ANTIOXIDANT THERAPY FOR PANCREATITIS
BIO-ANTOX INFORMATION SUMMARY

February 1995

During the last decade the Pancreato-Biliary Service (PBS) at the Manchester Royal Infirmary (MRI), has pioneered the antioxidant therapy of pancreatitis. Placebo-controlled trials in patients with recurrent non-gallstone pancreatitis revealed a deficiency of several antioxidants which was rectified by appropriate antioxidant supplementation leading to clinical benefit. Discussions, between the PBS and Pharma Nord UK, led to the drug formulation known as Bio-Antox. This preparation allows substantial reduction in daily tablet intake by combining the essential amino acid methionine, antioxidant vitamins and trace element selenium.

Detailed background evidence, to support the use of antioxidants in pancreatitis is given in the summary which follows. It is stressed that treatment should be part and parcel of a shared care protocol, so that blood antioxidant and free radical marker profiles can be checked at intervals to ensure compliance and adequacy of dosage.

PROPRIETARY NAME: BIO-ANTOX

MANUFACTURER: Manufactured in Denmark by Pharm Nord and distributed by
Pharma Nord (UK) Ltd
Spital Hall
Mitford
Morpeth
NE16 3PN

PRESENTATION Tablets (150 in a box) typically containing:

selenium (organic)	75 ug
methionine	400 mg
beta-carotene	3 mg
vitamin C	150 mg
vitamin E	47 ug

LICENSED INDICATIONS: None

CURRENT STATUS: Pharma-Nord have given Pancreato-Biliary Consultants an undertaking that Bio-Antox, the formulation of which is based entirely on the work of the Manchester group, will not be available "over-the-counter". The same company markets a range of food supplements, one of which is called Bio-Antioxidant, but this should not be confused with Bio-Antox. Both contain micronutrients and vitamins but the formulations of each markedly differ.

DOSAGE OF Bio-Antox IN PANCREATITIS

The usual dose is four tablets daily, adjusted at intervals according to the results of blood and urine analyses. For most patients the initial dosage is required for ten weeks and a few will require supplementary methionine (250 mg four times daily). Thereafter a proportion will continue to need a similar dose, with or without methionine, for a further 10 weeks with a 25 per cent reduction in dosage for the next six months or so. During the following six months 50per cent of the initial dose is given, reducing to 25 per cent as a maintenance dose indefinitely thereafter. Ordinarily, blood antioxidant and free radical marker profiles are checked at ten weeks and 20 weeks, then six months later and then annually via

the MRI PBS. A share-care protocol prepared jointly by the PBS team and MRI pharmacists is available on request.

DEVELOPMENT OF ANTIOXIDANT THERAPY

Background:

There is increasing evidence that habitually poor diets render body organs vulnerable to oxidative stress, and hence tissue injury, when free radical load exceeds antioxidant defence capability. In general terms this load may derive from such dissimilar sources as ultraviolet light, substance abuse (for example alcohol or cigarettes), and, above all, environmental pollutants.

The notion that antioxidant supplementation might be protective to a population by increasing its defence against pro-oxidant factors, is gaining ground, as witnessed by a plethora of studies in the field of atherosclerosis. The therapeutic corollary was exploited by the Manchester group almost a decade ago and has been validated by placebo-controlled trials, while sporadic reports from other groups are beginning to offer independent endorsement of this treatment.

Evidence of oxidative stress in recurrent non-gallstone pancreatitis

The MRI workers have documented increased free radical activity in serum and duodenal secretions collected in the asymptomatic period between disease attacks in Manchester patients. They have gone on to show that this is due to a combination of factors, ie:

regular exposure to inducers of cytochrome P450 mono-oxygenase enzymes which metabolize exogenous lipophilic substrates (currently referred to as xenobiotics).

concurrent exposure to a volatile chemical, usually in the occupational environment, which undergoes biactivation by induced pancreatic cytochrome P450 enzymes.

most significantly, an absolute or relative lack of antioxidants, especially vitamin C, methionine and selenium because of poor dietary habits.

The situation is not unlike that of paracetamol-induced liver toxicity where the damage is due to a relative metabolite generated by hepatic cytochrome P450, especially if this enzyme has been previously induced by exposure to alcohol or anticonvulsant drugs; treatment is based on increasing tissue gluthione levels by means of intravenous N-acetycysteine or oral methionine.

Chronic pancreatitis, with its propensity to early development of intraductal calculi and an aggressive course towards premature death from malnutrition, diabetes or superimposed pancreatic cancer, is endemic among underprivileged communities as in Madras, South India, or among black South Africans in Soweto. The Manchester team, therefore, engaged in collaborative studies with workers in these areas. The three same component causes for chronic pancreatitis were identified as with patients in Manchester. The very poor viability of vitamin C in outwardly healthy controls in these areas was underlined, as was the lower selenium status in Sowetan controls and the deficiency of beta-carotene in those at Madras.

Controlled clinical studies of antioxidant supplements are now underway in those areas but the scope for community prophylaxis, through a daily tablet containing the deficient antioxidant, should be especially rewarding.

Use of antioxidants in recurrent non-gallstone pancreatitis

Since antioxidant treatment for chronic disease is unprecedented in clinical medicine, progress had to be made by trial and error. The resulting anecdotal experiences - in a child with grossly distorted pancreatic ducts and calculi, an elderly lady with small duct disease and numerous attacks and five young men with non-alcoholic disease - have been reported in full. They formed the basis for the antioxidant combination that was chosen for testing in the first of three-consecutive double-blind, crossover, placebo-controlled studies. Each was of 20 weeks duration.

Of 28 patients with recurrent pancreatitis of diverse aetiology, 20 adhered to the full protocol. There were 15 with chronic pancreatitis and 5 with recurrent acute disease. Active treatment consisted of six tablets daily of an antioxidant preparation providing a total daily intake of organic selenium (600 ug), beta-carotene (the non-toxic precursor of vitamin A) (900 i.u.), vitamin C (540mg) and vitamin E (900 i.u.) as well as eight tablets of methionine(a glutathione precursor) delivering a total daily dose of 2g. Analysis of attack frequency, background pain (using visual analogue scores) and pain score diaries collectively indicated a significant advantage in favour of active treatment over placebo. When blood and urine samples, taken during the course of the trial, were subsequently analysed, it was evident that oxidative stress had been substantially corrected by the active treatment. The next two placebo-controlled trials were designed to identify which of the many components in the first trial might be most important in ameliorating symptoms and controlling oxidative stress; the combination of ascorbate and methionine was identified as pivotal. Contemporaneous studies from other centres have indicated close working links between these antioxidants in the removal of both reactive oxygen species and toxic metabolites derived from xenobiotics.

Surgeons of the pancreato-biliary team went on to audit outcome in 103 consecutive patients, with painful chronic pancreatitis of diverse aetiology, over a nine-year period from 1985.

Patients were excluded who were addicted to narcotic analgesics at the time of referral, who had end-stage pancreatitis (characterised more by chronic discomfort from steatorrhea and diabetes than by pain), or who had pain more likely to represent concurrent disease such as peptic ulcer or costochondritis. Those with suspected pancreatic cancer were also excluded. In 42 per cent of the patient’s alcoholism was an aetiological factor, miscellaneous factors may have contributed to the disease in 28 per cent and the remainder were idiopathic. Using the successful antioxidant regimen identified from the placebo-controlled trials, combined with periodic dose adjustments through biochemical monitoring of free radical markers and antioxidants, it was found that 73 per cent of patients became pain free and fully rehabilitated while 26 per cent reported substantial pain relief. Surgery was required in only seven patients, six of whom required pseudocyst drainage and one underwent cholecystectomy. This outcome is vastly different from that with the usual surgical approach to management. The attendant mortality, social upheaval and expense of surgery is difficult to justify when pancreatic pain is seldom completely eliminated and return to full-time employment is prevented.

Adverse effects and precautions

Long-term observations have not shown significant adverse effects in a clinical experience of some 500 patients. One subject developed symptoms of schizophrenia two years after starting on a dose of 4g methionine per day in conjunction with other antioxidants.

In the light of a published review which had exonerated methionine from side-effects, unless given to patients with chronic schizophrenia, it was of interest to discover that the patient's mother had committed suicide against a background of schizophrenia and that two maternal aunts had suffered chronic depressive illness. There has been no such problem at MRI before or since.

Hypercarotenaemia has been a predictable biochemical outcome in patients treated with Bio-Antox because the of extremely high bio availability of beta-carote from this formulation compared to the commercial "over

the counter" preparations with which the clinical trials were done, and which were used at the MRI until Bio-Antox became available.

Hypercarotenaemia has no clinical implications, except for possible cosmetic embarrassment, and the preparation has now undergone reformulation to avoid this. Careful monitoring is advisable in patients with organic brain syndromes, haemachromatosis, renal failure andglucose-6-phosphate-dehydrogenase deficiency.

For further information, please contact either of the following:

Dr FN Leach,
The Regional Drug Information Service
St Mary's Hospital
Hathersage Road
Manchester
M13 OJH
0161 225 2063
0161 276 6270

Dr JM Braganza
The Pancreato-Biliary Service
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL
0161 276 4168
0161 273 4884

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