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

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Summary

In this thesis we have focussed on chronic dyspeptic patients with long-term use of acid suppressant drugs (ASD). The patients were prescribed long-term ASD treatment since the relapsing character of peptic ulcer disease (PUD), gastro-esophageal reflux disease (endoscopy negative or esophagitis grade 1) (GERD) or functional dyspepsia. However, costs for ASD treatment are high and new treatment options have become available like eradication of Helicobacter pylori infection and on demand use of ASD. In the present thesis it was investigated whether a reduction of long-term use of ASD is feasible in general practice. For those who would like to read the structured abstracts we refer to the various chapters in this thesis.

1. The characteristics of long-term ASD use in the general population
At the start, long-term use of ASD was analysed in 24 general practices (chapter 1). It was observed that in general practice about 2% of all patients were prescribed ASD for a prolonged period. This is a high figure and reflects the high costs for acid suppressant drugs in the overall drug budget. Comparable numbers of patients on long-term use of ASD have been reported in other countries. About one third of patients had a history of PUD. However, most of them, had never received H. pylori eradication treatment. Other important groups of long-term users were patients with reflux disease and functional dyspepsia. Investigations had never been performed in approximately one quarter of patients. Many of these patients were rather “invisible” for the GP since they were treated with routinely repeated prescriptions for ASD without further consultation.

2. Factors that may be associated with long-term ASD use: psychological factors and health status
Depression and phobia are as common in chronic dyspeptic patients as in a control population (chapter 2). However, anxiety is more frequently reported among chronic dyspeptic men than among controls. Most likely, depression, anxiety or phobia were not that well recognised by the GPs, since only a small minority of patients had such a diagnosis somewhere mentioned in their GP’s files, although the majority of patients had sought help for such disorder. Possibly, GPs focussed too much on dyspeptic problems or these patients had difficulties presenting their psychological symptoms. Fear for cancer is a well-recognised phenomenon in dyspeptic patients, as was also observed in our study. Remarkably, half of patients who had been examined by endoscopic / radiographic investigation still manifested cancerophobia.

The health status of chronic dyspeptic patients was in all aspects worse than in an open population. This was mainly attributed to the patients with a self-reported psychiatric disorder. In contrast, patients on long-term ASD, without a self-reported psychiatric diagnosis had a health status comparable to the control population. H. pylori was not related to the psychological disorders nor was it related to the health status of chronic dyspeptic patients. We suggest, that paying attention to the fears of patients and psychiatric disorders will contribute to improve the health of chronic dyspeptic patients on long-term ASD and may thereby be a better option than the mere prescription of ASD on a long-term basis.
Summary

3. The most efficacious way to diminish ASD use

a. Diminishing ASD use in patients with peptic ulcer disease

- The most effective way to detect peptic ulcer disease
The discovery of a causal relationship between PUD and infection by H. pylori brought a new aspect in the management of dyspepsia. PUD patients do benefit from anti-H. pylori treatment. Ulcers will heal and recurrence of ulcers does not occur in these patients after H. pylori eradication. So the target in primary care is to find the most efficacious way to detect PUD. Since endoscopy for detection of H. pylori infection and PUD is laborious for a patient and expensive, alternative non-invasive ways for detection of PUD were explored in order to reduce the number of endoscopies.

- The performance of three non-invasive tests to assess H. pylori infection
Because of the strong relation between H. pylori infection in PUD patients, we have tried to identify patients with PUD by three non-invasive tests to detect H. pylori infection (chapter 3). A desktop test, performed in primary care, had a rather poor to moderate sensitivity but good specificity. The two other tests (ELISA and breath test) manifested better performance characteristics, however the breath test had quite some operational and technical problems. Therefore our test of choice is the ELISA test.

In uninvestigated young chronic H. pylori positive dyspeptic patients participating in our study, the prevalence of PUD was rather low (20%). H. pylori negative ulcers were not observed in our population. So, in a test and treat approach, 80% of H. pylori positive patients would have been treated with an H. pylori therapy without an underlying diagnosis of PUD. No symptomatic improvement was observed in our study in these patients. In a subgroup we even observed a deterioration. Our conclusion is therefore not to advise a test and treat strategy.

Does a negative test result has consequences for management of dyspepsia? Remarkably, among the subgroup of immigrant patients the prevalence of H. pylori infection was high (around 80%). Such a high prevalence results in poor to moderate negative predictive values of the tests in this patient group, as demonstrated in chapter 3. Hence, too many false negative test results may be obtained, consequently PUD may be missed too often. Since testing has no value in immigrants, they all should be referred for endoscopy. In natives the chance on a false negative result is minimal. Our conclusion was that in young natives the endoscopic workload could be decreased by 50% by referring only patients positive for H. pylori (by the ELISA). Therefore we suggest a test and scope approach in natives.

- The value of testing the CagA status
A serological test for detection of CagA+ H. pylori could be useful for detection of PUD patients, since CagA+ H. pylori has been found associated with PUD in Western populations. In our study, the prevalence of CagA+ H. pylori and its relation with PUD depended on the patient’s origin (chapter 5).

In native Dutch patients, a relation between CagA+ H. pylori and PUD could be demonstrated, but we could not reveal such a relation in immigrants. Since the prevalence of CagA+ is approximately
80% in *H. pylori* positive patients this marker will not help to discriminate in between patients with PUD and non ulcer disease patients (NUD).

- **The most effective way to eradicate *H. pylori***

*H. pylori* eradication therapies are considered to be effective if they reach cure rates > 90% by per protocol analysis and > 80% by intention-to-treat. The efficacy of regimens, consisting of metronidazole, clarithromycin and proton pump inhibitor, may be affected by poor patient compliance, infection with metronidazole- or clarithromycin-resistant *H. pylori* or with more virulent CagA-positive *H. pylori* strains. A simple and highly effective *H. pylori* eradication regimen without serious side effects is essential to assure a high patient compliance. In general, the shorter the regimen, the better the compliance. Although usually seven days treatments are prescribed, in our study a four days eradication regimen, consisting of metronidazole, clarithromycin and omeprazole, was sufficient to cure 100% of PUD patients (chapter 4). Even in a population with moderately high metronidazole resistance, which is seen as a major factor in failure of treatment, this regimen was still highly efficacious.

The *H. pylori* eradication rates in studies with a mixture of patients with and without PUD are lower than in studies with PUD patients only. It is assumed that CagA-positive *H. pylori* strains, which in western populations are closely related to PUD, are responsible for this effect. However, in our study, neither *H. pylori* related disease, nor CagA status or metronidazole resistance affected the efficacy of a *H. pylori* eradication regimen, consisting of metronidazole, clarithromycin and omeprazole (chapter 5).

- **ASD use after *H. pylori* eradication treatment**

As expected, patients with PUD do benefit from a successful *H. pylori* eradication. After a 3-week period of gradually diminishing the ASD, almost all of these patients could stop the use of ASD (chapter 6). Minor complaints during the follow-up period could be controlled by escape antacids. Possibly, due to this 3-week tapering period the percentage of patients that could stop was higher than in other studies though this was not tested. In general, patients were satisfied with the treatment.

**b. Diminishing ASD use in *H. pylori* positive patients without ulcer disease**

- **ASD use after *H. pylori* eradication treatment**

It was questioned whether *H. pylori* positive NUD patients, will benefit from an *H. pylori* eradication. We found that eradication of *H. pylori* in chronic dyspeptic patients with functional dyspepsia had no beneficial effect on the use of ASD by these patients. Several other studies have shown similar results, although data are still conflicting. In chapter 7 of this thesis it is shown that in patients with GERD, it had even a disadvantageous effect on the reduction of ASD use, consistent with the notion that *H. pylori* may be a protective factor for GERD through suppression of acid secretion.

In some recent studies it is stated that *H. pylori* eradication (test and treat) is a cost-effective option which should be preferred above empirical treatments and investigations. However, costs of drugs and investigations, prevalence of *H. pylori* infection and ulcer disease may differ between patient populations in different countries and even between different clinical settings in the same country. From the results presented in chapter 7 of this thesis it was concluded that the approach of asking
chronic dyspeptic patients to taper their ASD in a gradual way, and in addition using antacids as initial escape medication and if necessary using ASD on demand in a low dose, may lead to a more cost effective option than blind *H. pylori* eradication in these patients.

c. Diminishing ASD use in *H. pylori* negative patients

- the effect of support by the GP on reduction of ASD use

About half of the study patients did not have an *H. pylori* infection. In *H. pylori* negative patients who were not using NSAIDs, the risk for ulcer disease or other serious pathology was minimal. Reducing ASD may be difficult due to rebound acid hypersecretion or fears of relapsing symptoms. It was questioned whether a supportive intervention of the GP could contribute to the reduction of ASD use (chapter 8). The GP’s intervention, consisted of three consults in which the results of the endoscopy, life style aspects, the 3 weeks period of titrating down ASD to zero and use of escape antacids were discussed. The supportive strategy by the GP had only a minor effect on the proportion of patients that could abstain from ASD. However, the amount of ASD used by patients not supported by their GP was significantly higher the amount of ASD used by patients coached by their GP.

In general, of patients who were endoscopy negative more patients abstained ASD than of patients with a diagnosis of esophagitis grade one / hiatal hernia. In addition, of patients initially on proton pump inhibitors less stopped ASD than of patients on H<sub>2</sub>-receptor antagonist at study entry. In our study restart of ASD use during follow-up took place mainly in the first weeks after complete withdrawal of medication.

These observations may be indicative of increased esophageal acid exposure in these patients due to rebound acid hypersecretion, which is observed after withdrawal of long-term treatment with ASD. It might well be that prescription pattern of physicians in a subset of dyspeptic patients induce the dependence of maintenance ASD therapy.

d. Diminishing ASD use in all study patients (observational)

In this study the intake of ASD and antacids during follow-up was used as endpoint.

- the effect of titrating of ASD to zero

In general, restart of ASD took place in the first 8 weeks after the 3 weeks of titrating down the dose of ASD. Further analyses are needed to investigate which determinants are responsible for this observation. Rebound acid hypersecretion, which is observed in healthy subjects after treatment with H<sub>2</sub>-receptor antagonists or PPIs may lead to relapse of dyspeptic symptoms. We were unable to draw conclusions about the effect of rebound acid hypersecretion on the restart of ASD use, since this was not tested in our study. Despite the risk on rebound effects, half of the patients stopped ASD intake.

- the use of antacids as escape medication

Not every patient who stopped ASD use, was symptom free. However, they could control their symptoms with low dose of escape antacids.
- the use of ASD on demand

We followed during 6 months a primary care based cohort of long-term ASD using patients with chronic dyspepsia (n=360) previously after H. pylori treatment or placebo and a period of titration of ASD to zero over 3 weeks (supported or not supported by the GP). Patients were asked to use antacids as first escape medication and ASD, if needed, on demand in low dosage. About 50% of patients abstained ASD and those who used, used less. An almost 80% reduction of ASD use was observed. Those who did not stop, reduced the maintenance ASD dosage.

In general, reduction of ASD use is feasible in patients with ulcer and non ulcer disease who are on long-term use of ASD. Patients should be told to stop ASD or to reduce ASD in a gradual way, to use antacids as escape medication and if needed ASD on demand in low dosage. Furthermore, patients should be told that no serious disease is responsible for their symptoms.

The control of dyspeptic symptoms is returned to patients, after some initial guidance: if the physician leaves decisions to use escape antacids, to taper -, to discontinue -, to restart - or to change the dosage of ASD to the patient, according to the severity of symptoms. In this way the use of ASD might be reduced considerably in patients with functional dyspepsia or GERD.