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The use of antacids and alginates during pre-investigation PPI washout: impact on compliance and symptom burden.

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Introduction

Gastroesophageal reflux disease (GORD) affects 10-30% of the world population and cost more than $9-10 billion per year in the US, mainly due to use of proton pomp inhibitors (PPIs) [1,2]. PPIs are currently the most efficacious pharmacological therapy for GORD and peptic ulcer disease, and are very effective at suppressing gastric acid secretion. Although there are reports of important adverse effects (most reliably increased risk of enteric infection and reduced bone density), PPIs are safe drugs with few side effects.

The tolerability and safety of PPIs has led to widespread (often empirical) prescription, and indeed NICE guidelines on reflux and dyspepsia therapy advocate PPI therapy without further investigation. As such, there are extremely high levels of PPI prescription in the UK. In 2017 there were nearly 60 million PPI prescriptions written in England, at a drug cost of nearly £100 million *(Prescribing and Medicines Team ND. Prescription Cost Analysis: England 2017 2018 [Available from: http://digital.nhs.uk/pubs/prescostanalysiseng2017.).* Although PPIs are often used for initial management of reflux symptoms as a "PPI trial", it has only moderate sensitivity of 62% and specificity of 67% for the diagnosis of GORD[3]. Thus, many patients may continue PPI unnecessarily[4,5,6.] .

Often attempts to stop PPIs are made, because of patient preference, concern about their safety, and/or cost[7]. Unfortunately, PPI cessation can be challenging because of exacerbation of reflux symptoms, and attempts frequently fail[8]. This leads to PPI re-prescribing and perpetuation of long term use.

This problem can be encapsulated by observing patients who need to stop PPIs in order to undergo upper gastrointestinal testing such as gastroscopy or reflux studies. We recently demonstrated that, in patients attending our unit for reflux studies (for which they need to stop PPI for 1 week), exacerbation of symptoms is common after PPI cessation (submitted for publication 2019). Over 80% of patients suffered distressing worsening of symptoms in the week preceding the test when stopping PPIs and, when asked anonymously, 15%

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admitted to surreptitiously taking PPIs during the abstinent period (with potential impact on test accuracy).

The phenomenon of post-PPI cessation symptoms is not limited to symptomatic patients. After cessation of an 8 week course of esomeprazole, even previously asymptomatic healthy volunteers developed heartburn and dyspeptic symptoms[9,10]. This highlights the difficulty faced when trying to stop PPIs, and shows that mitigating clinical strategies are required.

Rationale for PPI washout before investigation

There are several situations where PPI therapy is mandated or recommended to be stopped before investigation.

Prior to H pylori antigen testing:

In patients with dyspepsia, NICE guidance in patients without red flag symptoms includes 'test and treat' for Helicobacter pylori. It is also recommended that a 2-week washout from PPI therapy is observed before testing for H pylori stool antigen or carbon-13 urea breath testing. This is because PPI use adversely affects the sensitivity of tests. In the absence of PPI therapy, the sensitivity and specificity of these tests is excellent (sensitivity and specificity over 95%)(1). When urea breath test or stool antigen is performed on PPI therapy sensitivity is significantly reduced, with over 30% false negative results(2, 3).

Prior to upper gastrointestinal endoscopy:

Oesophagogastroduodenoscopy (OGD) is a frequently performed test to investigate upper gastrointestinal symptoms, including dyspepsia and gastro-oesophageal reflux symptoms. Gastric biopsies can be tested rapidly and inexpensively with the rapid urease test for H pylori, with a sensitivity of 90-95%. Again, use of PPIs results in a significant false negative rate of the rapid urease test(4). To make an endoscopic diagnosis of H pylori in patients taking PPI requires immunohistochemical assessment of gastric biopsies, at significant time and financial expense.

When the endoscopy is being done for investigation of gastro-oesophageal reflux symptoms, the use of PPIs is likely to reduce the diagnostic yield. Up to 40% of patients with GORD have erosive oesophagitis(5). PPIs are very effective in healing reflux oesophagitis (~90% healing at 8 weeks)(6). Whilst there are clear advantages to PPI therapy in these

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cases, it does mean that definitive diagnosis may not be made at endoscopy where oesophagitis has healed.

Finally, there is a small risk of PPI use masking a serious diagnosis at OGD. Although unusual, there are reports of PPIs masking early gastric and oesophageal adenocarcinoma(7).

Prior to ambulatory oesophageal pH testing:

In most cases, where a diagnosis of gastro-oesophageal reflux is being sought, ambulatory reflux monitoring should be performed off PPIs for at least 1 week(8) to allow adequate time for parietal cell turnover to be complete before testing.

Potential role of routine alginates during PPI washout period

Alginate preparations (such as Gaviscon Advance, Gaviscon Double Action) have raft-forming properties(9) and variable antacid effects that are effective in reducing reflux and dyspeptic symptoms in affected individuals(10, 11). Furthermore, alginate and antacid use does not reduce the sensitivity or specificity of H pylori testing or endoscopy(3). It is unknown whether using regular alginates can reduce rebound symptoms on stopping PPIs.

Hypothesis

Regular alginate use during the pre-investigation PPI washout period reduces patient symptom burden and improves compliance with PPI abstinence.

Aim

To evaluate the effect of regular Gaviscon Advance on dyspepsia and reflux symptom burden in the week after stopping PPI therapy.

Primary Outcome

- Change in GERD-HRQL score

Secondary Outcomes

- Change in gastrointestinal symptom score
- PPI and H2-receptor antagonist use

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- Mean nocturnal baseline impedance measurement (12)

Methods

Study population

Adult patients will be recruited from sites where The Functional Gut Clinic have regular oesophageal physiology clinics.

Patients will be having ambulatory reflux testing off PPI medication as part of their standard clinical investigation for dyspepsia and/or reflux symptoms.

Inclusion criteria:

- Adult patients ≥ 18 years age.
- Clinical investigation for reflux symptoms (heartburn and/or regurgitation) or dyspepsia (nausea, upper abdominal discomfort, early satiety and/or upper abdominal bloating).
- Already established on ≥4 weeks of standard or double dose PPI therapy.
- Clinical requirement for pre-investigation PPI washout period.
- Ability to communicate well with the study team and comply with the requirements of the entire study.
- Has the capacity to understand written English.

Exclusion criteria:

- Red flag symptoms or urgent (2 week wait referral).
- Known Barrett's oesophagus, reflux oesophagitis, peptic ulcer disease, or upper gastrointestinal malignancy.
- Other clinical indication for PPI continuation.
- Previous oesophageal or gastric surgery.
- Intolerant of alginate preparations.
- Patients on a low salt diet.
- Unable to tolerate the nasogastric reflux probe for a minimum of 18 hours.

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Patients are typically referred to The Functional Gut Clinic for reflux testing by their upper Gastro-Intestinal (GI) consultants. When patients make contact with the clinic to book their tests, they will be told about the trial and invited to participate.

They will be told that we are investigating symptoms on stopping PPIs for upper GI testing. If they agree, they will be sent the study patient information sheets. The information sheet will include a secure web address for electronic signing of consent (also sent by text message). A face to face meeting will be offered to discuss further if required.

Eligible, consenting patients will be randomised into observation or treatment arms.

Study protocol

After selection, patients will be randomised in a 1:1 fashion into an observation or treatment arm.

All participants will be sent:

- Baseline questionnaires (GERD-HRQL score, gastrointestinal symptom score, perceived symptom response to PPI – see appendix) to be completed just before stopping PPI therapy.
- Clinical questionnaire detailing past medical history

Participants in the control arm will be sent:

- Leaflet explaining the physiology test, and importance of stopping PPIs for accurate testing.

Participants in the intervention arm will additionally be sent:

- A supply of Gaviscon Advance
- Instructions to take 10ml Gaviscon Advance 4 times per day (after each meal and at night) from the day of stopping PPI until the day before the procedure.
- Instructions to diary record Gaviscon use.

All participants will hand in questionnaires on arrival for their physiology tests 7 days later, and will complete repeat GERD-HRQL and gastrointestinal symptom score questionnaires.

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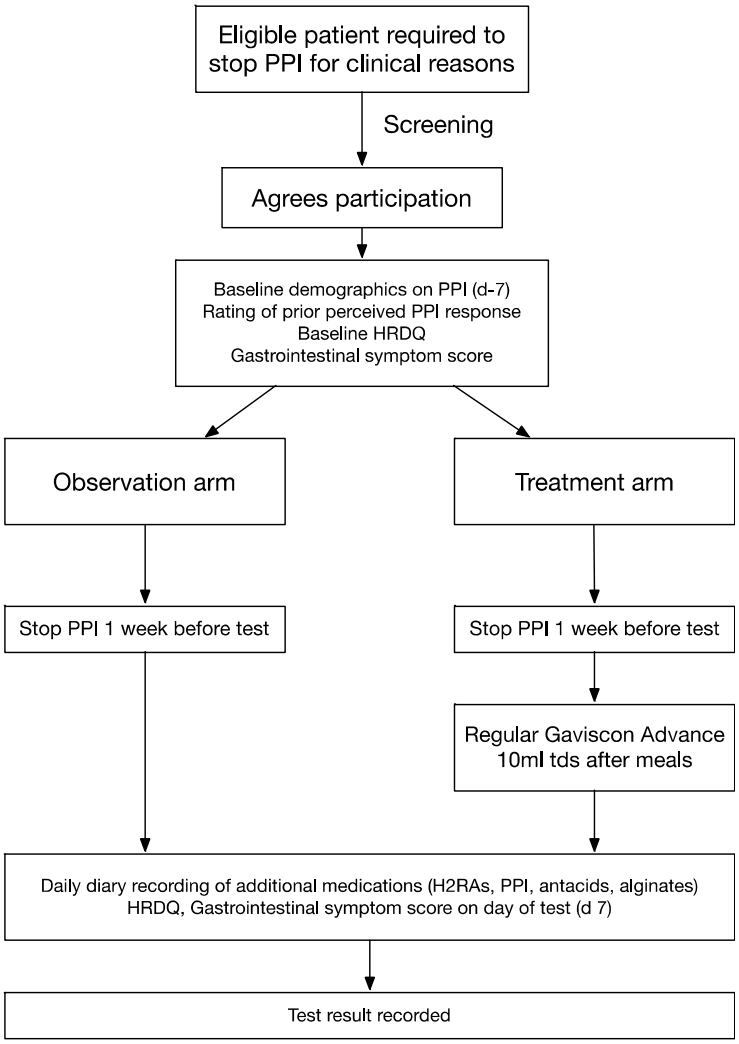
They will be invited to record surreptitious taking of PPIs and/or H2-receptor antagonists in an anonymous questionnaire (this will be sealed in an envelope and will only be looked at in final analysis, untraceable to the participant).

GI physiology testing will be performed as per standard clinical practice, and will be reported according to standard practice (13) (14).



Statistics and analysis

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The primary outcome will be measured by comparing mean GERD-HRQL scores in the observation and treatment arms. Statistical significance will be tested by a paired t-test. Power calculation: A previous study of Gaviscon in patients with persistent symptoms (the population most likely to be studied in our hospital setting showed a baseline mean HRDQ score of 9.5 (SD 6)(15). Treatment with Gaviscon reduced the mean score to 4.5. If we expect this in the treatment arm, and expect no change in the observation arm, *23 patients* in each arm would identify this difference with a power of 90%. To allow for a 30% dropout, we will recruit 30 patients in each arm.

Timeline:

From agreement of the project, ethical approval would be expected to take 2 months. We would expect to recruit 5 patients per week, and allowing for dropouts would expect to recruit over 16 weeks. We would intend for the first patient to enter the study in December 2019, and the last patient to leave the study in May 2020. Analysis and write up would be predicted to take 2 months, with anticipated submission of results in July 2020.

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Diary record of Gaviscon

Please tick when Gaviscon Advance is taken as instructed

	After breakfast	After lunch	After evening meal	Before bedtime
Day 1	☐	☐	☐	☐
Day 2	☐	☐	☐	☐
Day 3	☐	☐	☐	☐
Day 4	☐	☐	☐	☐
Day 5	☐	☐	☐	☐
Day 6	☐	☐	☐	☐
Day 7	☐	☐	☐	☐

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Anonymous Questionnaire

	YES	NO
Did you take any additional PPI medications (e.g. omeprazole, lansoprazole) over the past 7 days?	☐	☐

If yes, on how many days in the past week did you take a PPI tablet? _____

	YES	NO
Did you take any additional ranitidine/zantac medication over the past 7 days?	☐	☐

If yes, on how many days in the past week did you take a ranitidine/zantac tablet? _____

	YES	NO
Did you take additional Gaviscon medication over the past 7 days? (this was allowable)	☐	☐

If yes, on how many days in the past week did you take Gaviscon? _____

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If you suffer from heartburn (burning sensation behind the breastbone), how much do you perceive your heartburn symptoms have worsened since stopping your PPI (e.g. omeprazole/lansoprazole) for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10

If you suffer from regurgitation (unpleasant sensation of material moving up from the stomach behind the breastbone), how much do you perceive your regurgitation symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10

If you suffer from epigastric pain (pain at the top of the abdomen, just below the breastbone, how much do you perceive your regurgitation symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10

If you suffer from excessive burping, how much do you perceive your burping symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10

If you suffer from excessive bloating, how much do you perceive your bloating symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10