The Medical Management of Chronic Pancreatitis

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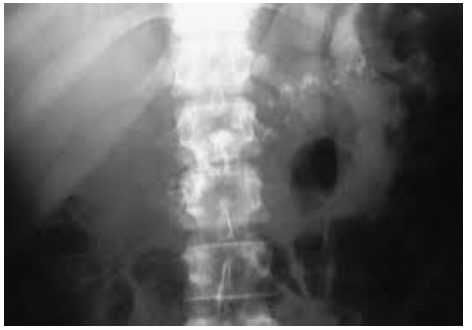
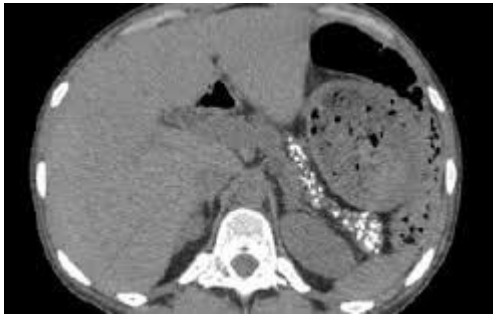
Medical management of CP

Treatment of:

- Pain
- Exocrine insufficiency
- Endocrine insufficiency





Pain and chronic pancreatitis

- The cardinal feature of CP in most patients
- The reason majority seek medical attention
- Difficult to treat
- Unsatisfactory outcomes for both patient and physician

- Set realistic goals upfront
- Often impossible to render patients 100% pain free
- Knowledge of mechanisms of CP pain is still evolving
- There is still a large unmet therapeutic need
- The 'right' drugs are not yet available

Medical management of pain

- Exclude other causes of pain
- Start low and go slow
- Avoid exposure to highly potent and addictive opiates until absolutely necessary

- Patients should abstain from alcohol and tobacco
- These both hasten disease progression
- Increase the risk of malignancy
- Alcohol abstinence may reduce pain
- The magnitude of the effect is unpredictable

Lowenfels AB, et al. Clin Gastroenterol Hepatol 2011;9:196–197

Medical management of pain

- Trial of simple analgesia
- Paracetamol
- Short courses of NSAIDS (beware PUD)
- Often insufficient if there is significant pain

- Combine paracetamol with tramadol
- High doses have similar efficacy to equivalent dose morphine with a better side-effect profile
- A weak opiate with negligible risk of dependency
- Codeine is a poor analgesic

Wilder-Smith CH et al. Dig Dis Sci 1999; 44 ,1107–1116

Drugs targeting neuropathic pain

- Increasingly a neurological component is recognised
- Peripheral sensitization of pancreatic nocioceptors
- Neuritis and hypertrophy of pancreatic nerves
- Aberrant central processing of pain in the cortex

- TCAs (amitryptiline) have been shown to be effective in other neuropathic states
- Excellent analgesic properties
- Effective in treating insomnia
- Anti-depressive properties

Drugs targeting neuropathic pain

- Drugs inhibiting serotonin reuptake
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Selective serotonin-reuptake inhibitors (SSRIs)
- Never evaluated in the setting of CP
- Can cause diarrhoea
- Cannot use with Tramadol (Serotonin syndrome)

Anti-epileptics: gabapentoids

- Gabapentin and pregabalin
- Inhibit central sensitization
- Effective in diabetic neuropathy and post-herpetic neuralgia

- Only pregabalin has been tested in a RCT in CP
- Significant reduction in pain score in the pregabalin arm 36% (95% CI:43-29) *vs.* 24% (95% CI-31-16, p= 0.02)

Olsen SS, et al. Gastroenterology 2011;141:536-543

- Nortriptyline & gabapentin in combination is better than either alone for chronic pain

Gilron I, et al. Lancet 2009; 374: 1252

Opiates for refractory pain

- If not candidates for endoscopic or surgical therapy
- The decision to use opiates should not be made lightly

CDC guideline for prescribing opioids *2016 JAMA. 2016;315(15):1624*

- Start with lowest potency opiates at the lowest effective dose
- Prescribe immediate-release opiates instead of extended-release/long-acting opiates

- Increased risk of overdose

- If possible use intermittently and not continuously
- Should be managed together with a pain specialist

Narcotic bowel syndrome

- A type of opioid-induced bowel dysfunction
- Characterized by paradoxical worsening of pain
- In the context of escalating or continuous chronic opioid therapy

- May confuse cause of pain
- Precipitate an erroneous increase in dose
- When the dose should actually be decreased

Other therapies for pain control

Anti-oxidants

- Oxidative stress hypothesis
- ROS produced by the metabolism of xenobiotics
- ETOH and cigarette smoke
- Can further damage acinar cells exacerbating pain

- Data supporting anti-oxidants is conflicting
- Recent meta-analyses of RCTs show beneficial effect
- Combination of Vitamin A, C, E, selenium, and methionine

Zhou D, et al. Clin Nutr 2015 ;34:627

- Recommended in a recent guideline

A.M. Drewes et al. Pancreatology 2017, 17: 720-731

Pancreatic enzyme replacement therapy for pain

- Proteases released in duodenum inhibit CCK
- Reduce pancreatic secretions & ductal HT
- Not proven to be effective & use is not recommended

But the PERT formulations used were not ideal

- Concentration of proteases too low to be effective
- Enteric coated to protect against inactivation by acid
- Enzymes release at PH > 5.5 (duodenal PH in CP < 5.5)
- So released too distally to initiate negative feedback
- A trial of high dose PERT with a PPI may be of value
- Especially if there is no exocrine insufficiency

Exocrine insufficiency

- Tends to develops in advanced disease
- Mostly affects fat & fat-soluble vitamin absorption
- Also impairs digestion of proteins and CHOs
- Classic symptoms:

- Diarrhoea
- Steatorrhoea
- LOW

Pancreatic exocrine insufficiency

- Steatorrhoea and associated symptoms are not evident until duodenal lipase falls below 5–10% of normal levels

- Maldigestion may be sub-clinical
- Vitamin/mineral deficiency often missed/undertreated
- Check fat-soluble vitamin levels, B12 levels annually
- Replace as required
- Metabolic bone disease
- Baseline DEXA and calcium, Vitamin D supplementation

Pancreatic enzyme-replacement therapy (PERT)

- Currently only enteric coated PERTs are available in SA
- Initiated when there are GIT symptoms
- Should it be started for sub-clinical malabsorption?
- Start at a low dose: 25-40 000 units of lipase with each meal and 10-20 000 with snacks
- Should be given during the meal
- Titrate per clinical response: resolution of diarrhoea
- May benefit from addition of a PPI

Pancreatic endocrine insufficiency: type 3C diabetes

- Tends to occur even later than exocrine insufficiency
- Islets resist damage to a greater extent than acini

- 25% are 'brittle" due to loss of counter-regulatory hormones glucagon and PPP
- Prone to hypoglycaemia
- Hyperglycaemia is often mild and typically post-prandial
- Seldom get DKAs

Treatment of type 3C diabetes

- No real evidence base so treated as per DM2
- Metformin 1st line
  - However poorly tolerated (GIT side effects)
  - Targets insulin resistance which is rare in DM type 3C
- Sulfonylureas: increase insulin release
  - Need some B cell reserve to be effective
  - Risk of hypoglycemia
- In time most patients need insulin therapy
  - Need closely monitoring with dose adjustment
  - Settle for less stringent glycaemic control (HBA1C 8-9)
  - Best done by an Endocrinologist

Newer DM2 therapies

- No evidence in DM type 3C
- Unlikely that any of these will be of value in type 3C DM

Drug	Mechanism of action	Advantages	Disadvantages
DPP-4 inhibitors GLP-1 analogues	Enhances the incretin effect	No hypoglycaemia	**Association with pancreatitis: CI**
Glitazones	Reduces insulin resistance	Weight gain	**Target primarily insulin resistance**
Alpha-glucosidase inhibitors	Inhibit amylase and sucrase	Target postprandial hyperglycemia	**Diarrhea, abdominal pain and bloating. Worsten malabsorption**
SGLT-2 inhibitors	Inhibits sodium-glucose cotransporter	Actions are independent of insulin	**Weight loss**

Conclusion

- Before starting opiates try TCA and/or pregabalin
- When prescribing opiates: start low and go slow
- Avoid sustained release preparations
- Remember sub-clinical exocrine insufficiency
- Check Vitamin levels & supplement calcium/Vitamin D
- Be aware of high risk of hypoglycaemia in DM type 3C
- Treat conservatively and avoid very tight control
- The medical management of CP is challenging
- Current therapies are far from ideal
- Improved understanding of pathophysiology will identify new therapeutic targets with better efficacy