EDITORIAL

Pancreatic Extracts for Painful Chronic Pancreatitis: Micronutrient Antioxidant Therapy by Proxy

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Pancreatic extracts have found their way into clinical practice to treat painful chronic pancreatitis, despite consensus from analysis of randomized controlled trials (RCT) that there is no clear evidence of benefit [1-3].

Proponents argue that success depends upon the use of non-enteric coated material to ensure delivery of proteases into the duodenum as in two RCT [4, 5], compared to several unsuccessful RCT using enteric coated preparations that deliver the enzymes further downstream [1-3]. It is posited that intraduodenal delivery 'puts the pancreas to rest' by dampening the feedback loop that otherwise leads, via high circulating levels of cholecystokinin - pancreozymin (CCK), to pain from pancreatic ductal hypertension. Clinicians are informed that patients with small-duct disease and mild to moderately impaired pancreatic secretory capacity will benefit, whereas those with advanced disease / steatorrhea will not. A proton pump inhibitor is advised, to safeguard the extracts in transit through the stomach. Treatment is advocated for four weeks in the first instance, to be continued for six months in responders, and indefinitely should pain resurface upon attempted withdrawal of treatment [6].

Each aspect of the argument and advice is questionable. In the original successful RCT active treatment ameliorated pain within just a week [4]. The apical exocytosis apparatus in acinar cells is paralysed in a pancreatitis attack, and remains hindered thereafter in patients with chronic pancreatitis [7]; hence the gland needs to be coaxed into activity, not lulled into further inertia. There is debate as to whether stimulation or inhibition of pancreatic secretion results from intra-duodenal perfusion of pancreatic proteases [8]. The advice on gastric acid inhibitors speaks from hindsight, as none was used in either RCT [4, 5]. Apparently so too is the restriction to patients with small-duct disease, which seems odd in that their big complement of secretory parenchyma, relative to that in patients with

large-duct disease [9, 10], should ensure sufficient intra-duodenal protease to maintain physiological levels of CCK release.

A more plausible explanation might be that pancreatic enzymes in non-enteric coated formulas are irrelevant, and that what matters is the fortuitous delivery of other antinociceptive substances. Micronutrients with antioxidant potential are the prime candidate for several reasons. (i) There is incontrovertible evidence that electrophilic/oxidative stress is tied in with disease pathogenesis [7, 11]. (ii) The pancreas actively assimilates selenium, zinc, and methionine. (iii) A prescription designed to provide selenium, methionine, and vitamin C - based on studies of habitual diets [12] - impacted on the positive outcome of three meta-analyses of RCT [13-15], even though each included a seriously flawed report [16]. The pain-ameliorating effect of these micronutrients likely reflects provision of methyl and thiol (principally glutathione) moieties to facilitate apical exocytosis [7, 11], coupled with stabilization of mast cells, products of which fuel the disastrous upward spiral from peripheral to central pain sensitization [16]. (iv) A study of patients with mainly alcoholic disease and very low blood levels of vitamin C showed that the spontaneous production of reactive oxygen species and concentration of lipid peroxides in peripheral blood varied inversely with disease degree as gauged by pancreatograms: 12 months' treatment with vitamins C and E resulted in marked reduction of pain, the concurrent decrement in free radical activity significant in subgroups with minimal or moderate-change-pancreatitis but not in the severe-change group although it displayed the greatest increment in plasma ascorbic acid. In other words, no improvement can be expected when there is no secretory parenchyma for free radical attack or its correction by antioxidant assimilation [17].

Selenium and other trace metals that contribute to the antioxidant repertoire of tissues [18-21], should survive procedures to extract pancreatic enzymes from porcine glands, and the sulphur amino acids might, whereas at risk of denaturation are the vitamin antioxidants - including choline which interacts with methionine to guarantee pancreatic integrity [11]. Attempts to settle the question - upon shrinkage of the productive pancreatic laboratory at Manchester Royal Infirmary - were unfruitful (requests to IS Young at Belfast in 2010, PM Garg at Delhi in 2013).

Table 1. Metal antioxidants in pancreatic extracts.

Name	(n) Selenium µg/g	(n) Zinc µg/g	(n) Copper µg/g
'Lyopase'	(3) 0.42	(2) 44	(2) 1.1
'Cotazym Forte'	(5) 0.53	(6) 49	(7) 1.7
Pancreatic grain	(12) 1.46	(8) 119	(8) 5.5
Pancreatic capsule	(6) 0.29	(6) 34	(6) 1.2
'Prolipase'	(6) 0.50		
'Creon'	(6) 0.85		
'Creon granules'	(4) 0.53		
'Creon forte'	(4) 1.40		
'Panzytrat'	(7) 1.30		

The top 4 entries are from ref [22], where n is the number of samples analysed. The next 5 entries are from ref [23] wherein all preparations were enteric coated, and n is the number of capsules analysed in duplicate: only selenium was measured. Entries in inverted commas indicate commercially registered products.

However, repeated interrogation of the literature has unearthed two papers, both in the context of cystic fibrosis, that support the principle.

The first paper, from Holland in 1992 [22], documented the presence of selenium, zinc and copper in four pancreatic enzyme preparations among which 'pancreatic grain' - probably non-enteric coated - scored highest (Table 1). The second report from Switzerland in 1998 went further [23]. Analysis of five enteric-coated preparations confirmed the presence of selenium (Table 1). More importantly, a longitudinal study showed that, as a result of increased selenium intake from increasing doses of pancreatic enzymes to control steatorrhea, plasma selenium and selenium-glutathione peroxidase activity increased significantly and in parallel, peaking by the eighth month but evident from the first sampling point at four months. The authors calculated that extracts provided the young patients with a selenium supplement amounting to 50% or higher of the recommended dietary allowance of 1µg/kg/day.

A subnormal concentration of selenium in serum / plasma has been reported in patients with chronic pancreatitis, irrespective of geography [11]; in a study from the UK, the lowest values were in patients with painful disease[24], in contrast to relatively high values in patients with painless disease in south India [25]. A subnormal level of zinc has been noted in plasma or erythrocytes of patients with the disease [26-28]. The information on copper is dichotomous: pancreatic acinar cells have virtually no copper-superoxide dismutase [11], but an increase in serum copper as caeruloplasmin is recorded in patients [26, 29] and does not represent an acute phase reaction [29]. Like selenium, zinc stabilizes mast cells [30].

Selenium is maximally absorbed from the duodenum [21]. The increment in circulating levels is more rapid when the element is delivered in organic form, whereupon an increase in plasma selenium can be expected in 1-2 weeks of supplementation at doses of 50-200 µg / day in selenium-deficient individuals [23]. Almost certainly, selenium in pancreatic extracts is in organic form, as selenomethionine, selenodiglutathione, selenocysteine and other compounds [21] - which means increased availability of sulphur amino acids that are critical for pancreatic viability. Unfortunately however, it is impossible to estimate selenium intake in the two relevant RCT of pancreatic extracts in chronic pancreatitis because neither the weight nor enzyme composition was specified of 'Pankreon' granules, 7.5 ml five times per day [4], or 'Ilozyme', six tablets four times per day [5] which has been interpreted as yielding 720,000 USP of protease daily [3]. Provision of the extracts as a liquid in the Swedish study might explain the rapidity of pain relief, if from absorbed selenium, especially in that Scandinavia is a low selenium area [22]: however, this deduction is predicated on the assumption that heat treatment of granules to destroy pancreatic enzymes in the placebo somehow curbed selenium absorption too [4]. The western states of the USA constitute a high-selenium area. It is unclear if this extends to Florida in the east, from where the second RCT originated [5]. A gradual increase over time in assimilation of selenium, zinc, copper, and sulphur amino acids could rationalize the reported improvement in life quality and pain in two long term observational studies of pancreatic extract therapy - coated material in one, unspecified in the other [3]. Of note, the co-prescription of a gastric proton pump inhibitor would enhance antioxidant activity in many ways [31].

In summary, the long-term administration of pancreatic extracts to patients with painful chronic pancreatitis can be regarded as antioxidant therapy by proxy, irrespective of whether an additional benefit accrues by virtue of contained proteases. A comprehensive analysis of representative enteric coated and non-enteric coated formulas for micronutrient antioxidants is needed urgently.

Conflicting Interest

The Author declares to have no conflict of interest

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