Long-term outcome of patients with chronic pancreatitis treated with micronutrient antioxidant therapy

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BACKGROUND: Micronutrient antioxidant therapy did not relieve pain in a European randomized trial of patients with chronic pancreatitis without malnutrition. However, intervention was undertaken only for 6 months leaving unanswered the question of whether long-term antioxidant therapy may modulate chronic pancreatitis. The aim of this study is to assess the outcome of long-term use of micronutrient antioxidant therapy in patients with chronic pancreatitis.

METHODS: This is a single center clinical cohort report of patients with chronic pancreatitis prescribed micronutrient antioxidant therapy and followed for up to 10 years. Data were collected on demographic detail, clinic pain assessment, insulin requirements, interventions and outcome.

RESULTS: A group of 30 patients with a diagnosis of chronic pancreatitis constitute the study population. Median age at time of diagnosis was 40 years (range 14-66); 19 (63%) were male and the median duration of symptoms was 2 years (range 0-18). Alcohol was the dominant cause in 22 (73%) patients and 16 (53%) patients were Cambridge stage 1. Twenty-four (80%) patients had pain at presentation. During antioxidant treatment of 4 years (range 1-10), pain decreased but the proportion with abdominal pain compared to those who were pain-free remained constant (*P*=0.16; two-way ANOVA with Bonferroni correction). There was a significant increase in requirement for insulin (*P*=0.028) with time together with use of both endoscopic and surgical interventions.

CONCLUSIONS: This is the first study to report long-term disease-specific outcome in patients with chronic pancreatitis prescribed micronutrient antioxidant therapy. There appears to be no effect of intervention on outcome.

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KEY WORDS: chronic pancreatitis; antioxidant therapy; micronutrient; Antox; outcomes

Introduction

The micronutrient antioxidant-deficiency hypothesis of cellular injury in chronic pancreatitis proposes that acinar damage is mediated by short-lived oxygen free radicals.[1] Deficient intracellular free radical quenching pathways combined with excess free radical production leads to cellular injury.[2] Specifically, deficiencies in key co-factors of endogenous protective free-radical quenching mechanisms such as the glutathione peroxidase pathway are proposed to be causally linked to injury and it was postulated that these deficiencies could be addressed by exogenous micronutrient antioxidant supplementation.[3] Selenium, vitamin C (ascorbic acid) and methionine were proposed as key antioxidants.[3]

After two small randomized trials of selenium, β-carotene, vitamins C & E and methionine-based antioxidant therapy reported a reduction in severity and frequency of episodes of pain in patients with recurrent and chronic pancreatitis, a commercially available formulation, Antox (Pharma Nord, Morpeth, UK) was developed comprising vitamin C, vitamin E, β-carotene, selenium and methionine.[4-6] Despite the obvious attraction of a pharmacologic intervention for this difficult disease, antioxidant therapy for chronic pancreatitis never became accepted as standard therapy. The small, heterogeneous

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clinical trial base was thought to be a main reason for the lack of acceptance.

The 2009 publication of a report from Delhi in which 147 patients were randomized to antioxidant therapy or placebo and which reported as main outcome measure a reduction in "painful days" appeared to alter the position of equipoise.[7] However, the Delhi study population comprised mainly young patients (aged 31.3±11.4 years in the antioxidant group) with a high proportion of individuals with malnutrition [median study population BMI (body mass index) 19.7±3.5] and 28 of 71 patients in the antioxidant arm having a BMI of <18.5.

The ANTICIPATE study was a similarly designed, contemporary randomized controlled trial evaluating the effect of micronutrient antioxidant therapy (Antox, Pharma Nord) undertaken in a European population of older patients with a predominantly alcohol-related etiology and a disease phenotype featuring mass-forming chronic pancreatitis.[8] The principal finding of this study was that 6 months intervention with Antox did not reduce clinical pain scores compared to placebo despite demonstrating a significant elevation in blood antioxidant levels.[8,9]

In both modern studies, the duration of intervention was six months. However, in a chronic disease such as chronic pancreatitis the effect of long-term treatment is not known and the question of whether long-term intervention is required to modulate the course of this chronic disease is unanswered. Thus the aim of this study is to assess the long-term outcome in patients with chronic pancreatitis prescribed micronutrient antioxidant therapy with specific reference to effects on pain and the natural history of the disease.

Methods

Study design

This is a clinical cohort study based on retrospective analysis of case notes.

Ethics committee approval

The study was approved by the United Kingdom Health Research Authority (NRES Committee North East, 14/NE/1117). Site-specific approval was also obtained from Central Manchester University Hospitals NHS Foundation Trust's Research board.

Setting and study population

Patients with a final discharge diagnosis of chronic pancreatitis were identified from the clinical coding department of the Manchester Royal Infirmary. The International Classification of Disease (ICD) version 9 code 577.1 was used together with the ICD version 10 codes K86.0 (alcoholic chronic pancreatitis) and K86.1 (chronic pancreatitis other).[10]

Data retrieval and collection

The case notes or microfilmed records of these patients were retrieved. The notes were reviewed by two researchers and information extracted to populate a predefined case report form. Data were collected on the following: gender, age at enrolment into this study, disease duration in years at time of enrolment, body mass index (BMI), cigarette smoking status, alcohol use, diabetes mellitus at first presentation, insulin treatment at first presentation and use of opiate analgesia.

Data reporting and categories

Inclusion period

The inclusion period is the eight years from 1st January 1990 to 1st January 1998. During this period, all patients were managed by a specialist multi-disciplinary pancreatobiliary service (including medical and surgical pancreatology) with micronutrient antioxidant therapy being used as first-line treatment. After 1998 the policy of regular use of micronutrient antioxidant therapy was discontinued for new diagnoses of chronic pancreatitis but those who were already taking this therapy were continued on it. Patients enrolled during the 8-year period were eligible for follow-up for up to 10 years.

Inclusion/exclusion criteria

Patients were included in this study if they had a discharge diagnosis of chronic pancreatitis within the study time frame and were prescribed micronutrient antioxidant therapy and had at least 12 months of follow-up. Patients were excluded if they did not meet these criteria or if they were in contemporaneous trials of antioxidant therapy.

Diagnosis of chronic pancreatitis

The diagnosis of chronic pancreatitis was by the Cambridge classification of chronic pancreatitis (class 1 to 5).[11] For the purposes of the present study, case notes and the reports of radiological and endoscopic imaging were systematically reviewed for all patients in order to allocate category.

Allocation of etiology

The etiology allocated by the treating clinician was noted and divided into alcoholic chronic pancreatitis and non-alcoholic chronic pancreatitis. Non-alcoholic