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Acute pancreatitis

Antioxidants in acute pancreatitis

C D Johnson

Antioxidant supplements may be ineffective for the treatment or prevention of organ failure in predicted severe acute pancreatitis

Oxygen-derived free radicals are produced when a period of intracellular anaerobic respiration is followed by re-oxygenation. These extremely reactive radicals combine with a large number of different protein and lipid molecules causing tissue damage and cell injury. The normal defences against such free radical attack include the presence in the tissues of antioxidant compounds and pathways of metabolism. A lack of sufficient antioxidant reserve during times of increased production of free radicals leads to the state of oxidative stress.

There has been increasing awareness over the last 20 years of the role played by oxidative stress in many inflammatory illnesses. Acute pancreatitis is no exception and in several models it has been demonstrated that oxygen-derived free radicals are generated during acute pancreatitis. It has been suggested that free radical generation, or the inability to quench free radicals, is an important factor in the pathogenesis of acute pancreatitis.[1] However, a careful experimental study suggested that oxidative stress alone cannot cause pancreatitis.[2] It is much more plausible that oxidative stress may contribute to worsening of the local inflammatory changes after onset of pancreatitis.[3–6] Some experimental studies suggest that antioxidant therapy can diminish tissue injury in acute pancreatitis.[3 7] It is also clear that oxidative mechanisms are an integral part of the inflammatory response and oxidative stress may contribute to pulmonary injury in severe acute pancreatitis.[8 9] Oxidative stress is recognised as part of the pathophysiology of adult respiratory distress syndrome,[10] and there is experimental evidence that antioxidants can protect against lung injury in acute pancreatitis.

There is a convincing body of evidence that antioxidant blood levels diminish during severe acute pancreatitis,[11 12] and that supplements of antioxidants can prevent these falls in experimental[3 7] and clinical[13] pancreatitis. However, the evidence of clinical benefit to support the therapeutic use of antioxidants is sparse and uncontrolled.

Given the supposed harmful nature of oxidative stress, and observation of antioxidant depletion in human pancreatitis,[11-13], it has been postulated that the harmful effects of oxidative stress in this condition could be ameliorated by supplementation with naturally occurring antioxidants. Unfortunately there is little published evidence to support this theory. One randomised trial[14] reported reduced frequency of attacks of recurrent acute pancreatitis, in a small study population (20 patients). This study made no observations relevant to the treatment of patients with severe acute pancreatitis. A case controlled series from Manchester (where the treatment rationale was developed) demonstrated that although antioxidant supplements could indeed prevent the fall in blood levels seen in severe acute pancreatitis, there was no observed effect on clinical outcome.[13]

Until now, there has been no reliable randomised trial that investigates the use of antioxidants to reduce the severity of complications in acute pancreatitis. In this issue, Siriwardena and colleagues[15] report just such a randomised controlled trial ***(see page 1439)***.

Siriwardena *et al*.[15] report a trial that carefully selected patients who might be expected to benefit from antioxidant treatment. They were recruited to the study within 72 hours of onset of pancreatitis and they had an APACHE-II score >8. That is, only patients with predicted severe acute pancreatitis were included, and treatment was started as early as possible. These patients are relatively few, and recruitment in three hospitals extended over 41 months. Interim analyses were conducted by a trial statistician at planned annual intervals and patients were treated according to the UK National Guidelines for the Management of Acute Pancreatitis. This trial therefore focuses on the patients most at risk, who were managed to a high standard of care. The authors are to be congratulated on achieving a relatively low mortality rate, below 10%, for these potentially seriously ill patients.

Patients were randomised to receive a placebo injection or a mixture of antioxidants (n-acetylcysteine, selenium, vitamin C), by intravenous injection for 1 week. The two groups were well matched except that the active treatment group were older.

The primary trial endpoint was the incidence of organ dysfunction after 1 week of treatment. Secondary endpoints included the severity of organ dysfunction (assessed by Marshall score[16]) at 1 week, and overall mortality. There were no significant differences between the groups on any of the endpoints reported. The authors chose the presence of organ dysfunction as their primary endpoint. This could have masked a beneficial effect of reduction in severity of organ dysfunction, but Marshall scores were not significantly different in the two groups, and there was no difference between the groups in the numbers of patients with or without organ failure (Marshall score 2 or greater). Indeed, at 7 days organ failure was more frequent in the treatment arm than the placebo arm, and all four deaths occurred in the treatment arm.

One possible explanation for the negative findings is that the active treatment group may have had more patients with very severe disease. However, the multiple organ dysfunction scores in the two arms were equal, suggesting that this was not the case. The active treatment group was older, and in the multivariate analysis age was confirmed as an independent predictive factor, so this may have influenced the results, limiting the ability of the trial to find in favour of antioxidant treatment. Another possibility is that one of the components of the antioxidant mixture may have had specific (if unknown) adverse effects that counterbalanced potential benefits of other components. However, there was good theoretical and experimental rationale for choosing this mixture of antioxidants and this explanation seems unlikely.

Despite the apparent lack of any clinical effect, patients in the active treatment arm had significant increases in blood levels of antioxidants. We can only speculate why there was no clinical benefit in outcome in patients in whom antioxidant supplements raised blood antioxidant levels. Perhaps the systemic antioxidant depletion that often accompanies severe acute pancreatitis is part of the regulatory mechanism that helps activate the anti-inflammatory cytokine response.

What are the implications of these trial findings? It is clear that intravenous supplementation with antioxidants can achieve substantial increases in blood antioxidant levels. This, however, had no discernible beneficial effect on organ failure or death. Indeed, the trial data raise the (unsubstantiated) possibility that antioxidant therapy in predicted severe acute pancreatitis might be harmful.

The only reservation about the applicability of the findings of this trial is the large number of patients considered for randomisation who were found to be ineligible (152 of 205). The authors do not give reasons why these patients were considered ineligible. If they were excluded because the pancreatitis was relatively mild, that is of no consequence, but if the exclusions were largely for delay in recruitment that would raise the possibility of a bias in the study that would weaken its generalisability.

The findings of Siriwardena and colleagues have no bearing on the use of oral antioxidant therapy to prevent recurrent episodes of acute pancreatitis, or for the prevention of pain in chronic pancreatits, two related areas that have been proposed for this type of therapy. However, it is difficult to escape the conclusion that antioxidant supplements as given in their study are ineffective for the treatment or prevention of organ failure in predicted severe acute pancreatitis.

In conclusion, the study by Siriwardena and colleagues[15] has closed the book on the antioxidant story in the treatment of severe acute pancreatitis. The lack of any benefit in this well-planned and well-conducted study tells us that antioxidant therapy has no place in the management of this condition. Once again, a randomised controlled trial has provided clear if disappointing evidence that a new therapy in acute pancreatitis has little to offer over the best supportive care. Definition of a strategy to reverse organ failure during the first week of severe acute pancreatitis remains an important objective, but is not yet achieved.

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