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Discussion

1. Case Studies: Non-erosive Reflux Disease and Atypical Manifestations of Gastro-oesophageal Reflux Disease

Audience response outcomes to case study clinical management questions discussed below are presented in figure 1.

Question: What approach would you suggest for a 55-year-old obese woman with a 5-year history of heartburn and regurgitation who continues to have symptoms three to four times a week despite taking a proton pump inhibitor (PPI) twice a day, and who now has a chronic cough and hoarseness (figure 1a)?

Prof. James Freston: It is useful to bear in mind that there is no one 'right answer' for these case study questions. Indeed, the choice of best management option will in some cases be controversial. Also, best-practice choices may not always be practical because of local practice guidelines and the availability of diagnostic tests or treatments. In this patient, currently, many gastroenterologists continue to undertake endoscopy, although it is highly unlikely that erosive disease will be seen in a patient on a twice daily PPI such as lansoprazole 30 mg. The use of a 48-h Bravo capsule pH study to determine whether acid reflux is responsible for the symptoms would be highly unlikely to be positive for acid in a patient on a twice daily PPI, although it could provide a very useful indication for increasing the PPI dosage if a pH drop is seen. However, a combined 24-h pH and impedance study will prove if the patient has reflux and whether it is acid or non-acidic, as well as whether or not it is reaching the oropharynx and is a likely cause of the cough and hoarseness. Finally, some would say the patient should be referred for anti-reflux surgery if it turns out she has non-acidic reflux.

Prof. Roy Orlando: Currently, we are not doing combined pH/impedance testing at our clinic. Impedance is an ideal tool for determining the non-acid reflux issue; however, it has not yet been clearly established that non-acid reflux is causal for the symptoms of cough and hoarseness such as experienced by this patient. A controlled trial needs to be performed to demonstrate whether or not the detection of a non-acid reflux event, even if it correlates with the symptom index, for instance, would be reliable as an indication for an anti-reflux procedure. We look forward to additional trials to document that what impedance demonstrates essentially has clinical impact on how we manage our patients.

Prof. Jean Paul Galmiche: In Europe many gastroenterologists continue to perform endoscopy. In this case, after 2 months of PPI treatment it is likely that endoscopy will be negative, especially with respect to reflux oesophagitis. On the other hand, endoscopy may be useful in the individual patient to provide reassurance by excluding other diagnoses such as malignancy. The cost of the investigation is also a consideration. Despite a preference for combined 24-h pH and impedance investigation, at the moment I do not believe that many centres are equipped for pH/impedance monitoring.

Question: How would you proceed with a 48-year-old man with recurrent atypical chest pain with no evidence of coronary heart disease on cardiological assessment, and occasional regurgitation, but no dyspepsia or weight loss (figure 1b)?

Prof. Freston: In the United States, a trial of twice daily PPI for up to 2–3 months is recommended for economic reasons as a first step in non-cardiac chest pain, based on small PPI trials. Performing upper endoscopy to examine the mucosal lining of the oesophagus is also a well-accepted choice, whereas a 24-h ambulatory pH study while off medication may perhaps be a preferred option in Europe and elsewhere, where pH-metry is readily available.

Prof. Galmiche: Twenty-four-hour pH monitoring could be useful in this case to establish the

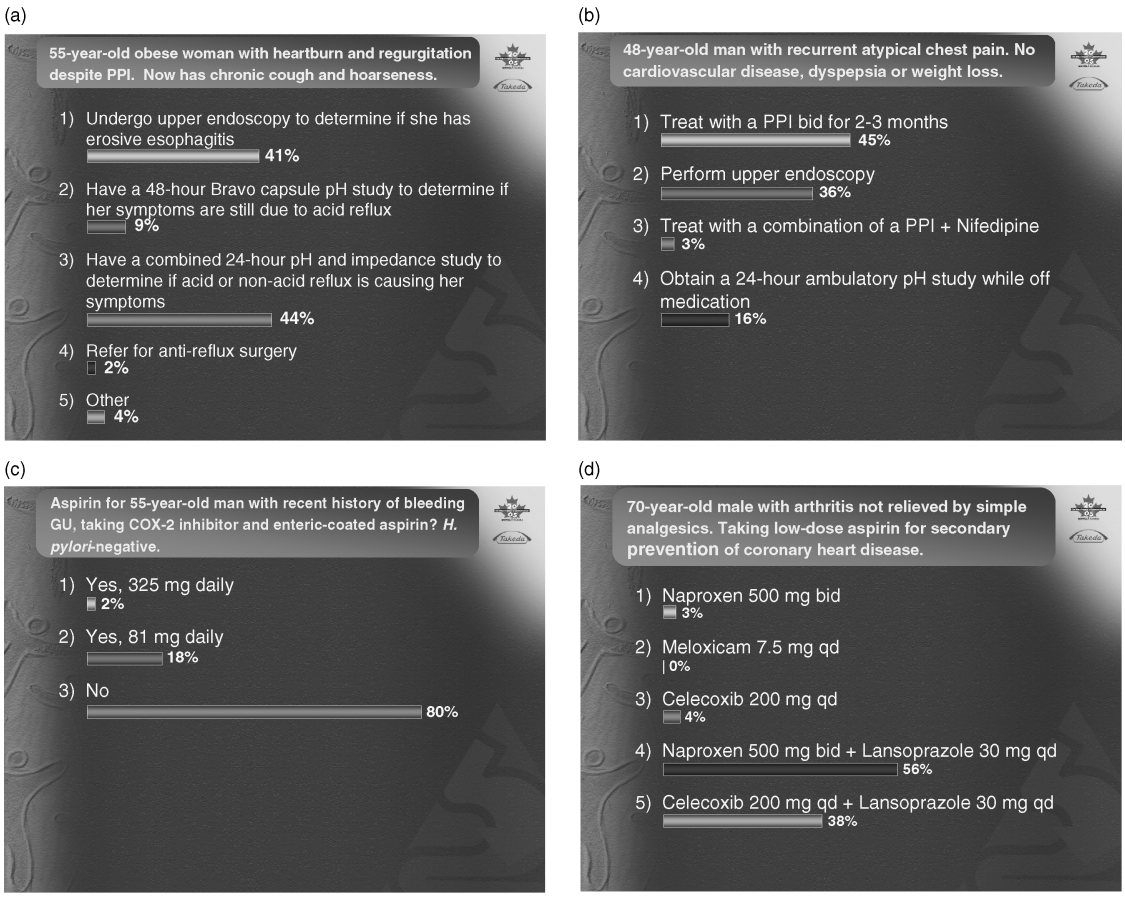

Fig. 1. Audience response outcomes to case study clinical management questions discussed at the Looking to the Future: Unmet Needs in Understanding and Managing Upper GI Diseases symposium at the World Congress of Gastroenterology held in Montréal, Canada, 2005.

temporal relationship between symptoms and the acid reflux, even if oesophageal acid exposure is normal. However, 24 h is a very short period and perhaps in the future, and especially in patients with frequent chest pain, the Bravo capsule with prolonged pH recording may be useful.

Prof. Orlando: I would probably recommend an upper endoscopy initially, to exclude significant pathology. Although I like the idea of a PPI trial, in this case if the chest pain were an acid-mediated problem I would expect it to get better within 2–3 weeks of empirical PPI treatment, rather than extending treatment for 2–3 months. If the patient was not better after 2–3 weeks of PPI treatment, I would pursue a broader diagnostic approach as opposed to chasing the diagnosis of gastro-oesophageal reflux disease any further.

Question: How would you proceed with a patient with typical heartburn and episodic regurgitations, without endoscopically apparent erosions and who is non-responsive to standard dose PPI?

Prof. Galmiche: In practice, many clinicians first switch PPI, which is not the best choice. On the contrary, there are data based on pharmacological studies favouring increasing the dose of PPI or doubling the dosing frequency.

Prof. James Scheiman: Increasing the PPI dose makes the most sense. It is also important to make

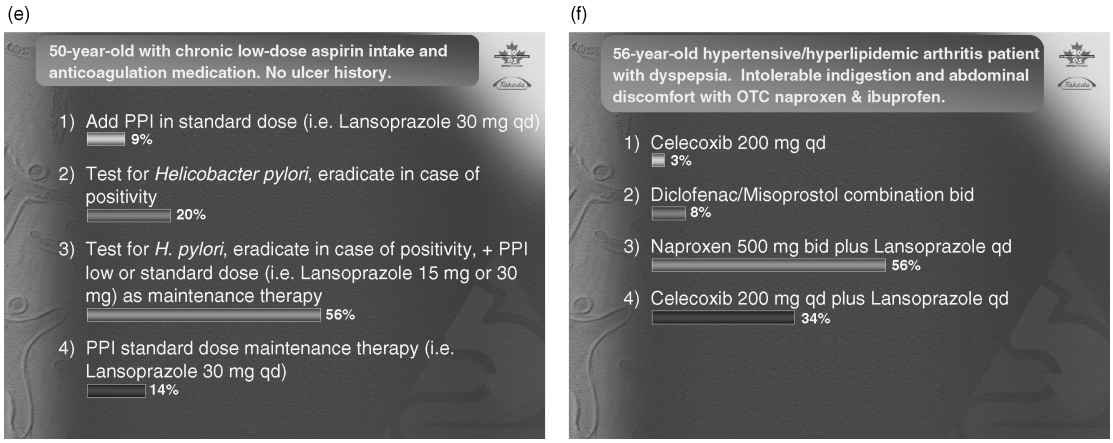

Fig. 1. *(Continued).*

sure the timing of medications is appropriate. If there is no response to increased dose PPI, 24-h pH-metry while on standard dose PPI should be considered. It could be useful to undertake motility assessment, with or without impedance study, to confirm that reflux is the cause of the symptoms. Surgery would be the final option.

Question: How would you proceed with the management of a patient who has had severe heartburn symptoms (more than three times per week) for 2 months?

Prof. Galmiche: Initially, standard-dose PPI such as lansoprazole 30 mg once a day should be tried, proceeding to twice a day PPI if the response is insufficient. However, many clinicians in Europe would advise early endoscopy for this patient. Despite enabling the clinician to grade oesophagitis, if present, there is no more than a 40% chance that endoscopy will significantly affect the initial management strategy. On the other hand, a search for Barrett's oesophagus is a legitimate indication for endoscopy, but this is best done after 8 weeks of PPI treatment to minimize the likelihood of inflammation confounding the interpretation of dysplasia. The choice of an early endoscopy is, however, important when the symptom of heartburn is not typical or predominant, to exclude malignancy and provide reassurance to the patient.

Prof. Scheiman: I would just add that in the United States erosive disease is rarely seen, as many patients have already tried PPI that are available over the counter.

2. Case Studies: Non-steroidal Anti-inflammatory Drug-related Gastrointestinal Disorders

Question: A 55-year-old generally healthy man who had a bleeding gastric ulcer treated successfully with endoscopic therapy a month earlier is taking 'one of those new safer NSAID' for knee osteoarthritis. He also takes an enteric-coated aspirin at night 'because all his friends take one too', but takes no other medications and has normal blood pressure and lipids. *Helicobacter pylori* status was dealt with at the time of endoscopy. Should this patient be taking aspirin (figure 1c)?

Prof. Masahiro Asaka: This patient should not be taking even low-dose aspirin. Primary prevention for low cardiovascular risk patients such as this case (normal blood pressure and lipids profile) does not improve mortality, and the risk of other adverse events such as gastrointestinal bleeding or haemorrhagic stroke balances out the reduction in myocardial infarction.

Question (follow-up): Was a cyclooxygenase (COX)-2 inhibitor the appropriate non-steroidal anti-inflammatory drug (NSAID) for this patient?

Prof. Asaka: For the same reason that he does not need aspirin, the patient is an ideal candidate for a selective COX-2 inhibitor if his aspirin use is discontinued. He has low cardiovascular risk (so any cardiovascular concerns with this class of NSAID are minimal) and a high gastrointestinal risk. Continuing to take the COX-2 inhibitor in combination with aspirin would further increase the gastrointestinal risk for this patient.

Question: What is the most appropriate treatment for a 70-year-old man requiring an anti-inflammatory for arthritis pain not relieved by simple analgesics? He is receiving low-dose aspirin for the secondary prevention of coronary heart disease (figure 1d).

Prof. Asaka: Given multiple NSAID use in this patient, a gastroprotective agent is appropriate, as this patient has two risk factors for NSAID-related gastrointestinal toxicity: age and aspirin use, which negates the gastrointestinal benefits of COX-2 inhibitors.

Prof. Scheiman: Prof. Chan and I are probably going to disagree on the management of this patient. I think that with established cardiovascular disease, we are hard pressed to give this patient a COX-2 inhibitor. Truly evidence-based recommendations would suggest that celecoxib 200 mg once a day does not have any adverse cardiovascular outcome. On the other hand, the absence of evidence is not the evidence of absence. Because of that, I personally would select naproxen 500 mg twice a day plus lansoprazole 30 mg once a day for this patient. There is very strong evidence from meta-analysis, irrespective of what the US Food and Drug Administration has said, that naproxen is the most aspirin-like medication we have. Having said that, I would continue the aspirin along with the naproxen, to minimize the cardiovascular risk. Naproxen plus lansoprazole is also a more cost-effective option than celecoxib plus lansoprazole.

Prof. Francis Chan: First of all, the use of a PPI is certainly required in this patient who is at high gastrointestinal and cardiovascular risk, requiring both NSAID plus aspirin. I think either naproxen 500 mg twice a day or celecoxib 200 mg once a day can be used in this patient. I would choose celecoxib because there is not even a single study suggesting that the short-term use of low-dose celecoxib 200 mg or less a day has a significant cardiovascular hazard, and once-daily dosing has benefits in terms of patient compliance.

Question: How would you manage a 50-year-old patient without a history of gastric ulcer on low-dose aspirin and anticoagulation therapy (figure 1e)?

Prof. Asaka: There may be some differences of opinion here, and it is very difficult to choose between starting maintenance therapy with a standard dose PPI such as lansoprazole 30 mg a day or first testing for *H. pylori* infection, eradicating in the case of positivity, and then starting maintenance therapy with low-dose or standard-dose PPI.

Prof. Scheiman: This is another situation in which the evidence of the value of both strategies alone is strong, but I think that the combination of *H. pylori* eradication and PPI maintenance does make the most sense, although Francis (Prof. Chan) showed some persuasive data that the eradication of *H. pylori* alone was effective. Factors such as the local availability of *H. pylori* testing, the likelihood of successful eradication therapy, the likelihood of reinfection, and the economic issues relating to chronic PPI will all influence the individual clinician's choice. Personally, I would just give the patient a PPI and not bother with testing and treating *H. pylori* infection. The United States is a country where the *H. pylori* infection rate is not very high, and I would be satisfied to get our cardiologists or primary care doctors, who are unlikely to adopt adequate diagnosis and treatment of *H. pylori*, at least to think about this issue and treat these patients with PPI therapy.

Prof. Chan: In places where the prevalence of *H. pylori* infection is high, and also where the prevalence of ulcer disease is high, there is a very good argument for testing for and eradicating *H. pylori* infection. Current evidence indicates that the eradication of *H. pylori* alone substantially

reduces the risk of aspirin-induced ulcer complications.

Question: What treatment would you recommend for a 56-year-old man with knee pain not relieved by acetaminophen (paracetamol)? The patient has a history of hypertension and hyperlipidaemia and is taking once-daily lisinopril 10 mg, atorvastatin 10 mg and aspirin 325 mg. Over-the-counter ibuprofen and naproxen both relieve his knee pain but lead to intolerable indigestion and abdominal discomfort (figure 1f).

Prof. Chan: My preference for this patient is to use celecoxib 200 mg once a day plus lansoprazole 30 mg once a day, rather than naproxen 500 mg twice a day plus lansoprazole once a day. Lansoprazole is indicated in this patient for two reasons. First, he has dyspepsia, and there is good evidence that PPI can relieve NSAID-associated dyspepsia. Second, PPI is effective in preventing NSAID plus aspirin-induced gastroduodenal damage. Although a diclofenac/misoprostol combination twice a day might be effective, the incidence of side-effects, especially diarrhoea and abdominal discomfort, limit its usefulness. I would choose celecoxib instead of naproxen in this case because this patient is already on multiple drugs and compliance is likely to be a real issue.

Prof. Scheiman: Prof. Chan has stated the key message very well. The only reason to choose celecoxib here would be a non-gastrointestinal reason. It is clear that in combination with aspirin the ulcer risk reduction of celecoxib will be lessened, and there is not much dyspepsia benefit, which this patient is really in need of. The real issue is 'is it worth the money?', and for many patients and clinicians this will be an individual decision. Comparing the compliance benefits of once-daily versus twice-daily dosing may, in many circumstances, not justify the additional cost of the selective COX-2 inhibitor.

Prof. Asaka: I would like to close this discussion session with a personal comment. My scientific judgement led me to choose naproxen plus lansoprazole in this case. However, to use a PPI for the prevention of gastric mucosal injury is not approved by the Japanese medical insurance system, which creates a dilemma and illustrates how best-practice choices may not always be possible in the clinical situation.