Clinical opinions in general medicine

The final issue of Clinical Opinions for 2002 looks at developments in a variety of areas within general medicine. Simpson looks at the sublime and the possibly not quite so ridiculous as first thought – the evidence for curative gene therapy and the role of acupuncture in asthma respectively – with interesting and informative insight. Jones looks at the difficulties inherent in treating paracetemol poisoning in alcoholics while Kerr sheds more light on the intriguingly named cardiac Syndrome X. Finally, Jenkins tells us about an important breakthrough in the administration of analgesia in children.

As always, we hope these short summaries and accompanying opinions will help busy clinicians stay in touch with interesting and important developments outside their own specialist areas. Please send any comments by e-mail to cme_editor@rcpe.ac.uk.

Clinical opinion: progress in gene therapy

TITLE: Sustained correction of X-linked severe combined immunodeficiency by *ex vivo* gene therapy.

AUTHORS: Hacein-Bey-Abina S, Le Deist F, Carlier F *et al.*

JOURNAL: *N Engl J Med* 2002; **346(16):**1185–93.

SUMMARY:

Severe combined immune deficiency (SCID (deficiency in adenosine deaminase)) is associated with a propensity to overwhelming infection. X-linked SCID is usually caused by a mutation in the gene encoding the common g chain, a molecule central to the normal maturation of T-cells and natural killer (NK) cells. The authors identified five boys with X-linked SCID attributable to mutations in the g chain and retrieved autologous bone marrow from each. The marrow aspirate was then transfected with a replication-deficient recombinant retrovirus into which the g chain gene had been inserted. Transfected cells were ultimately infused intravenously. The patients were followed up for between 0·7 and 2·5 years after gene therapy. No serious side-effects were described. In four of the five boys clinical improvement was associated with a move from sterile isolation to living in normal conditions at home. Four of these boys had no severe infections during follow-up. The fifth boy failed to respond and had a stem cell transplantation from an unrelated donor after developing disseminated infection.

Convincing evidence of T-cell restitution was demonstrated for the four boys who improved but not in the patient who failed to improve, despite the observation that the g chain was detectable in peripheral blood mononuclear cells from all patients. In general there was good evidence for the production of functional, g chain-expressing T-cells and NK cells, for normal thymic development, and for secretion of sufficient quantities of immunoglobulin in the four patients who improved clinically.

OPINION:

A different form of SCID was the subject of the first approved clinical trial of gene therapy. As such the principles of *ex vivo* correction of genetic defects in lymphoid cells by recombinant retrovirus are well established. Indeed targeted *ex vivo* gene transfer has also been achieved using recombinant adenovirus. It might be argued therefore that the findings of Hacein-Bey-Abina *et al.* cover known territory to some degree. However, their observations are hugely significant to gene therapy as a clear re-assertion that a single targeted treatment can result in effective and sustained genotypic and phenotypic restoration in patients with single gene defects. Whilst the treatment was not uniformly restorative – in one patient it was unsuccessful and in others there was evidence of decline in efficacy with time – these data add to the body of evidence demonstrating proof of principle for curative gene therapy. In the specific context of X-linked SCID the hope must be that further technical improvements will offer long-term restitution that can rival or even supercede stem cell transplantation. In the broader context of gene therapy, this study provides renewed encouragement. The challenge now must be to adapt the technologies and applications

available to conditions more common than SCID. The emerging message is that *ex vivo* genetic manipulation of selected cell populations is readily achievable and safe – this has important implications for cancer gene therapy, and suggests novel strategies for gene delivery to organs such as the lung and kidney.

Clinical opinion: the role of acupuncture in asthma

TITLE: Short-term acupuncture therapy is of no benefit in patients with moderate persistent asthma.
AUTHORS: Shapira MY, Berkman N, Ben-David G *et al.*
JOURNAL: *Chest* 2002; **121:**1396–400.

TITLE: Laser acupuncture in children and adolescents with exercise induced asthma.
AUTHORS: Gruber W, Eber E, Malle-Scheid D *et al.*
JOURNAL: *Thorax* 2002; **57:**222–5.

SUMMARY:
These recently published studies used different strategies with the aim of determining whether acupuncture has a potential benefit in the management of asthma.

Shapira *et al.* recruited 23 adults with asthma whose treatment consisted only of short-acting $ß_2$-agonists taken on an 'as required' basis. Patients were randomised to receive either four sessions of needle acupuncture tailored specifically to each individual's disease pattern (given over a one week period), or four sessions of sham acupuncture. The study had a crossover design such that after a three week washout period the other treatment arm was administered. At the end of each week of treatment, lung function tests were performed in a double-blind fashion (i.e. neither the patient nor the lung function technician knew which acupuncture treatment had been received). Under these conditions, at one week, specific acupuncture and sham acupuncture showed no differences with respect to forced expiratory volume in one second (FEV_1), bronchial reactivity to methacholine, symptom scores or frequency of $ß_2$-agonist use. Furthermore, no differences were detected in FEV_1 or bronchial reactivity at three weeks.

Gruber *et al.* studied the short-term effects of laser acupuncture in children and adolescents with exercise-induced asthma (n=44), most of whom (n=37) were receiving regular inhaled corticosteroids. Patients were randomised to receive laser acupuncture administered either to six pre-determined sites thought to be important in asthma, or to six pre-determined sites believed to have no influence on asthma. Bronchial constriction was then provoked using cold air challenge, and lung function tests recorded at three and 15 minutes in a double-blind fashion (again both the patient and the lung function technician were blinded to acupuncture treatment). A crossover design was incorporated in that the protocol was repeated using the other treatment arm the following day. No differences were detected in FEV_1, small airway narrowing or in symptoms when comparing the two groups.

OPINION:
Patients with asthma often enquire as to the efficacy of alternative medicines. Until now we have had little firm evidence with which to answer their questions. In this regard these two papers are very much welcomed as attempts to apply rigorous scientific methods in assessing the role of acupuncture. The studies were generally well designed; however, neither provides support for the use of acupuncture in the prevention or amelioration of bronchoconstriction in patients with chronic asthma. Both of the studies were small, and only provide us with information specific to certain groups of patients, namely children/adolescents with moderate asthma (Gruber *et al.*) and in adults with relatively mild asthma (Shapira *et al.*). There is no doubt that further information is required to determine whether certain patients might benefit from acupuncture under specific circumstances. In particular it is plausible that the timing, frequency and technical administration of acupuncture may have been suboptimal for detection of efficacy in the studies described. Furthermore it would be interesting to determine whether acupuncture has anything beneficial to offer patients with more troublesome asthma such as those with steroid-resistant airways, for whom novel and effective long-term treatments are badly required.

Nonetheless these studies add significantly to a much needed evidence base in the meantime. Indeed even the conclusion that there is presently no good evidence to support acupuncture in chronic asthma may help sceptic and enthusiast alike. The sceptic will long have argued that alternative medicines (outwith the NHS) can be expensive; these data may allow him or her to inform patients in a way that makes them less susceptible to exploitation. The sceptic would further argue that a proportion of patients inherently wary of pharmaceutical products (and especially steroids) are less compliant with prescribed medications *because* treatments like acupuncture exist; the compelling evidence for efficacy of inhaled corticosteroids in asthma and the emerging evidence for relative lack of efficacy of acupuncture may help him or her to allay patients' concerns. On the other hand, the enthusiast may now seize the potential to apply sound scientific principles to the evaluation of acupuncture (and other alternative medicines) in the hope that we can derive novel evidence based therapies for asthma.

Dr John Simpson, Senior Lecturer in Respiratory Medicine, Edinburgh

Clinical opinion: when to treat paracetamol poisoning in chronic alcoholics

TITLE: Should a lower treatment line be used when treating paracetamol poisoning in patients with chronic alcoholism?

AUTHORS: Buckley NA, Srinivasan J.

JOURNAL: *Drug Safety* 2002; **25:**619–24.

SUMMARY:

Paracetamol poisoning has no specific clinical features in the early phase and so diagnosis is usually based on a history of ingestion and measurement of plasma paracetamol concentrations plotted on a nomogram related to the estimated time of ingestion. The use of a lower treatment line (the '100' line) joining 100 mg/L at four hours and 15 mg/L at 15 hours has been widely adopted for patients in a high-risk group for paracetamol poisoning in the UK. This paper examines the evidence to support the use of a lower treatment line for administration of N-acetylcysteine in chronic alcoholics who present with paracetamol poisoning. It illustrates that practice is largely based on animal studies. Two studies have shown small increases in formation of toxic paracetamol metabolites in humans. The clinical evidence for increased risk amongst those who use excessive alcohol is limited to four retrospective studies, whose methodological flaws (potential for referral and reporting bias) and conflicting results are eloquently explained in the paper. The paper also points out that no study has specifically addressed the issue of treatment threshold in humans in a prospective way. Potential risks of not treating patients however currently outweigh the risks of N-acetylcysteine (three to five per cent of patients get an anaphylactoid reaction).

OPINION:

Whilst it is possible that chronic exposure to excessive amounts of alcohol does predispose patients with paracetamol overdose to hepatotoxicity, the literature to date in humans is unconvincing. In addition to the points made by Buckley and Srinivasan, one of the problems in the literature to date is that insufficient information is available on the timing of the alcohol intake in relation to the ingestion of paracetamol. Acute ingestion at the time of a paracetamol overdose is probably protective. If patients with chronic alcoholism (however that is defined!) are at risk of paracetamol poisoning their most vulnerable time should be during the alcohol withdrawal phase, because at this time any enzyme induction would be unopposed by the presence of acute alcohol. However, studies rechallenging patients with chronic alcoholism who are withdrawing, with maximum supratherapeutic does of paracetamol, showed no effect on liver function tests. Alcoholic patients may also appear to be more susceptible to paracetamol because of other confounding variables. In particular they present late and this is an independent predictor of outcome in paracetamol poisoning, regardless of alcohol intake. The use of the lower treatment line continues to be recommended in review articles and national guidelines because there is no conclusive clinical evidence to the contrary.

Dr Alison Jones, Head of Medicine, Consultant Physician and Clinical Toxicologist, London

Clinical opinion: despite normal epicardial coronary vessels, cardiac pain in Syndrome X may relate to episodes of sub-endocardial ischaemia

TITLE: Abnormal sub-endocardial perfusion in cardiac Syndrome X detected by cardiovascular magnetic resonance imaging.

AUTHORS: Panting JR, Gatehouse PD, Yang G *et al.*

JOURNAL: *N Engl J Med* 2002; **346:**1948–53.

SUMMARY:

Between ten and 20 per cent of patients with classical cardiac pain have normal coronary arteries. Syndrome X, in which patients also show significant exercise induced ST depression, forms a sub-group of this population. Previous studies, using a variety of techniques, have failed to establish a convincing link with myocardial ischaemia.

Using myocardial perfusion cardiovascular magnetic resonance imaging with adenosine stress in 20 patients with documented Syndrome X and ten controls, the authors demonstrated sub-endocardial hypoperfusion in the Syndrome X group. Quantitative perfusion analysis was performed to derive the myocardial perfusion index and the myocardial reserve index defined as the ratio of the myocardial perfusion index during stress to the index at rest.

In the controls, the myocardial perfusion index increased significantly during adenosine stress in both the sub-endocardium and sub-epicardium. However, in the Syndrome X patients, the myocardial perfusion index did not increase significantly in the sub-endocardial region when compared with controls but did increase in the sub-epicardium. Sub-endocardial myocardial perfusion index, normalised to heart rate, fell in patients with Syndrome X but not in controls. The ratio of sub-endocardial to sub-epicardial myocardial perfusion reserve index was significantly lower in patients with Syndrome X.

Adenosine infusion induced low intensity chest pain in 40% of controls and high intensity chest pain in 95 per cent of Syndrome X patients.

OPINION:

This study shows that Syndrome X patients have significantly different perfusion responses to adenosine infusion compared with matched controls. Contrary to previous work, this study supports the contention that chest pain in Syndrome X occurs as a result of sub-endocardial ischaemia. Further research with perfusion cardiovascular magnetic resonance energy and quantification of absolute sub-endocardial perfusion will be required for confirmation of these findings. Patients with Syndrome X have a good risk profile in comparison to those with coronary artery disease and they have a low incidence of complications such as myocardial infarction and sudden death. Furthermore, Syndrome X patients do not respond well to drugs used in coronary artery disease such as antianginal agents. Accordingly, they should be reassured and drug therapy can be withdrawn. We will have to await further understanding of the mechanisms of the disease before we can offer more effective treatment.

Dr Finlay Kerr, Consultant Physician (Cardiology), Inverness

Clinical opinion: nasal diamorphine provides pain relief in children superior to IM administration

TITLE: Multi-centre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical features.

AUTHORS: Kendall JS, Reeves BC, Latter VS on behalf of the Nasal Diamorphine Trial Group

JOURNAL: *BMJ* 2001; **322:**261–5.

SUMMARY:

This study was a multi-centre randomised control study set in eight emergency departments within the UK. Four hundred and four children aged between three and 16 years who presented to an accident and emergency department with a clinical fracture were recruited to this study. A comparison was made of nasal diamorphine with an intra-muscular injection of morphine. The diamorphine was given in a solution that resulted in a dose of 0·1 ml/kg in 0·1 ml. Onset of pain relief was faster in the nasal group with no difference at 30 minutes. Eighty per cent of patients given the nasal diamorphine showed no obvious discomfort when given an intramuscular injection of morphine. Parents preferred the nasal route as did the staff administering it. There was no difference in adverse effects between the two groups.

OPINION:

This paper highlights an important step in the administration of analgesia. Intra-nasal administration of diamorphine has a more rapid onset than intra-muscular morphine and is as safe. The practice of intra-muscular pain relief in children and especially when trauma has been involved should be avoided. If intra-venous access is difficult, then the nasal route should be the next option to provide analgesia.

Dr MG Jenkins, Consultant A & E Medicine, Antrim