Combined antioxidant therapy reduces pain and improves quality of life in chronic pancratitis.

Kirk, G. R., White, J., McKie, L., Stevenson, M., Young, I., Clements, W. D., & Rowlands, B. J. (2006). Combined antioxidant therapy reduces pain and improves quality of life in chronic pancratitis. *J Gastrointest Surg.*, *10*, 499-503.

Published in:
J Gastrointest Surg.

Combined Antioxidant Therapy Reduces Pain and Improves Quality of Life in Chronic Pancreatitis

Gareth R. Kirk, M.D., F.R.C.S., Jonathan S. White, B.Med.Sci.(Hons), Ph.D., F.R.C.S. (Gen Surg), Lloyd McKie, M.D., F.R.C.S., Mike Stevenson, B.Sc. (Hons), F.S.S., CDip.A.F., P.G.C.H.E.T., Ian Young, B.Sc., M.D., F.R.C.P., F.R.C.Path, W.D. Barry Clements, B.Sc., M.D., F.R.C.S., Brian J. Rowlands, M.D., F.R.C.S., F.A.C.S.

Patients with chronic pancreatitis (CP) typically suffer intractable abdominal pain that is resistant to most analgesic strategies. Recent research indicates that the pain of CP may be in part due to oxygen free radical induced pancreatic damage. Using a randomized, double-blind, placebo-controlled crossover trial, we evaluated the efficacy of a combined antioxidant preparation in the management of CP. Patients with confirmed chronic pancreatitis (N = 36) were randomized to receive treatment with either Antox, which contains the antioxidants selenium, betacarotene, L-methionine, and vitamins C and E, or placebo for 10 weeks. Each group of patients then switched to receive the alternative treatment for a further 10 weeks. Markers of antioxidant status were measured by blood sampling, whereas quality of life and pain were assessed using the SF-36 questionnaire. Nineteen patients completed the full 20 weeks of treatment. Treatment with Antox was associated with significant improvements in quality of life in terms of pain (+17 antioxidant vs. −7 placebo), physical (+9 vs. −3) and social functioning (+8 vs. −7), and general health perception (+10 vs. −3). We conclude that treatment with antioxidants may improve quality of life and reduce pain in patients suffering from chronic pancreatitis. (J GASTROINTEST SURG 2006;10:499–503)

KEY WORDS: Antioxidants, chronic pancreatitis, pain, quality of life

Chronic pancreatitis (CP) is a progressive inflammatory disorder that is characterized by recurrent episodes of severe abdominal pain. Affected patients typically suffer years of disabling pain, and conventional therapeutic interventions are often unable to offer satisfactory analgesia. The majority of cases in Europe and the United Kingdom are associated with alcohol abuse; these patients often become dependent on opiate analgesics and are usually unable to remain in employment. Relationships may also become difficult to maintain, and patients often become physically and socially isolated.

Recent literature suggests that heightened free radical activity and oxidative stress may be important in the pathogenesis of chronic pancreatitis.[1–3] In normal metabolism, exogenous nonbiologic chemicals (xenobiotics) are metabolized via the mitochondrial enzyme cytochrome P450 (cP450) pathway. During this process, reactive oxygen free radicals are produced that are capable of causing cell damage by peroxidation of lipids and lipoproteins in the cell membrane. Endogenous antioxidants, in particular, products of methionine metabolism such as glutathione are important in preventing cellular damage caused by these free radical species.

Induction of the cP450 pathway by chronic ingestion of alcohol or anticonvulsants can increase the yield of reactive oxygen species released by metabolism of xenobiotic materials. Combined with a deficiency in antioxidant defense mechanisms, increased levels of oxygen free radicals may be capable of impairing normal pancreatic structure and function.

In the last decade, evidence has emerged which suggests that levels of oxidants and antioxidants are altered in patients with chronic pancreatitis. In

Pancreatology Section; American Gastroenterology Association, Presented at the American Gastroenterological Association, Atlanta, Georgia, May 20–23, 2001.

From the Departments of Surgery (G.R.K., J.S.W., L.M., W.D.B.C.), Medical Statistics (M.S.), and Medicine (I.Y.), Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom; and Department of Surgery (B.J.R.), University of Nottingham, Nottingham, United Kingdom. Reprint requests: Jonathan S. White, Department of Surgical Oncology, Tom Baker Cancer Centre, 1331 29 St NW, Calgary, AB T2N 4N2, Canada. e-mail: calgarysurgeon@mac.com

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2005.08.035

1990, Guyan et al.[2] demonstrated increased levels of oxygen free radicals in the serum and pancreatic secretions of patients with the condition. Subsequent research has identified three main factors that are thought to increase oxidative stress in patients with chronic pancreatitis:[4–8] (a) chronic induction of the cP450 enzyme system, with increased levels of the products of lipid peroxidation;[9] (b) increased exposure to exogenous chemicals metabolized by the cP450 system;[10] and (c) a relative deficiency of antioxidant substances such as carotenoids, vitamins C and E, methionine, and selenium, which are essential to maintain adequate levels of glutathione.[11,12]

These findings suggest that antioxidant therapy in patients with chronic pancreatitis might reduce levels of reactive oxygen species, thereby reducing cellular damage and alleviating symptoms of pain. Initial reports of trials of antioxidant therapy were limited to the use of single antioxidants in small numbers of patients,[13,14] but more recent studies have examined the administration of combinations of antioxidants in patients with chronic pancreatitis.[15,16] These studies suggested that vitamin C and methionine were effective in reducing background pain and preventing further attacks of chronic pancreatitis, but the authors noted problems with delivery and obtaining satisfactory bioavailability of the administered antioxidants.[17] There were also problems with compliance, as treatment involved taking as many as 14 tablets per day. A combined antioxidant preparation (Antox) has since been developed that contains selenium, vitamins C, E, betacarotene, and methionine. This preparation is based on those used in previous studies[17,18] and has been shown to possess improved bioavailability compared to individually administered preparations. This study examined its efficacy and used quality of life as an outcome measure of relief of symptoms in patients with chronic pancreatitis.

METHODS

Patients appearing at the Department of Surgery, Royal Victoria Hospital between 1996 and 1999 with abdominal pain suspected to be due to chronic pancreatitis were considered for inclusion in this study. Three criteria were used to confirm the presence of chronic pancreatitis in these patients: (1) radiological abnormality of the pancreas consistent with CP (e.g., calcification), (2) pancreatic duct abnormality at endoscopic retrograde cholangiopancreatography, and (3) evidence of exocrinepancreatic insufficiency on para-aminobenzoic acid testing.

Patients with chronic abdominal pain and at least one of these criteria were invited to enter the study. Patients with gallstones and those requiring surgical intervention were excluded. Those under 16 and over 75 years of age were also excluded. In total, 36 patients (23 men and 13 women) were recruited. Ethical approval was obtained from the local Ethics Committee.

The study was designed as a double blind, placebo-controlled, crossover trial. The trial period was 20 weeks; treatment was allocated using a randomized block design and started with either Antox or placebo. After an initial 10 weeks of treatment, patients changed to the alternative treatment for a further 10 weeks. By the inherent nature of the recruitment policy, many of the patients had alcohol and/or drug dependence problems, and their level of compliance to the protocol was expected to be poor. In an effort to improve compliance and reduce drop-out rates, no "washout period" was incorporated into the study.

The constituents of each Antox tablet were as follows: 75 μg of selenium, 3 mg betacarotene, 47 mg d-alpha-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C), and 400 mg methionone.

This formulation was based on the combination of antioxidants employed in previous studies[16,17] but utilizing tablets with a higher concentration of active ingredients. Placebo tablets were identical in appearance to Antox tablets but lacked any antioxidant components. Patients were instructed to take one tablet four times daily with food and to complete a daily pain diary. They were also asked to record adverse reactions and any additional analgesic requirements. Patients were interviewed and assessed at the start of the study and at 5, 10, 15, and 20 weeks thereafter. Venous blood sampling was performed at each attendance to measure plasma levels of the administered antioxidants selenium, betacarotene, tocopherol, and ascorbic acid. As an estimate of endogenous antioxidant status, retinol, α-carotene, and lycopene were measured. Four other indicators of antioxidant capacity were also estimated: malondialdehyde, glutathione peroxidase, serum total antioxidant capacity, and ferrous oxidation in xylenol orange.

The pain diaries used three visual analogue scales to assess pain intensity, pain relief, and mood. Patients were asked to fill in each of these scales on a daily basis. The impact of treatment on general health and quality of life was also assessed using the short form 36 (SF-36) questionnaire.[19] This is a generic quality of life instrument, which has been fully validated[20,21] and shown to be reliable in a wide range of diseases.[21,22] It comprises 36 questions which address physical, emotional, and social functioning, mental health, energy, pain, and health

perception. Subjects receive a score of between −100 to +100 in each of nine dimensions. Each questionnaire was administered at personal interview by the investigator at the start of the study and again 10 and 20 weeks thereafter. The change in dimensional scores was calculated over the treatment period, with each subject acting as his/her own control. The mean change in SF-36 score was determined for each treatment period. Data were analyzed using a one-tailed Student's *t* test with the alternative hypothesis (antioxidant greater than placebo). Statistical significance was accepted at the 5% level.

RESULTS

Nineteen subjects (13 men and 6 women) completed both periods of treatment. Eight of these were from the group given placebo treatment first and 11 were from those given Antox first. The other 17 patients either decided to withdraw from the study or failed to attend for follow-up. Two patients complained of nausea and one of an unpleasant taste during treatment with Antox. This was probably due to the presence of methionine, which is a sulfur-containing amino acid. No side effects were reported during treatment with the placebo.

Analysis of data from visual analogue scales in the pain diaries showed that their completion was inconsistent and erratic. There was also evidence that data had been entered retrospectively rather than on a daily basis. Because of these factors, further analysis on data from the pain diaries was not performed.

Analysis of data from the SF-36 questionnaire showed that treatment with Antox was associated with a significant improvement in quality of life in six of the nine dimensions when compared with the placebo (Fig. 1). There was a reduction in pain, and an improvement in physical and social functioning, and in health perception. No differences were detected in emotional functioning, energy, or mental health. There was no significant difference in quality of life between those patients who had received Antox in the first or second 10-week period.

Treatment with Antox was also associated with a significant increase in plasma levels of selenium, vitamin C, vitamin E, and betacarotene compared with placebo (Table 1). No difference was detected in serum levels of lycopene, retinol, α-carotene, nor in total serum antioxidant capacity. Analysis of data from patients treated with Antox in the first treatment period suggested that the serum levels of water-soluble antioxidants such as vitamins C and selenium tended to return to pretreatment levels within 5 weeks, whereas those of fat-soluble vitamins such as vitamin E tended to remain slightly elevated until the end of the study.

DISCUSSION

Long-term pain control in chronic pancreatitis can be difficult to achieve.[23–25] Affected patients

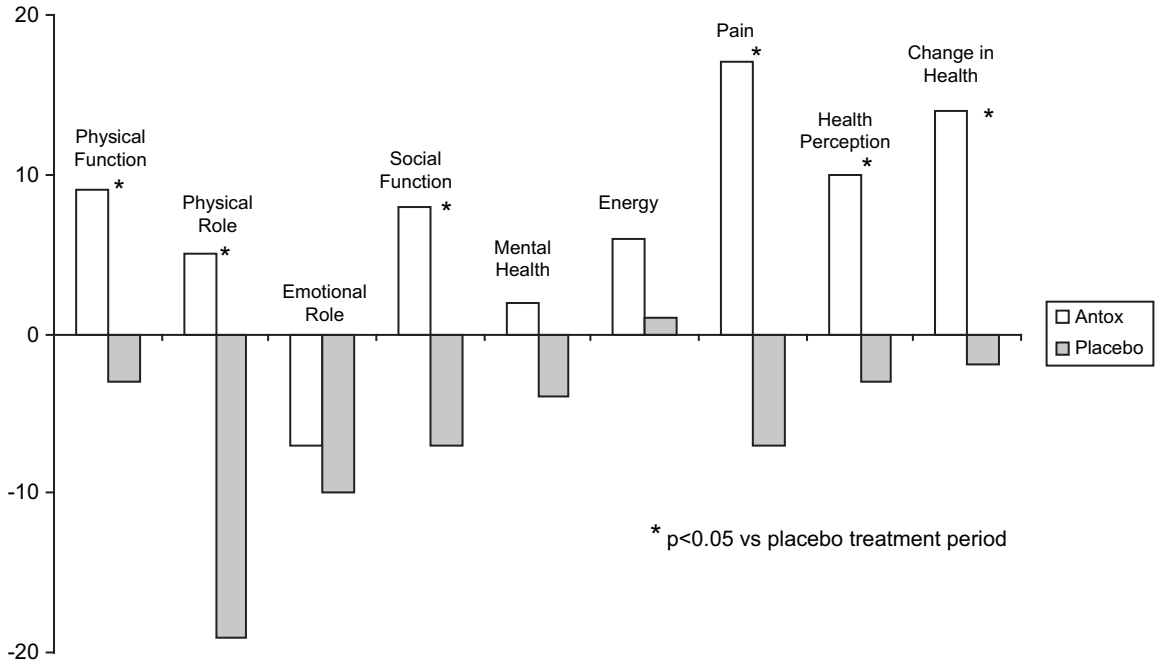

Fig. 1. Change in SF-36 quality of life dimensional scores after treatment period (Antox vs. placebo).

Table 1. Mean serum concentration of various antioxidants after 10 weeks of treatment

	Antox	Placebo
Vitamin C (mmol/L)	25.7 ± 7.1*	17.94 ± 5.4
Selenium (mmol/L)	1.43 ± 0.11*	1.03 ± 0.07
Retinol	2.03 ± 0.19	1.90 ± 0.22
Tocopherol	40.7 ± 5.3*	30.0 ± 2.2
Lycopene	0.070 ± 0.012	0.084 ± 0.021
α carotene	0.013 ± 0.003	0.018 ± 0.003
Betacarotene	0.53 ± 0.14*	0.23 ± 0.05
MDA (μM)	2.60 ± 0.45	1.87 ± 0.25
TAC (mmol/L)	1.4 ± 0.02	1.39 ± 0.02
FOX 1 (μM)	3.24 ± 0.48	2.55 ± 0.335
GPX (Iu)	300 ± 19	293 ± 15

FOX 1 = ferrous oxidation in xylenol orange; GPX = glutathione peroxidase; MDA = malondialdehyde; TAC = serum total antioxidant capacity.
*$P < 0.05$ vs. placebo.

typically require repeated hospital admissions for pain relief and often become dependent on opiate analgesia. A multidisciplinary approach to their management is required, with appropriate dietary and lifestyle modification. Diagnostic differential nerve blockade can help identify the visceral pain of CP and recognize those who may benefit from celiac nerve blockade. Thoracoscopic splanchnicectomy is usually reserved for those with intractable symptoms.

Surgery for chronic pancreatitis is still widely practiced, and a decision to proceed is largely based on pancreatic duct morphology. Typical procedures involve resection of all or part of the pancreas, or decompression of the pancreatic duct. Although these procedures have been associated with pain relief in the immediate postoperative period, many patients report a recurrence of pain in the longer term.[26] Pancreatic surgery is also not without risk, and carries a significant perioperative morbidity and mortality.[27] Total pancreatectomy results in endocrine and exocrine insufficiency. Although many of the symptoms of exocrine dysfunction can be controlled, patients often develop brittle diabetes mellitus, which in itself has significant long-term morbidity and mortality. For these reasons, surgery for chronic pancreatitis has fallen from favor in many centers.

Recent research has implicated oxidative stress as a factor in the causation of chronic pancreatitis and suggested that antioxidant therapy may reduce pancreatic damage and improve symptoms in this condition. The utilization of this therapeutic strategy would avoid the risks and complications associated with pancreatic surgery and would also have the advantage of preserving remaining pancreatic function.

The study presented here examined the effects of antioxidant treatment under controlled conditions for the relief of symptoms in chronic pancreatitis. It is the first such study to show a significant improvement in quality of life and reduction in pain levels associated with the combined antioxidant preparation Antox in patients with chronic pancreatitis.

Only 19 of the 36 patients recruited (53%) completed the entire study period. The remainder either withdrew or failed to attend for follow-up. Such a high dropout rate had been anticipated in this group of patients due to the length of the study period, poor patient motivation, and in some cases, ongoing problems with alcohol dependence. The study was designed as a crossover trial without a washout period in an attempt to reduce the length of the study and to limit the dropout rate further. In those patients who did complete the trial, compliance was good and was confirmed by serum estimation of the various antioxidants (Table 1). The incidence of side effects was also low, with only two patients reporting nausea while undergoing the antioxidant treatment. There is some evidence that selenium may accumulate in the presence of renal failure, but no toxicity was observed in the population studied. There was some evidence that serum levels of the fat-soluble vitamins remained elevated for a short time after switching from antioxidant treatment to placebo, but levels were noted to return to baseline by the end of the treatment period.

Data in the pain diaries were poorly recorded and were often incomplete. We quickly learned that this information was of limited value, so the pain diaries were abandoned and pain was assessed using the SF-36 questionnaire only. This questionnaire was also used to compare subjective changes in the quality of life during the two treatment periods of the study. Eight of the nine dimensions of the SF-36 analyzed were found to have improved in the antioxidant treatment period, and changes in six of these dimensions were confirmed as statistically significant (Fig. 1). The two most striking improvements were observed in pain (+17 antioxidant vs. −7 placebo) and physical functioning (+9 antioxidant vs. −3 placebo). There were also significant benefits observed in physical role (+5 vs. −19), social functioning (+8 vs. −7), health perception (+10 vs. −3), and overall change in health (+14 vs. −2). Despite improvement, remaining changes in mental health (+2 vs. −4) and energy level (+6 vs. +1) did not reach statistical significance.

With no washout period, one potential source of error in our study may have been prolonged elevation of fat-soluble antioxidants after stopping treatment. Because the quality of life score reached at the end

of the first period acted as the baseline for the second, bias could have been introduced and could have affected whether a patient's score changed. Taking this into account, and with baseline adjustments, statistical analyses were, as expected, more conservative but still statistically significant in the same six modalities where a positive result had been observed.

These findings confirm those of previous studies that investigated the effects of individual antioxidants and demonstrated a reduction in pain levels and a decrease in the requirement for surgical intervention.[15–18,24] The improved pain scores demonstrated by this study suggest that antioxidant therapy should be considered as a means of pain relief in patients with chronic pancreatitis and may be of use as an adjunct, particularly where other pain-relieving strategies have failed.

The data from this short study strongly show that the effects of antioxidant therapy are not only limited to pain relief, but are also capable of improving several aspects in the quality of life of patients with chronic pancreatitis. These findings indicate that a longer period of treatment with a combined antioxidant preparation may prove effective in improving the day-to-day function of patients with chronic pancreatitis, as well reducing their pain. A larger and longer term intervention trial of antioxidant therapy in chronic pancreatitis is now required to confirm these findings and to establish the role of this treatment in the management of this disabling condition.

We thank Karen Clements and Moyra Mills of SRN Royal Victoria Hospital, Belfast for their help with this study.

REFERENCES

1. Basso D, Panozzo MP, Fabris C, et al. Oxygen derived free radicals in patients with chronic pancreatic and other digestive diseases. J Clin Pathol 1990;43:403–405.
2. Guyan PM, Uden S, Braganza JM. Heightened free radical activity in pancreatitis. Free Radic Biol Med 1990;8:347–354.
3. Schoenberg MH, Birk D, Beger HG. Oxidative stress in acute and chronic pancreatitis. Am J Clin Nutr 1995;62 (6 Suppl):1306S–1314S.
4. Tsai K, Wang SS, Chen TS, et al. Oxidative stress: An important phenomenon with pathogenetic significance in the progression of acute pancreatitis. Gut 1998;42: 850–855.
5. Szuster-Ciesielska A, Daniluk J, Kandefer-Szerszen M. Oxidative stress in blood of patients with alcohol-related pancreatitis. Pancreas 2001;22:261–266.
6. Sweiry JH, Mann GE. Role of oxidative stress in the pathogenesis of acute pancreatitis. Scand J Gastroenterol Suppl 1996;219:10–15.
7. Salim AS. Role of oxygen-derived free radical scavengers in the treatment of recurrent pain produced by chronic pancreatitis. A new approach. Arch Surg 1991;126:1109–1114.
8. Braganza JM. Pancreatic disease: A casualty of hepatic "detoxification"? Lancet 1983 29;2:1000–1003.
9. Acheson DW, Hunt LP, Rose P, Houston JB, Braganza JM. Factors contributing to the accelerated clearance of theophylline and antipyrine in adults with exocrine pancreatic disease. Clin Sci (Lond) 1989;76:377–385.
10. McNamee R, Braganza JM, Hogg J, Leck I, Rose P, Cherry NM. Occupational exposure to hydrocarbons and chronic pancreatitis: A case-referent study. Occup Environ Med 1994;51:631–637.
11. Rose P, Fraine E, Hunt LP, Acheson DW, Braganza JM. Dietary antioxidants and chronic pancreatitis. Hum Nutr Clin Nutr 1986;40:151–164.
12. Uden S, Acheson DW, Reeves J, et al. Antioxidants, enzyme induction, and chronic pancreatitis: A reappraisal following studies in patients on anticonvulsants. Eur J Clin Nutr 1988;42:561–569.
13. Braganza JM, Jeffrey IJ, Foster J, McCloy RF. Recalcitrant pancreatitis: Eventual control by antioxidants. Pancreas 1987;2:489–494.
14. Braganza JM, Thomas A, Robinson A. Antioxidants to treat chronic pancreatitis in childhood? Case report and possible implications for pathogenesis. Int J Pancreatol 1988;(3): 209–216.
15. Uden S, Bilton D, Nathan L, Hunt LP, Main C, Braganza JM. Antioxidant therapy for recurrent pancreatitis: Placebo-controlled trial. Aliment Pharmacol Ther 1990;4: 357–371.
16. Uden S, Schofield D, Miller PF, Day JP, Bottiglier T, Braganza JM. Antioxidant therapy for recurrent pancreatitis: Biochemical profiles in a placebo-controlled trial. Aliment Pharmacol Ther 1992;6:229–240.
17. McCloy R. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. Digestion 1998;59(Suppl 4):36–48.
18. Braganza JM. The pathogenesis of chronic pancreatitis. QJM 1996;89:243–250.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992;30:473–483.
20. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–263.
21. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care 1988;26:724–735.
22. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40–66.
23. Andren-Sandberg A. Pain relief in pancreatic disease. Br J Surg 1997;84:1041–1042.
24. Moossa AR. Surgical treatment of chronic pancreatitis: An overview. Br J Surg 1987;74:661–667.
25. Trapnell JE. Chronic relapsing pancreatitis: A review of 64 cases. Br J Surg 1979;66:471–475.
26. Huang JJ, Yeo CJ, Sohn TA, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000; 231:890–898.
27. Sohn TA, Campbell KA, Pitt HA, et al. Quality of life and long-term survival after surgery for chronic pancreatitis. J GASTROINTEST SURG 2000;4:355–364.