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GASTRO-INTESTINAL UPDATE

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Long Term SIDE EFFECTS OF PPI's

Proton Pump Inhibitors (PPIs) have transformed the management of peptic ulcers, gastritis and gastro-oesophageal reflux disease (GORD) due to their remarkable effectiveness and apparent lack of side effects. Patients with moderate to severe GORD whose symptoms have not been adequately controlled by lifestyle modifications or antacids may come to surgery, but the vast majority will be treated with PPI's. PPI's need to be continued long term, and probably life-long.

Can suppressing stomach acid secretions for such long periods cause consequences?

1. **Iron and B12 malabsorption** has not been clinically significant and seems to be a theoretical risk only.

2. There is a link between long term PPI's and **hypomagnesaemia**, but this is very rare. Blood testing is only advised in patients with appropriate symptoms such as dizziness, confusion, and muscle cramps or weakness.

3. Initial observational studies raised concerns that **decreased calcium absorption** might lead to osteoporosis and bone fractures, particularly hip fractures. Recent large prospective trials have not, however, shown any link. Supplemental calcium is not routinely required.

4. Acid suppression may allow **bacterial proliferation** in the upper gastrointestinal tract, theoretically giving rise to increased incidence of Clostridium difficile infections, travellers' diarrhoea and small intestine bacterial overgrowth. There is, however, no conclusive evidence. C. difficile infections are more common in a hospital setting in an ill patient, on multiple medications including a PPI for prophylaxis against upper GIT bleeds.

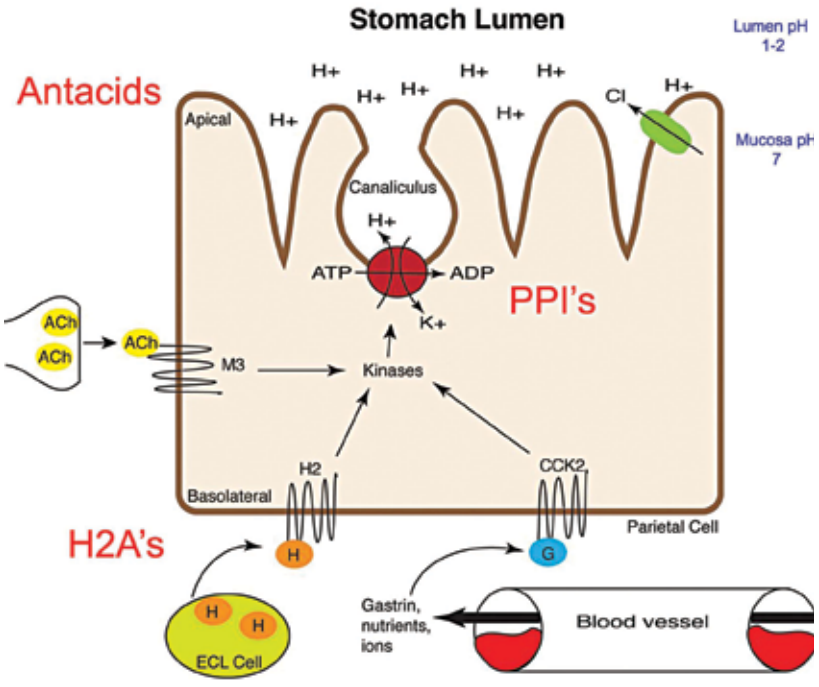
5. A small number of patients (< 2 %) develop **constipation or diarrhoea, nausea, abdominal bloating, abdominal discomfort and headaches** while on PPIs . These symptoms are usually transitory and very few patients need to discontinue PPIs because of them. Allergic reactions also seem to be very uncommon with PPIs but can happen as with any drug.

6. A third of patients on long term PPIs develop small **polyps** in the fundus of the stomach or hyperplastic polyps elsewhere in the stomach These are benign and resolve if PPIs are discontinued. Animal studies have shown development of gastric carcinoid tumours, but this has not been observed in humans as yet.

7. Caution needs to be exercised if patients are on other **medications**. PPIs increase blood levels of warfarin, phenytoin and methotrexate, but decrease levels of ketoconazole and oral contraceptives. There are very rare reports of hepatotoxicity and interstitial nephritis but these numbers are negligible considering the number of people taking PPIs. There are also rare reports of depression, anxiety, insomnia and apathy but these conditions are less easy to attribute to PPIs.

Weight loss, and use of antacids can control symptoms. In patients who require long-term PPIs, aim to use the smallest dose that controls symptoms, e.g. 10 mg daily or 20 mg on alternate days. Despite extensive use worldwide, the incidence of both short term and long term side effects of PPIs is remarkably low.

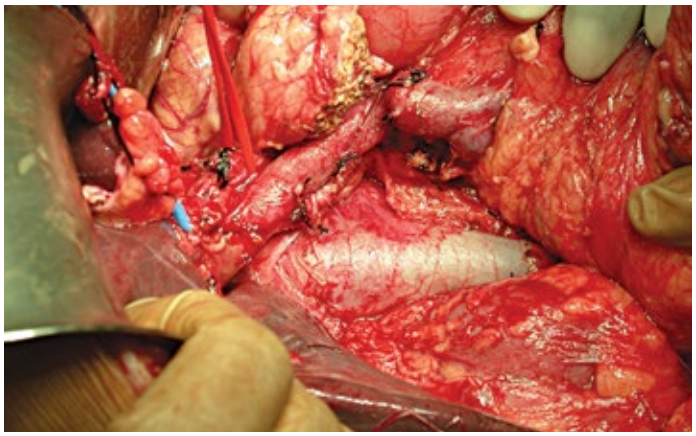
POSSIBLE SIDE EFFECTS OF LONG-TERM PPI's	
1. Iron and Vit B12 malabsorption	5. Abdominal symptoms
2. Magnesium malabsorption	6. Polyps
3. Calcium malabsorption	7. Interaction with medications
4. Bacterial proliferation	8. Renal and Hepatic toxicity



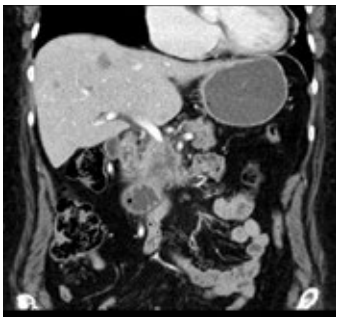
Sites of Drug Action: PPI's are pro-drugs that require activation in an acidic environment and irreversibly bind to and inactivate H+,K+- ATPase

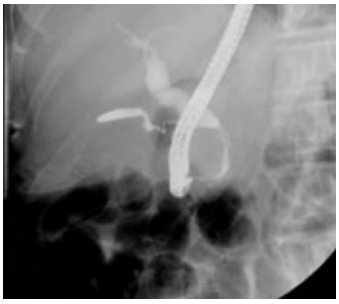
Pancreatic Cancer

Pancreatic ductal adenocarcinoma makes up 90% of solid pancreatic tumours, and is thus the type of tumour referred to when patients, and their doctors, talk about "pancreatic cancer". It is obviously important to distinguish these from neuroendocrine tumours, which make up most of the remaining 10%. Pancreatic neuroendocrine tumours are usually reasonably easy to tell apart on imaging, and are associated with a good long term survival, even when metastatic. Pancreatic cancer is the 4th commonest cause of cancer death.



Whipple's resection: The pancreatic head has been removed, exposing the portal vein and IVC. The pancreatic body awaits anastomosis to the jejunal loop.





Top: **CT Scan of an incurable pancreatic cancer involving the portal vein, with evidence of multiple liver metastases.** Bottom: **Jaundice is the commonest presenting symptom for curable tumours. This ERCP picture shows a distal biliary stricture confined to the region of the pancreatic head.**

DIAGNOSIS

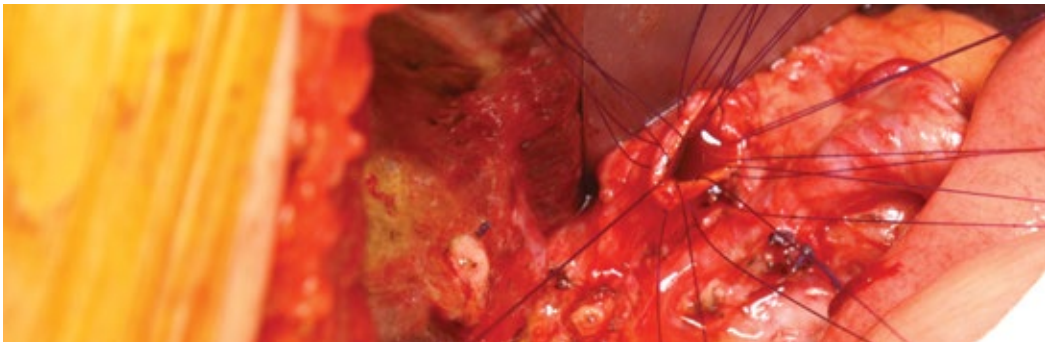
Pancreatic cancer remains an extremely difficult condition to deal with. Due to the retroperitoneal situation of the pancreas, and the poor nerve supply to the pancreas itself, early pancreatic tumours are typically asymptomatic. To make matters worse, the earliest symptoms are extremely vague, with dyspepsia or "indigestion" being the commonest – symptoms many times more commonly associated with conditions such as biliary colic, gastritis, peptic ulcers or irritable bowel syndrome. The classic symptoms of pancreatic cancer – central back and abdominal pain associated with weight loss – are frequently only seen in tumours that have already grown beyond the confines of the pancreas, and are already incurable. Jaundice is the commonest presenting symptom for patients who still have resectable tumours of the pancreatic head. Investigations offer further challenges. Standard abdominal ultrasound is inaccurate for examining the pancreas, with a high false negative rate. Tumour markers (GI 19.9) have a very low sensitivity, and are of no use for screening. And the more accurate investigations such as contrasted CT or MRI are prohibitively expensive for routine use.

TREATMENT

Surgery remains the only modality available for cure. Chemotherapy and radiotherapy are used in the adjuvant or palliative settings with limited benefit, but are not curative on their own. Distal pancreatectomy is used for tumours of the body and tail, while pancreatico-duodenectomy (Whipple's resection) is for tumours of the head of the pancreas. Advances in surgical technique and peri-operative care have greatly improved the morbidity and mortality rates of these procedures in appropriately trained hands. However it should not be forgotten that this remains major surgery, often for elderly patients, and fitness for surgery must be carefully judged. Surgery should only be performed with curative intent. Palliative surgery has been almost completely replaced with endoscopic management. Biliary metal stents are preferably placed via ERCP for relief of jaundice and associated pruritus. Duodenal stents can be used for relief of gastric outlet obstruction caused by tumour invasion of the duodenum.

Unfortunately pancreatic cancer is associated with the lowest cure rate of any cancer. This is primarily due to the biology of the cancer itself, with its tendency to very early perineural and vascular invasion leading to both local recurrence following surgery and early distant metastases. More than 90% of tumours are locally advanced or metastatic at diagnosis, rendering cure impossible. And even in resectable cases many patients suffer tumour recurrence. The surgical focus is on patient selection for curative surgery, with a careful weighing up of risks and benefits for each individual patient.

Pancreatic cancer presents a uniquely difficult combination of factors that contribute to its poor prognosis. Late onset of symptoms, vague symptomatology, difficult anatomic location, inaccuracy of basic imaging, the lack of an easy diagnostic test, and early progression of disease all make for a depressing overall picture, despite advances in the surgical recovery process.



Whipple's resection: The sutures are placed in the bile duct, for anastomosis to the jejunal loop.

NSAID enteropathy

The serious side effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the stomach and duodenum are well documented. Damage to the small bowel is actually more frequent.

NSAID enteropathy can be associated with significant complications, including bleeding, protein loss, perforation, obstruction, and sudden death. There is a lack of awareness of the distal small bowel damage that can be caused by the NSAIDs because the condition is usually asymptomatic and the diagnosis is difficult to establish.

Non-specific small intestinal ulcerations can be found in about 8% of patients who recently used NSAIDs.

Up to 4% of all small bowel resections are attributable to small bowel side effects of NSAIDs. 47 % of patients on NSAIDs for rheumatoid arthritis with chronic iron deficiency anaemia have small bowel ulceration contributing to their anaemia.

PATHOGENESIS

The typical findings are penetrating longitudinal ulcers in the distal jejunum and ileum accompanied by an overgrowth of caecal-type organisms. The damage to the small bowel mucosa is dose dependent and is caused by both COX-1 and COX-2 inhibition, as well as a topical effect that compromises mucosal cell integrity and increases epithelial permeability. The initial mucosal injury caused by NSAIDS is the same for the stomach and the small intestine. This breach in mucosal integrity then leads to pathology via different agents. In the stomach this exposes the mucosa to luminal aggressors such as acid and pepsin while in the small bowel the permeability increase exposes the mucosa to bile acids and bacteria and their degradation products. In both locations this leads to inflammation, erosions, and ulcers. This is associated with bleeding and protein loss, and the ulcers may heal with a degree of fibrosis causing obstruction.

DIAGNOSIS

The diagnosis of NSAID enteropathy may be difficult to confirm. Faecal calprotectin is increased, but it is not disease specific and may also be raised in inflammatory bowel disease and colorectal cancer.

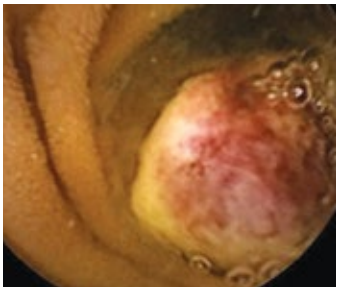
Push and Double Balloon enteroscopy are more specific but invasive, time-consuming, and difficult to perform. Capsule endoscopy is a more recent diagnostic tool and has proved to be of significant value in the diagnosis of NSAID enteropathy.

TREATMENT

The mainstay of treatment is the withdrawal of NSAIDs. Unfortunately this is not always possible for patients who rely on NSAIDs for the symptomatic relief of chronic inflammatory conditions. In these cases one has to consider prophylactic treatment, treat the inflammation in established cases, and switch over to anti-inflammatory analgesics that cause less damage.

The literature suggests that misoprostol, metronidazole, or sulphasalazine may be beneficial in the treatment of NSAID enteropathy. However these are not controlled studies. Proton pump inhibitors reduce the gastric damage attributable to NSAIDs, but do not protect the small bowel mucosa. Surgery is usually required for some of the complications of NSAID enteropathy, such as massive bleeding or perforation. Endoscopic balloon dilatation can be used for accessible strictures, but most cases of obstruction require surgical intervention.

There is no doubt that NSAIDs cause small bowel damage in humans and that this injury is common. Difficulty accessing the small bowel to make a visual assessment, makes the diagnosis of this condition problematic. A high index of suspicion is required, and NSAIDs should be discontinued if possible.



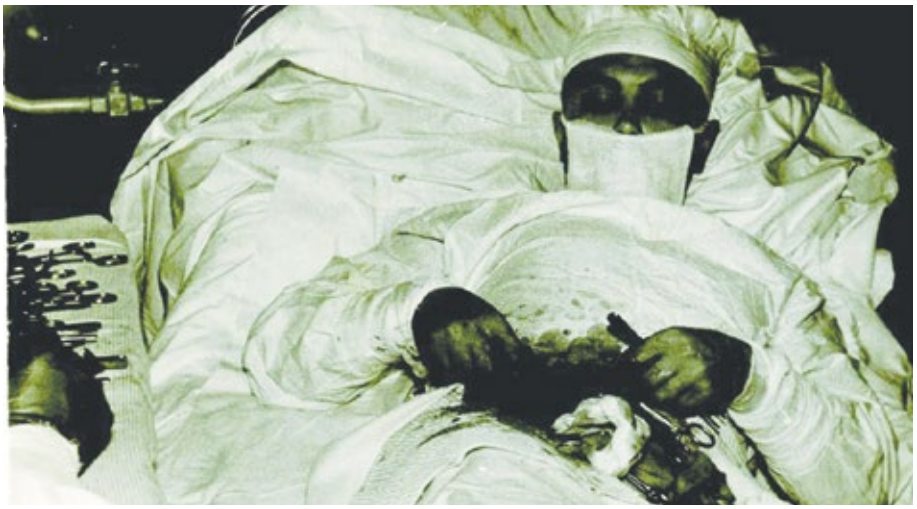
Capsule endoscopy showing ulceration of terminal ileum

An **appendicectomy** with a difference

A 27 year old man developed progressive abdominal pain which radiated to the right iliac fossa and was associated with vomiting and an increasing pyrexia. He obviously needed an appendicectomy BUT the date is the 30th April 1961 and the place Novolazarevskaya, a Russian base on the coast of Antarctica 500km East of the newly established South African base in Dronning Maud Land. The winter night has started so no evacuation is feasible and the patient, Leonid Rogozov, is the only doctor on the base – albeit a surgeon in training.

Despite conservative treatment he got progressively worse and realised that he would have to operate on himself. The meteorologist handed him the instruments and the mechanic held a mirror and adjusted the table lamp. The station commander held himself in reserve in case either of the other two fainted. Rogozov put gloves onto his assistant but decided to work without gloves himself.

He adopted a semi-reclining position and injected local anaesthetic. Working mainly by feel he made his way gradually through the abdominal wall. In opening the peritoneum he nicked the caecum which he then sewed up. Despite a fair amount of bleeding he eventually mobilised and removed the appendix, which showed signs of imminent rupture. The operation had lasted 1hour and 45 minutes. The worst part for the assistants was when his small bowel which had prolapsed out through the wound started gurgling. Although sweating profusely and nearly fainting when he removed the appendix, he was able to sew up the wound and see that the instruments were all clean and put away correctly before taking a sleeping tablet.



The next day, although still having a temperature of 38.1 degrees, he felt much better. After 4 days his bowels worked and in 2 weeks he returned to his duties.

A year later he left Antarctica, returning to Leningrad where he worked in the department of General Surgery of the First Leningrad Medical Institute.

He never returned to Antarctica and died in St Petersburg, as it then was, in September 2000.

Reference: BMJ 19-26 December 2009; Vol 339; Pgs 1420 - 1422

WELCOME

Dr Bhavesh Natha

MBChB (UCT) FCS (SA) Cert Vascular Surgery (SA)

Matley and Partners is pleased to welcome our newest recruit to the team.

Bhavesh grew up in Cape Town and matriculated from Westerford High School in 1996. He completed his undergraduate medical training at the University of Cape Town in 2002 and did his internship at Tambo Memorial Hospital in Boksburg. Thereafter he worked as a Community Service Medical Officer at the Robertson District Hospital.

In 2005 Bhavesh was appointed as a registrar in the Department of Surgery at the University of Cape Town/Groote Schuur Hospital. After completing his postgraduate training in March 2010, he joined the division of Vascular Surgery at Groote Schuur hospital to further training in this field. He spent a further two years training as a fellow in Vascular Surgery that provided training in open and endovascular arterial and venous procedures. During this time he was also actively involved in teaching, vascular research and presented at numerous vascular surgery congresses and meetings. In October 2012 Bhavesh completed the sub-specialist exam in Vascular Surgery. To consolidate his skills and increase his experience in vascular surgery, he spent 2013 at Groote Schuur Hospital as a Vascular Surgery Consultant.

Bhavesh practices in all aspects of vascular surgery and has a special interest in venous and minimally invasive arterial endovascular techniques. He is also involved in undergraduate and postgraduate teaching in the Department of Surgery at Groote Schuur Hospital and the University of Cape Town.

Bhavesh has diverse interests that include a variety of sporting activities, cooking and music. He is married to Claudia.