

Medibytes

Medibytes offer Fellows and Members short, informative, synopses of important or interesting papers published in speciality and other general medical journals. They are edited by Dr J Ferguson.

LIST OF ABBREVIATIONS Atrial fibrillation (AF), C-Reactive Protein (CRP), percutaneous coronary intervention (PCI), Pulmonary hypertension (PH), pulmonary vasculo-occlusive disease (PVOD), lymphadenopathies (LAP), chronic obstructive pulmonary disease (COPD), randomised controlled trial (RCT)

PAEDIATRICS

Human botulism immune globulin (BIG-IV) is effective in infants

In a five-year randomised, double-blind, placebo controlled trial on 122 infants with laboratory confirmed type A or B botulism, BIG-IV reduced the mean hospital stay from 5.7 to 2.6 weeks. BIG-IV also proved effective in an open study of 382 infants with confirmed disease. A single infusion of BIG-IV is effective for at least six months. In addition, antibiotics can be used to treat secondary infections of the gut since toxin released by the lysis of *C. botulinum* cells present in the lumen is readily neutralised after absorption. Although the supply of BIG-IV may be adequate for infant botulism in the US, effective treatment in the rest of the world will have to await the development of a recombinant product. Since botulinum toxin is also a category A bioweapon, this is a realistic hope.

JS Kelly

From Arnon SS, Schechter R, Maslanka SE et al. Human botulism immune globulin for the treatment of infant botulism. 2006 *N Engl J Med* 35:462–71.

Stem cells for studying embryogenesis

Human embryos are relatively inaccessible for research. Unfortunately, the mouse model displays major anatomical and growth differences from the human. Human embryonic stem cells (HESC) are derived from the inner cell mass of the blastocyst. They are pluripotent and can readily self-renew in culture. They can form practically any cell type in vivo and in vitro. HESC can recreate embryogenesis by expressing developmentally regulated genes and by activating molecular pathways as they occur in nature. More recently, HESC have been used to analyse the effects of specific mutations on developmental events. They may throw light on cell commitment, differentiation and adult cell reprogramming. HESC show great potential for basic research, especially into the mechanisms of development of the normal and abnormal embryo.

I Laing

From Dvash T, Ben-Yosef D, Eiges R. Human embryonic stem cells as a powerful tool for studying human embryogenesis. *Pediatr Res* 2006; 60(2):111–17.

CARDIOVASCULAR

Facilitated angioplasty and the treatment of myocardial infarction (ASSENT-4)

Early percutaneous coronary artery intervention in ST elevation myocardial infarction is superior to thrombolytic therapy; however, delays in time to intervention are common. This trial therefore compared facilitated angioplasty (administration of thrombolysis before planned angioplasty) to standard angioplasty. The trial planned to recruit 4,000 patients but was stopped early as significantly more patients randomised to receive tenecteplase prior to angioplasty died in hospital. Consequently, the strategy of thrombolytic therapy prior to angioplasty is not recommended.

J Ferguson

From Assessment of the safety and efficacy of a new treatment strategy with percutaneous coronary intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; 367:569–78.

C-reactive protein: more than a biomarker?

An increase in serum C-reactive protein (CRP) is commonly used as a clinical marker to monitor acute inflammatory disease. Delayed clearance of CRP is a bad prognostic sign. C-reactive protein also appears in the serum following cardiac damage and stroke, though there has been no evidence to date to suggest that it alters cardiac function. Now, Pepys has suggested that high levels of CRP in the blood increase the damage caused by heart attacks and stroke and has identified an inhibitor, 1,6-bisphosphocholine)-hexane (Bis(PC)-H). In rat models of myocardial and cerebral infarction, the injection of human CRP activates the rat complement system and increases the volume of ischaemic tissue. (Bis(PC)-H) blocks this increase. Using crystallography, five molecules of (Bis(PC)-H) were shown to bind to two pentamers of CRP occluding the ligand binding surface and blocking its ability to attenuate the action of CRP. The resulting decamer is rapidly catabolised. It is claimed that the therapeutic block of CRP will not only have a role in

cardiac dysfunction and stroke but in inflammation and infection. Equally controversial are a number of recent accounts linking new treatments for hypertension with a lowering of CRP.

JS Kelly

From Pepys MB, Hirschfield GM, Tennent G A *et al.* Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature* 2006; **440**:1217–21.
Derosa G, Cicero AF, D'Angelo A *et al.* Effect of doxazosin on C-reactive protein plasma levels and on nitric oxide in patients with hypertension. *J Cardiovasc Pharmacol* 2006; **47**:508–12.

INFLAMMATION

C-reactive protein and SSRI antidepressants

Major depression is associated with activation of the inflammatory response, which includes an increase in positive, acute phase proteins, C-reactive protein being one. Twenty women with depressive illness and no relevant physical conditions had their CRP levels measured before, and again three weeks after, introduction of SSRI antidepressant therapy (fluoxetine, paroxetine, sertraline). A significant ($p < 0.0001$) drop in CRP levels was found. Crucially, this reduction was unrelated to whether the depression had responded or not. SSRIs may have anti-inflammatory properties which are independent of their antidepressant action.

G Masterton

From O'Brien SM, Scott LV, Dinan TG. Antidepressant therapy and C-reactive protein levels. *Br J Psychiatry* 2006; **188**:449–452.

RESPIRATORY DISEASE

Pulmonary hypertension and sarcoidosis

Pulmonary hypertension is a rare complication of sarcoidosis, although it is not uncommon in advanced disease. This retrospective study looked at 22 sarcoid patients with PH divided into two groups depending on the presence or absence of pulmonary fibrosis. No other cause of PH was found in patients without fibrosis, suggesting a specific sarcoidosis vasculopathy. In patients with fibrosis, there was no correlation between haemodynamics and lung volumes or arterial oxygen tensions, suggesting mechanisms for PH in addition to pulmonary destruction and hypoxaemia. These included extrinsic arterial compression by LAP and histologically proven PVOD. In patients without fibrosis, corticosteroid may sometimes be efficacious for treating PH complicating sarcoidosis. The authors indicate that PH is a severe complication of sarcoidosis which has two very different phenotypes depending on the presence or absence of pulmonary fibrosis

A Mohammed

From Nunes H, Humbert M, Capron F *et al.* Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax* 2006; **61**:68–74.

Heliox in chronic obstructive pulmonary disease

Supplemental oxygen reduces breathlessness during exercise in patients with COPD. Replacing nitrogen with helium reduces expiratory flow resistance and may improve lung emptying. Combining these treatments should be independently effective. This randomised controlled trials involved 82 patients with severe COPD. Investigators measured endurance shuttle walking, resting and exercise oxygen saturation, and end expiratory dyspnoea (Borg scale) while patients breathed Heliox 28 (72% He/28% O₂), Heliox 21 (79% He/21% O₂), Oxygen 28 (72% N₂/28% O₂), or air. The main result was that endurance walking distance improved by 64% with Heliox 28 compared with Heliox 21 or 28% oxygen, and all three treatments demonstrated improvements in exercise capacity compared with exercising on air alone. This study indicates that reducing inspired gas density can improve exercise as much as inspired oxygen in COPD. These effects can be combined as Heliox 28 and are most evident in patients with severe airflow obstruction.

A Mohammed

From Laude EA, Duffy NC, Baveystock C *et al.* The effects of helium and oxygen on exercise performance in COPD. *Am J Respir Crit Care Med* 2006; **173**(8):825–6.

VIRAL HEPATITIS

Variant of hepatitis B virus with primary resistance to adefovir

Lamivudine, the reverse transcriptase inhibitor, is often the usual initial treatment for chronic hepatitis B infection. However, resistance to Lamivudine at four years approaches 70%. Once resistance develops, treatment is often switched to the reverse transcriptase inhibitor adefovir. Resistance to adefovir occurs in about 3% of patients within three years, but this brief report describes three cases of primary adefovir resistance. Interestingly, all three patients responded to the reverse transcriptase inhibitor tenofovir.

J Ferguson

From Schildgen O, Sirma H, Funk A *et al.* Variant of hepatitis B virus with primary resistance to adefovir. *N Engl J Med* 2006; **354**(17):1807–12.

THERAPEUTICS

Artemisinin: a new and inexpensive source – brewer's yeast!

Artemisinin, a natural product extracted from sweet wormwood, a native of China, is an extremely effective treatment for malaria, but is in very short supply and difficult to synthesise. Jay Keasling, funded by the Bill & Melinda Gates Foundation, has engineered brewer's yeast cells to secrete an easily manipulated precursor, artemisinic acid. This involved the introduction of a mevalonate pathway to produce amorphinone and a novel cytochrome P450 three stage oxidative pathway to produce artemisinic acid. Producing artemisinin by a bioprocess will remove uncertainties about the weather and the political situation where the natural product is harvested and interestingly is more environmentally friendly as it avoids the disposal of toxic contaminants normally co-extracted from the plant material. A new and cheap source of artemisinin should make it easier to manufacture anti-malarial combinations which make the development of resistant strains less likely. Artemisinin works by disabling the malarial calcium pump, but a single amino acid mutation has been shown to confer resistance.

JS Kelly

From Ro DK, Paradise EM, Ouellet M *et al.* Production of the antimalarial drug precursor artemisinic acid in engineered yeast. *Nature* 2006; **440**:940–3.

Platenicycin, a new antibiotic with a novel mode of action

The continual emergence of bacterial resistance to existing antibiotics is a cause for considerable concern. With the exception of linezolid and daptomycin, most of the antibiotics in current use are variants of antibiotics discovered 40 years ago. Against this background, the isolation of the small orally active molecule, platenicycin, from the fermentation broth of *Streptomyces platensis* must be considered a major breakthrough. The novel mode of action exploits a weakness in bacterial fatty acid synthesis and results in an antibiotic effective against multiple drug-resistant strains of staphylococci and enterococci. The work involved the screening of 250,000 natural product extracts from 83,000 different species using a combination of target based whole cell and biochemical assay. Crystallography has defined the unique binding site and specificity of the molecular interaction. Platensimycin shows broad-spectrum activity, low toxicity, no cross-resistance on assays using methicillin and vancomycin resistant staphylococci and enterococci.

JS Kelly

From Wang J, Soisson SM, Young K *et al.* Platensimycin is a selective FabF inhibitor with potent antibiotic properties. *Nature* 2006; **441**:358–61.

PSYCHIATRY

Debriefing following trauma

Should people exposed to severe traumatic events be offered routine, single-session, individual psychological debriefing? The answer is no. Two hundred and thirty-six adult survivors seen 11–19 days after a traumatic incident were randomly assigned to emotional ventilation debriefing, educational debriefing or no debriefing. Debriefing conferred no benefits with regard to reducing psychiatric symptoms, and indeed participants treated with emotional debriefing experienced greater hyperarousal subsequently. Psychological interventions, using cognitive behavioural therapy approaches and delivered over 4–12 sessions, remain appropriate for patients who have developed trauma-induced mental disorders – but leave the well alone!

G Masterton

From Sijbrandij M, Olf M, Reitsma JB *et al.* Emotional or educational debriefing after psychological trauma. A randomised controlled trial. *Br J Psychiatry* 2006; **189**:150–5.

VASCULAR MEDICINE

Deep Vein Thrombosis

This large Dutch case-control study included 1,906 patients aged 18–69 years with venous thrombosis; 57% had deep venous thrombosis, 32% had pulmonary embolus, and 11% had both. 233 patients had travelled continuously for >4 hours in the 8 weeks before the venous thrombosis.

Travel by air, train, bus or car all increased the risk of venous thrombosis two-fold. Additional risk factors were factor V Leiden, Body Mass Index >30, oral contraceptives, and height above 1.6m/6'2". Height below 1.6m/5'2" increased the risks of thrombosis only for air travel.

All prolonged travel increases the risk of venous thrombosis. Prophylaxis should be considered for those with additional risk factors.

NDC Finlayson

From Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR. Travel-Related Venous Thrombosis: Results from a Large Population-Based Case Control Study (MEGA Study) *PLoS Med* 2006; **3**(8): (Epub ahead of print).