A Novel Method for Pain Relief in Chronic Pancreatitis: an Old Drug in a New Pack: a Controlled Study

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Abstract Most of pain-relieving agents in chronic pancreatitis are nonspecific and unpredictable. Omeprazole induces hypergastrinemia due to reduced gastric acidity. Raised serum gastrin, in turn, modulates to reduce secretin level. Secretin is responsible for secretion of almost 80 % bicarbonate-rich pancreatic juice from the ductular epithelium without affecting enzyme output. It is a prospective randomized study in patients with CT-confirmed chronic pancreatitis. The control group got the standard care and 60 mg of omeprazole twice daily was added to the test group. Absence of pain relief at 14 days was considered as failure. Pain relief, weight gain and any toxic effect of omeprazole were reviewed at 12 months. One hundred thirty-seven cases were included, with an age range of 19 to 72 years. (mean 42.67). The majority of them were alcoholic males. At 2 weeks, pain relief was noted in 47/69(68.1 %) and 63/65(96.96 %) in the control and omeprazole group, respectively. At the end of 1 year, the omeprazole group had greater weight gain (95 %) than the control group (69.5 %). All the pseudocysts in the omeprazole group and most in the control group resolved. No side effect of omeprazole was seen. The high-dose omeprazole (HDO) group of patients had significantly better pain relief in chronic pancreatitis than those treated with conventional therapy. A high number of cases gained weight in the HDO group than the controlled group. No patient had clinical, endoscopic,

biochemical, or haematological toxicity of HDO. More studies are necessary.

Keywords Chronic pancreatitis · High-dose omeprazole · Pain relief · Weight gain

Background and Aim

Chronic pancreatitis (CP) is a common clinical entity. Pain in the abdomen is the most common presentation. The cause of pain is multifactorial, but one of the established causes is intraductal hypertension. There are many methods and medications which are used to treat pain. The basic guidelines for treatment of pain are cessation of smoking and alcohol consumption [1–4], a low fat diet, anti-oxidants [1, 2], analgesics to include NSAIDs, codeine, antispasmodic, non-opiates or low-potency opiate analgesics [2], suppression of pancreatic secretion (octreotide) [1], pain-modifying agents (antidepressants, gabapentin, pregabalin) [1, 5], and pancreatic enzymes and adjunctive agents [1]. Most of them are nonspecific and the pain relief is unpredictable at times with side effect. The preferred pain killer codeine has been reported to cause pancreatitis, possibly by inducing spasm of the sphincter of Oddi [6].

Histamine-2 receptor antagonist (H2RA) and proton pump inhibitors (PPI) have been used for over 20 years to reduce gastric acid secretion. PPI inhibit better than the H2RA. PPI therapy is known to cause gastric anacidity, leading to an alkaline gastric mucosal pH with G cell hyperplasia and hypergastrinemia. Hypergastrinemia leads to suppression of secretin level by negative feedback. A major portion of secretin-induced pancreatic juice output consists of bicarbonate-rich fluid, secreted by the pancreatic ductal cells [7, 8]. Secretin and gastrin hormones have been shown to

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modulate each other's production through a negative feedback mechanism [8, 9]. Hypergastrinemia is produced by PPI like omeprazole, which has a good safety record, and potentially leads to reduced secretin production, reducing the pancreatic juice output [10–12]. The cause of pain in CP is multifactorial, but the traditional mechanical cause of pain is thought to be related to anatomical changes to include evidence of increased ductal and interstitial pressure. Both the intraductal and pancreatic interstitial hypertension pressure is related to pancreatic juice secretion in conjunction with some form of obstruction to the natural flow of the pancreatic juice [13]. And if the gastrin-secretin feedback is operative, PPIs will reduce the secretions and thus reduce the intraductal pressure.

Materials and METHODS

Study Design

The study was a randomized single-blinded comparison of high-dose omeprazole (HDO—60 mg twice daily) plus conventional pain medication versus only conventional pain medication for treating CP. Patients were randomly assigned to either treatment groups.

Study Patients

Patients presenting with clinical features of CP and confirmed on computerized tomography (CT) scan with evidence of stone/calcification with or without ductal dilatation or any complication of the disease were prospectively recruited during the study period of 2004–2013.

Inclusion Criteria

The inclusion criteria were as follows: (1) CT-proven chronic pancreatitis, (2) follow-up of at least 12 months and (3) recurrence of pain even after surgery.

Exclusion Criteria

The exclusion criteria were as follows: (1) age less than 18 years, (2) CT scans showing no evidence of CP, (3) CP with complete gastric outlet obstruction, (4) painless CP, (5) unwilling patient, (6) unwilling to stop alcohol and smoking, (7) CP with cancer at presentation and (8) CP with other painful abdominal conditions like renal/ureteric stone, peptic ulcer, etc.

Randomization (Consort Chart)

Subjects were randomly allocated in a 1:1 ratio to a treatment group after consenting to the study. They were randomized to

receive either HDO with conventional pain medication or only conventional pain medication. Block randomization was in blocks of six (AABABB, BABAAB, etc.) divided into two separate groups using a computer-generated sequence of random numbers. Blinding of the patients was carried out to the treatment received. Allocation concealment was done.

Study Procedure

CP patients with proven diagnosis were admitted for rest, supervised medication and monitoring pain relief. The treatment and hospitalization including the diet was provided free of cost to the patients. Drinking alcohol and tobacco smoking and chewing was stopped. Small frequent meals were given. Diabetes was managed appropriately. For patients in the omeprazole group, omeprazole was started 60 mg twice daily before food and vitamin C 500 mg given twice daily after food for 8 weeks with other established modalities and pancreatic enzyme supplementation. Patients who were vomiting were administered parenterally. The dose of omeprazole was reduced to normal 20 mg twice daily after 8 weeks for a year. the pain killer injection tramadol 50/diclophenac sodium 75 were given on demand alternating to avoid toxicity. All were given calmpose 10 mg/alprazolam 0.5 mg at bed time. Alcoholic CP received an injection of thiamine 100 mg daily for 3 days to avoid deficiency. Patients were given emotional support by the council team and psychiatrist support if required. None were addicted to opiates. The conventional group was given the same treatment except for omeprazole.

Pain relief was monitored by Visual Analogue Scale (VAS) of 1–10 during the morning ward round by the author after the night dose of pain killer but before the morning dose. When the pain was tolerable and the VAS score was <04 for two consecutive days without any analgesic need is considered as good pain relief. They were discharged after 14 days or after adequate pain relief, whichever was later. When there is no pain relief at 14 days, treatment was considered a failure. Patients were advised to continue the treatment of the respective group. They included a monthly review for 3 months to check for recurrence of pain and any weight gain and adjusting the dose of omeprazole. The dose of omeprazole was reduced to 20 mg 12 h after 2 months. Periodic haemogram, liver and renal functions were monitored for any organ toxicity of the medication and USG was done to see the progress of any complications of CP. Upper GI endoscopy was done at the end of the year of follow-up to look for any effect of omeprazole on gastric mucosa.

Primary Outcome Measure The primary outcome measure was the relief of pain measured at 14 days, 3 months and at 1 year.

Table 1 Clinical presentation

Presentation	<i>n</i>	%
Pain abdomen	137	100
Biliary obstruction	9/3 ^a	6.57/2.16
GI bleed	02	1.46
Anaemia	01	0.7

^a Nine had dilated biliary tree with raised serum alkaline phosphatase and only three had raised bilirubin

Secondary Outcome Measures The secondary outcome measures were as follows: (a) weight gain at the end of 1 year, (b) improvement in complications of CP and (c) toxic effect of the omeprazole.

Statistical Analysis Analysis was carried out using SPSS v21.0. For all outcomes, a *p* value of less than 0.05 was considered to indicate statistical significance. Proportions were compared using Z test.

Results

A total of 143 cases were assessed for eligibility. But at the end of the year, 121 cases were followed up (Consort Flow chart-1). The majorities were alcoholic males, with only 7 females (three of them were alcoholic). Age range was from 19 to 72 yrs. (Mean 42.67 SD 11.69). Twenty-one (28.77 %) of them were diabetic. The mode of presentation is given in Table 1 and CT scan findings in Table 2. Two had leaking pseudocyst (one from each group (Fig. 1)) and one had a sterile pancreatico-duodenal groove abscess from (HDO group). The last patient with pancreatico-duodenal groove sterile abscess, a diabetic, developed prolonged fever after 3 months after a lateral pancreatico-jejunostomy; no cause was found and the patient failed to respond to 2 weeks of empirical antibiotics but did respond to antituberculosis therapy and improved (Flow chart 1). Overall, 96.92 % of the patients got pain relief in treatment with HDO and 68.11 % in the control group (*p* > 0.05) (Table 3). Pain relief was gradual and started only after 72 h, but it used to aggravate

Fig. 1 A leaking pseudocyst that did not respond to treatment in the HDO group

after meals for a week and then patients gradually became pain free. By the end of the 2nd week, none required any additional pain killers in the HDO group. Most of the complications like inflammatory mass and pseudocyst regressed very slowly. No time frame of the resolutions could be determined as there were many variables like the size of the cyst, single or multiple and duration of the cyst at the onset of medication, etc as well as variable follow-up. More so, the concentration was on the pain relief and recording of these data remain incomplete. No abnormality was found on haematological, biochemical reports in all cases. Endoscopy findings at the end of 1 year were normal.

Discussion

Omeprazole is the oldest and commonly prescribed PPI [14]. The standard dose is 20 mg twice a day for upper gastrointestinal symptomatology, where acid reduction is essential. Maximum dose is required in Zollinger-Ellison Syndrome (ZES). The mean initial maintenance dose in this setting is 60 mg QID with some exceptions. They require long-term treatment from 1 to 43 months has been used [15]. The acid reduction is better in divided doses of 60 mg every 12 h than a

Table 2 CT scan findings

Findings	A (controlled gp)	B (Omeprazole gp)	Total
Pseudocyst	47	49	96
Dilated main pancreatic duct with stones	45	43	88
Un dilated main pancreatic duct with calcification	15	19	34
Inflammatory head mass	12	11	23
Bleeding pseudocyst	00	01	01
Dilated biliary tree	4/1 ^a	5/2 ^a	11

^a Nine had dilated biliary tree with raised serum alkaline phosphatase and only three had raised bilirubin

Table 3 Comparison of the treatment groups on outcomes

	Group with omeprazole		Conventional pain management		<i>p</i> value
	<i>n</i>	%	n	%	
Pain relief					
14 days <i>n</i>	65		69		<0.05
Responders	63	96.92	47	68.1	
Non-responders	02	3.08	22	31.9	
Avg. analgesic doses day time	1.54		2.75		NS
Avg. analgesic doses night	0.12		0.88		<0.05
3 months	63	95.83	56	83.3	<0.05
Re-hospitalization within 1 year	xx		13		NS
1 year	62	95.83	59	93.7	
Weight Gain					
1 year <i>n</i>	62		59		<0.05
Weight gain	59	95.165	41	69.5	

single dose of 120 mg [16]. It is a safe drug and in an animal study of omeprazole toxicity, the oral dose of LD 50 value was above 4 G/Kg [17]. Omeprazole is now the drug of choice in patients with ZES and is safe for long-term treatment of up to 4 yr. with no evidence of hematologic, biochemical, or gastric toxicity [16]. It is primarily metabolized through the CYP2C19 enzyme, a member of the P450 mixed-function oxidases group [14]. Thus, Omeprazole toxicity appears to be oxidative and preventable with antioxidant therapy, including Vitamin C. Vitamin C may be a safe and efficacious addition to treatments requiring the use of proton pump inhibitors [18]. Thus the addition of vitamin C appeared appropriate in our study. The thinking process for adding vitamin C was to give some acidic pH in a state of gastric anacidity caused by omeprazole. High-dose (10 vs 1 g) vitamin C may also have therapeutic efficacy on acute pancreatitis. Potential mechanisms include promotion of antioxidation, blocking of lipid peroxidation and improvement of cellular immunity [19]. Many of the cases were acute-on-chronic pancreatitis and vitamin C is thought to have some immune actions, thus justifying its use in our patients. During strong acid inhibition, lower than recommended oral doses of pancreatic enzymes are therapeutically effective with respect to fat absorption and symptom reduction [20].

The present findings on the reduction of an inflammatory mass and the duct diameter are almost in the same proportion, but we have observed this after months during the repeated USG. This therapy also hastens pseudocyst resolution. Most likely all these processes are due to diffusion of amylase-rich fluid into the interstitium of the pancreas due to elevated intraductal pressure, and reduction of ductal pressure, in turn, reduced all these pancreatic complications. This is likely to be useful in deferring the date of elective surgery and CP with small duct disease. Most of the patients gain weight possibly because of improved intake of food, when the fear of pain after food goes and because of less acid deactivation of lipase and

other pancreatic enzymes with resultant better fat absorption [20]. We have observed a weight increase up to >20 kg in longer follow-up (Fig. 2). Weight gain is dependent on the control of the disease with improved available nutrition. All patients had enough money for food after stopping alcohol. Besides the gastrin-secretin feedback, there may be other modes of action of omeprazole on the pancreas currently not known. Upon extensive review of the literature, it was found that rabeprazole 20 mg a day reduces the pain in chronic pancreatitis faster than famotidine along with conventional treatments. MRI on a 7-day treatment was accompanied by a reduction of the pancreas size, the diameter of the main pancreatic duct and pancreatic edema [21]. This was a smaller study with limited follow-up. However, the present study is

Fig. 2 Images of a single patient showing weight gain after HDO therapy

the first of its kind demonstrating pain relief in CP. Our findings are comparable with a longer follow-up. Pain relief is significantly superior to conventional therapy (Table 3). All the cases with pseudocyst regressed gradually faster in HDO groups. But we are not sure of this finding as our data recording was inadequate. The inflammatory mass and the pseudocysts were not characterized well before and after the study as we were concentrating on the pain. The slower action of pain relief with the conventional group was due to elimination of the toxic agents like alcohol and smoking without any change of the ductal pressure. Most clinicians use some PPI/H2RA in the conservative therapy of CP. This group did not get any PPI so as to have better differentiation on the result.

One more option for pain in CP is octreotide, an analogue of sandostatin [22]. This longer-acting octreotide was confirmed to be a potent inhibitor of stimulated human exocrine pancreatic secretion [23, 24], thereby reducing pancreatic duct hypertension due to outflow obstruction and inhibiting pancreatic secretion thus reducing pain in CP [1]. It is the same mechanism as HDO. In a small study of only seven patients, it was concluded that octreotide may be reasonable in treating pain in CP [25]. No other proper study could be found during extensive search of literature.

The problem in using long-acting sandostatin is the parenteral therapy, requiring multiple injections, making it unsuitable for home therapy. Maintaining cold chain is difficult in temperate climate. The cost of the drug has reduced but still can be considered high for common patients of CP. This drug is a general depressant to the whole gastro-intestinal tract, reduces blood flow, causes atrophy of bowel wall, reduces the bile, insulin, glucagon, pancreatic polypeptide, gastric inhibitory polypeptide, gastrin as well as secretin [26]. The enzyme secretion, leading to pancreatic insufficiency, which is seen on its prolonged use in neuroendocrine tumour [27]. In contrast, HDO inhibit bicarbonate-rich ductular secretion, which constitute 80 % of total pancreatic juice keeping the enzyme-rich acinar secretion intact [7, 8]. It also inhibits intestinal secretion and prolongs bowel transit time and prevents gallbladder contraction, thus leading to poor absorption of nutrients including fat and exerts inhibitory effects on splanchnic hemodynamics [28]. Whereas, HDO causes no significant changes in the absorptive process except causing hypergastrinaemia [29] leading to negative feedback on secretin [8, 9] and that is the reason 96 % gain weight by the year end. In fact, secretin plays a key role in the regulatory mechanisms of exocrine pancreatic secretion [30].

This study is going to generate other studies in patients with pancreatic fistulas, pancreatic ascites/effusion, reducing the severity of acute pancreatitis and post-operative pancreatic anastomotic leak. Moreover, a drawback of the study is nonestimation of serum gastrin and secretin for correlation due to financial constrained. The additional issue is that the cause of pain is multifactorial [13] and is more subjective than

objective. It is also dependent of the pain tolerance of the individual, and not measuring any inflammatory markers is another drawback of this study. Being the first study of this kind, a double-blinding, multicentre randomized study estimating the gastrin-secretin level is needed for better ratification and higher weightage.

Conclusion

Pain relief with HDO (60 mg twice daily) in CP was found to be significantly better than the conventional therapy as early as 2 weeks [96.9 to 68.1 % ($p > 0.05$)]. Resolution of pseudocyst and inflammatory mass was faster in HDO. Most of the HDO patients gain weight (95 %) at 1 year. Additional studies are necessary using HDO for painful CP.

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Compliance with Ethical Standards

Conflict of Interest The author declares that there is no conflict of interest.

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