease (GERD) or functional dyspepsia. Several studies support the beneficial effect of ASD maintenance therapy in patients with relapsing GERD. The effectiveness of medication in functional dyspepsia is questionable because of the variable, but generally high placebo response rate.

Since mild GERD and functional dyspepsia rarely lead to complications, it is questioned whether maintenance ASD therapy could be replaced by a therapy of on demand ASD and rescue antacids. The few studies in which on demand ASD were investigated were promising considering symptom relief, quality of life and cost-effectiveness. However, in these studies the H. pylori status of the patient had not been considered. GPs have found that in dyspeptic patients, once started on long-term ASD, dyspeptic symptoms frequently recur rapidly when ASD’s are discontinued. These symptoms may recur so easily because of rebound acid hypersecretion after prolonged ASD use particularly in H. pylori negative patients. This effect may depend on the prior level of elevation of the intragastric pH, which is related to type and dosage of previously used ASD. Therefore, a period of tapering the dose might be beneficial before discontinuing ASD medication in this group of patients. Furthermore, neither the effect of supportive care by the general practitioner (GP) during the process of ASD withdrawal, nor the influence of the endoscopic diagnosis were previously studied.

We investigated prospectively the effect of a supportive care intervention by the GP, the influence of the endoscopic diagnosis and the effect of the sort of previously used ASD therapy on the feasibility of tapering the doses ASD in a H. pylori negative primary care population on ASD maintenance therapy.

Methods

Patient population

This prospective randomised intervention study was conducted during the period of April 1997-June 1999. Forty eight general practitioners (GPs) in the Amsterdam area participated in this study. Eligible for the study were chronic dyspeptic patients on ASD therapy in the age range 18-85 years. Chronic dyspepsia was defined as chronic upper abdominal
pain/discomfort requiring 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, IV (Savary-Miller) at endoscopy; gastroduodenoscopy in the previous four months; clinically significant cardiovascular, pulmonary, renal, hepatobiliary or pancreatic disease or malignancy; sinister dyspeptic symptoms such as bleeding and weight loss; abdominal surgery; pregnant or lactating women; patients requiring an interpreter; ingestion of antibiotics or bismuth containing compounds during the previous month, ingestion of NSAIDs other than carbasalate; any condition associated with poor compliance (e.g. drug or alcohol abuse, severe mental illness or dementia).

Data results of upper GI-endoscopy or radiology and previous ASD medication and co-medication, were obtained by the principal GP-investigator (G.H.) from the patient’s GP. A meeting between the principal GP-investigator and the GP was arranged to verify and complete the data for each patient.

All eligible patients were invited to participate in a letter from their own GP, in which the study and the study purpose, i.e. the tapering of ASD by several interventions, was explained. All participating patients underwent gastroscopy. They were asked to stop ingestion of their ASD at least one week before upper GI-endoscopy. During the two weeks between the upper GI-endoscopy and randomisation patients were allowed to continue to take their maintenance doses of ASD. Demographic and dyspepsia questionnaires were filled out in hospital. Patients were asked to contact the principal investigator in case of severe adverse events.

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.

**Endoscopy and H. pylori assessment**

The diagnosis of hiatal hernia and esophagitis grade one (Savary Miller) were based on the endoscopic findings at entry endoscopy and the data of previous endoscopy/barium meal. During each upper GI-endoscopy procedure, 3 antrum and 3 corpus mucosal biopsy specimens were obtained for histological and bacteriological assessment, respectively and were routinely processed as described before.\(^19\) *H. pylori* infection was considered to be absent if all bacterial cultures and histopathology data were negative for *H. pylori*. The histopathologist and microbiologist were blinded to each other’s results.

Two weeks after endoscopy *H. pylori* negative patients with functional dyspepsia or mild reflux-oesofagitis (Savary-Miller grade 1) were randomised according to a computer generated randomisation list in two groups: tapering ASD combined with supportive GP care (GP+) and tapering of ASD without GP support (GP-).
Tapering the doses of ASD and follow-up

Patients in the GP- group, were informed in hospital by the principal investigator about the results of the gastroscopy. Patients were asked to taper the dose of ASD within 3 weeks supported by rescue antacids (calciumcarbonate 680 mg/magnesiumcarbonate 80 mg, Roche Nicholas, Netherlands). If dyspeptic symptoms were not controlled by antacids, omeprazole 10 mg could be taken as required, or a higher dose could be taken, if necessary. H₂RA-users at study entry, who prefered to take H₂RA as required, were allowed to do so. Every patient was provided with antacids at the hospital and could get new supply of antacids and prescriptions for ASD at his GP office.

In the GP+ strategy, patients were briefly informed in hospital about the results of the gastroscopy and were asked to visit their GP within one week. According to protocol, the GP discussed the endoscopic results more in detail, general measures relevant for the patient (like the role of coffee, alcohol, weight, smoking, stress, use of NSAIDs, possible rebound effects after withdrawal of ASD) and the 3 weeks tapering period. At the end of the tapering period the patient consulted the GP again and tapering experiences were exchanged. If necessary, 6 weeks after the end of the tapering period or in case of the wish to restart ASD, patients contacted their GP.

Patients in both intervention groups reported the predominant dyspeptic symptom(s) and the amount of antacids and ASD ingested per week in a diary throughout a 24 weeks period. ASD use as reported by the patients, was compared to prescription data in the GP’s office and at the pharmacy.

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

Statistics.
Per protocol and intention to treat analysis were performed using the SPSS for Windows (version 7.5.3). The Chi-square test was used for comparison of proportions between groups. The Mann Whitney-U test was used for comparison of the mean use of ASD between groups. Wilcoxon Matched-Pairs Signed-Ranks Test was used for comparison of the mean use of ASD at entry and during follow-up of each patient. Significance was set at \( \alpha = 0.05 \) (two-sided). Univariate logistic regression analysis was carried out on the most important outcome variable, ASD free interval.
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Results

Patients

Nine hundred and forty six chronic dyspeptic patients on ASD maintenance therapy met eligibility criteria; 407 of these (43%) volunteered to participate in the study, including gastroscopy.

After gastroscopy, 17 patients of the 201 H. pylori negative patients were excluded for the following reasons: refusal to participate further (2), achalasia (1), esophagitis gr3 (2), Barrett’s esophagus (11), stomach operation (1). The remaining 184 patients were randomised in either GP+ (n=93) or GP- (n=91)(figure 1).

Figure 1. Flow of patients

Ten patients (four patients in the GP+, six patients in the GP- group) did not return their follow-up diaries and were excluded for per-protocol analysis. Thus data of 174/184 patients (95%) could be analysed per-protocol for tapering ASD: 89 patients in the GP+ and 85 patients in the GP- group.

Table 1 presents general characteristics of the patients for per protocol analysis. No significant differences between the GP+ and GP- groups were observed. In 45% (78/174) of patients a hiatal hernia was diagnosed. Reflux esophagitis grade 1 was a concomitant diagnosis in 51% (40/78) of these patients.
Table 1. Baseline characteristics of H. pylori negative dyspeptic patients on maintenance acid suppressant drugs (ASD)

<table>
<thead>
<tr>
<th></th>
<th>all patients</th>
<th>intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>174(100%)</td>
<td>GP +* 89(100%)</td>
</tr>
<tr>
<td>female</td>
<td>101(58)</td>
<td>49(55)</td>
</tr>
<tr>
<td>mean age (SD)</td>
<td>52 year SD 15</td>
<td>51 year SD 15</td>
</tr>
<tr>
<td>age &lt; 46 years</td>
<td>62(36)</td>
<td>34(38)</td>
</tr>
<tr>
<td>PPI-users at entry</td>
<td>95(55)</td>
<td>47(53)</td>
</tr>
<tr>
<td>H₂RA-users at entry</td>
<td>79(45)</td>
<td>42(47)</td>
</tr>
<tr>
<td>onset ≥ 5 years ago</td>
<td>123(71)</td>
<td>58(65)</td>
</tr>
<tr>
<td>endoscopy-negative</td>
<td>77(44)</td>
<td>42(47)</td>
</tr>
<tr>
<td>gastroesophageal reflux disease</td>
<td>97(56)</td>
<td>47(53)</td>
</tr>
<tr>
<td>isolated hiatal hernia</td>
<td>38(22)</td>
<td>22(25)</td>
</tr>
<tr>
<td>reflux esophagitis grade 1</td>
<td>59(34)</td>
<td>25(28)</td>
</tr>
</tbody>
</table>

* GP+ = tapering the dose of ASD with support of GP; GP- = tapering without support of GP

**ASD use during follow-up**

**In general**

During follow-up 40% of patients (69/174) had permanently stopped ASD use. The average daily prescribed ASD units/patient was significantly reduced from 2.24 units at entry of the study to 0.64 units during follow-up, a 71.4% decrease (table 2). Less than one unit ASD/day was used by 36% (63/174) of patients, 1-2 units by 18% (32/174) and ≥2 units ASD/day by 6% (10/174).

The patients who were able to abstain from ASD (69/174) were not necessarily symptom free during follow-up. Antacids were used by 72% of these patients (50/69) to keep dyspeptic symptoms under control: 0-1 tablet antacid/day by 48% (33/69), 1-2 tablets/day by 20%(14/69) and 2-4 tablets by 4% (3/69). One quarter of the ASD restarted patients (26/105), i.e.15% (26/174) of all Hp negative patients, consumed 57% of the total volume ASD used during the half year follow-up. The baseline variables sex, age and symptoms > 5 years were not significantly predictive for restart of ASD use (data not shown).
Table 2. Use of acid suppressant drugs (ASD)* at entry and during 24 weeks of follow-up

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>tapering support</th>
<th>diagnosis</th>
<th>medication at entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=174</td>
<td>n=89</td>
<td>n=85</td>
<td>H2RA</td>
</tr>
<tr>
<td>mean ASD units/day/patient at entry §</td>
<td>2.24</td>
<td>2.19</td>
<td>2.28</td>
<td>2.03</td>
</tr>
<tr>
<td>mean ASD units/day/patient during follow-up §</td>
<td>0.64</td>
<td>0.47‡</td>
<td>0.81‡</td>
<td>0.37 §§</td>
</tr>
<tr>
<td>mean reduction of ASD units/day/patient</td>
<td>1.60</td>
<td>1.72</td>
<td>1.47</td>
<td>1.65</td>
</tr>
<tr>
<td>reduction of ASD use (%)</td>
<td>71.4</td>
<td>78.5</td>
<td>64.5</td>
<td>81.8</td>
</tr>
<tr>
<td>% of patients who stopped ASD use completely</td>
<td>40</td>
<td>44</td>
<td>35</td>
<td>58**∥∥∥∥</td>
</tr>
</tbody>
</table>

* one unit Acid suppressant drug (ASD) = 10 mg omeprazole or its equivalent ASD
† tapering the dose of ASD supported by the general practitioner (GP+) and no support (GP-)
§ in all columns: p<0.0001 by Wilcoxon Matched-Pairs Signed-Ranks Test
‡ p=0.028 by the Mann Whitney U test;
§§ p<0.001 by the Mann Whitney U test;
∥∥∥∥ p<0.0001 by chi-square
Effect of supportive intervention by the GP

The feasibility to withdraw ASD was not significantly influenced by supportive care of the GP (table 2 and 3, figure 2). However, patients in GP+ group used significantly less ASD than in GP- group during follow-up (p<0.05).

Table 3. Prognostic factors of restart of acid suppressant drugs (ASD)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tapering ASD supported by GP</td>
<td>0.70 (0.38-1.29)</td>
</tr>
<tr>
<td>endoscopy-negative</td>
<td>0.23 (0.12-0.45)*</td>
</tr>
<tr>
<td>gastro esophageal reflux disease</td>
<td>4.28 (2.24-8.17)*</td>
</tr>
<tr>
<td>isolated hiatal hernia</td>
<td>2.54 (1.12-5.78)*</td>
</tr>
<tr>
<td>reflux esophagitis grade 1</td>
<td>2.60 (1.30-5.18)*</td>
</tr>
<tr>
<td>proton pump inhibitor use at study entry</td>
<td>3.91 (2.06-7.44)*</td>
</tr>
<tr>
<td>$H_2$-receptor antagonist use at study entry</td>
<td>0.26 (0.13-0.49)*</td>
</tr>
</tbody>
</table>

* p<0.05

Figure 2. Acid suppressant drug (ASD) free interval in patients supported (GP+) and not supported (GP-) by the general practitioner in tapering ASD.

* p>0.05 for proportions at 24 weeks
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Effect of endoscopic diagnosis on tapering ASD
In univariate analysis the diagnoses of reflux esophagitis grade 1 and isolated hiatal hernia were risk factors of restart of ASD use (table 3, figure 3).
In all three diagnostic groups medication use was reduced as compared to the use at entry of the study (p<0.05)(table 2). Endoscopic negative dyspeptics used significantly less ASD than patients with GERD (p<0.0001).

Figure 3. Acid suppressant drug (ASD) free interval in endoscopy negative patients and patients with hiatal hernia/esophagitis grade one

*  p<0.05 for proportions at 24 weeks

Effect of type of ASD used prior to entry
In general more patients with 
\[ H_2 \]
RA use than patients with PPI use at entry could abstain from ASD during 24 weeks (table 2 and 3, figure 4)(p<0.05). Restart of ASD took place mainly in the first weeks of follow-up (figure 2). More patients with PPI use (56/95) than patients with 
\[ H_2 \]
RA use (25/79) at entry restarted ASD during the first four weeks (p<0.05). This restart of ASD was not dose related (p>0.05)(data not shown).

In patients with the diagnoses of isolated hiatal hernia or mild esophagitis more patients with 
\[ H_2 \]
RA use than patients with PPI use at entry could withdraw the ASD during 24 weeks (p=0.035 and p=0.034). However, in patients with endoscopic negative dyspepsia no significant differences between 
\[ H_2 \]
RA - and PPI users at entry were observed.
Figure 4. Acid suppressant drug (ASD) free interval in patients with $H_2$-receptor antagonist and in patients with protonpump inhibitor use at study entry

- $p<0.05$ for proportions at 24 weeks

Intention to treat analysis

Of three patients (sent for evaluation of extreme severe reflux symptoms to gastroenterologist (1), colon cancer (1), moved (1)) the data about ASD intake were not available. The data of the 7 other patients, obtained by computerized prescription data of the patient’s GP, were used in intention-to-treat analysis: 92 patients in GP+ and 89 patients in GP-.

No substantial differences with the results obtained by the treatment per protocol analysis were observed in relation to general characteristics of patients, diagnosis, ASD intake free interval and medication use at entry and during follow-up. The proportions of patients that could stop ASD use in the two intervention groups and in subgroups were nearly equal with those observed in the treatment per protocol analysis.

Discussion

This study which was conducted in a primary care population differs from other studies of dyspepsia with respect to treatment goals. Goals of treatment in patients with dyspepsia should not only be an improvement in objective clinical measures of disease, but also improvement in general well-being. Currently, the treatment endpoints nowadays are often symptom- and quality of life scales. However, the significance of these endpoints is uncertain as they may be influenced by ASD use in the study period before the interviews. In this study the intake of ASD during follow-up was used as an endpoint. After initial guidance,
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.

In general, we observed that a substantial part of *H. pylori* negative patients from general practice on maintenance ASD with GERD or endoscopy-negative dyspepsia, which rarely leads to complications, are able to taper ASD. The ability to reduce the maintenance ASD dosage is in agreement with few other primary and secondary care studies.\(^\text{10,11}\) However, results of these studies, in which the *H. pylori* status was not taken in consideration, may have been influenced by the presence of *H. pylori* infection. In these studies ‘tapering ASD’ may have been facilitated by acid-buffering capacities by *H. pylori* in *H. pylori* positive patients.

In our study, a supportive intervention, consisting of attention for life style changes, by the GP in the tapering process could not influence the proportion of patients able to abstain from ASD. Life style changes are recommended by many guidelines as an (initial) part of treatment, although the evidence from trials on the therapeutic benefit of these measures is questionable.\(^\text{16}\) However the attention paid to life style aspects and the counselling by the GP may have facilitated the significant reduction in volume of ASD use observed in patients supported by the GP in comparison with patients not supported.

Significantly more chronic dyspeptic patients with mild esophagitis or hiatal hernia than patients without endoscopic abnormalities had to restart medication. This observation might be indicative of increased esophageal gastric acid exposure after tapering ASD in patients with an hiatal hernia or with esophagitis due to rebound acid hypersecretion. Rebound acid hypersecretion in healthy subjects is a well documented phenomenon after withdrawal of treatment with *H*\(_2\)RA becoming apparent by day three and is largely resolved by day ten posttreatment.\(^\text{17-19}\) In a recent study in *H. pylori* negative subjects using daily 40 mg omeprazole for 8 weeks, rebound acid hypersecretion became apparent 6 to 15 days after withdrawal.\(^\text{12}\) In our study restart of ASD use during follow-up took place mainly in the first weeks after complete withdrawal of medication. This phenomenon may support the concept of rebound acid hypersecretion after ASD withdrawal.

Patients at entry on maintenance PPI significantly more often restarted ASD compared to those on maintenance *H*\(_2\)RA at entry. An explanation for this may be that these PPI users are a selection of patients not sufficiently responding to *H*\(_2\)RA therapy who were finally prescribed these strong ASD because of the severity and fast relapsing character of symptoms. On the other hand one might argue that use of PPI itself may be responsible for a fast relaps of symptoms after discontinuation of therapy compared to use of *H*\(_2\)RA since the severity of rebound acid hypersecretion is related to the degree of elevation of pH level.
tapering ASD use in H. pylori negative chronic dyspeptic patients
during treatment. Although we did not perform intragastric pH measurements in our patients, it has been described that the pH in general is more elevated by PPI treatment than by H2R-antagonists. In addition, one would expect a relation between the dose of ASD and the feasibility to taper the drug. However, this was not observed in our study. These findings underline the importance of a well considered selection of sort, dosages and duration of ASD therapy. It might well be that prescription pattern of physicians in a subset of dyspeptic patients induce the dependence of maintenance ASD therapy. More research for the implications in ASD medication prescription in clinical practice is warranted.

In conclusion, three quarter of patients could discontinue ASD use during 24 weeks (40%) or could use less than one unit ASD/day (36%). The most important factor that contributed to taper the dose of ASD in patients with chronic H. pylori negative dyspepsia may be the advice to the patient that ASD intake be reduced gradually and the offer of alternative medications such as antacids and low dose ASD. Implementation of such an approach needs adaptation by primary and secondary care phycisians and may lead to substantial reduction in the use of maintenance ASD.

References