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Medibytes

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

LIST OF ABBREVIATIONS Adverse drug events (ADE), human embryonic stem cells (HESC), myocardial infarction (MI), intravenous (IV), subcutaneous (SC), hepatocellular carcinoma (HCC), Food and Drug Administration (FDA)

HEPATOLOGY

Variant of hepatitis B virus with primary resistance to adefovir

Lamivudine, the reverse transcriptase inhibitor, is often initially used to treat chronic hepatitis B infection. However, at four years, resistance to Lamivudine approaches 70%. Therefore, once resistance develops, treatment is often switched to the reverse transcriptase inhibitor adefovir. It is known that resistance to adefovir occurs (3% at three years in HBeAg +ve disease) however this brief report in the *New England Journal of Medicine* describes three cases of primary adefovir resistance. Interestingly, these three patients all 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.

Entecavir and lamivudine for HBeAg +ve chronic hepatitis B

Chronic hepatitis B is a huge worldwide problem and accounts for half the cases of cirrhosis and hepatocellular carcinoma. Chronic hepatitis B is now a treatable disease and the importance of therapy was demonstrated by a clinical trial from Asia which showed that long term treatment with Lamivudine improved survival and decreased HCC in patients with chronic Hepatitis B and fibrosis or cirrhosis. Sadly, after four years, 70% of patients on Lamivudine have developed resistance. In this study the selective guanosine analogue entecavir was compared to Lamivudine in the treatment of HBeAg +ve chronic hepatitis. The rates of virologic, and biochemical improvement were significantly higher with entecavir than with lamivudine and the safety profile of the two agents was similar with no evidence of viral resistance to entecavir.

J Ferguson

From Chang TT, Gish RG, de Man R *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; **354:**1001–10.

SCIENCE

Thrombocytopenia and mimicks of thrombopoietin

Thrombocytopenia can result from either low production of platelets in the bone marrow, or from increased destruction of peripheral blood platelets in idiopathic thrombocytopenia purpura. One approach to excessive destruction is to induce the overproduction of platelets. The usual treatment with repeated platelet transfusions, continuous immunosupression with steroids and splenectomy is at best palliative.

In a recent trial involving 95 patients, GlaxoSmithKline have shown their orally active thrombopoietin mimetic eltrombopag to raise platelet numbers to greater than 50,000. Amgen have also developed a ligand that binds with the thrombopoietin receptor, AMG 531, and shown it to be active when given IV or SC. Unfortunately, oprelvekin, recombinant human interleukin-11, (Neumega, Wyeth), the only thrombocytopoietic factor approved by the FDA, must also be given SC and is poorly tolerated. Oprelvekin is less specfic and acts on megakaryocytes to induce maturation.

JS Kelly

From McHutchison JJG, Afdhal N, Schiffman ML *et al.* Efficacy and safety of eltrombopag, an oral platelet growth factor, in subjects with HCV associated thrombocytopenia: preliminary results from a phase II dose-ranging study. *J Hepatology* 2006; **44:**S276.

Bussel JB, Kuter DJ, George JN *et al.* Long-term dosing of AMG 531 is effective and well tolerated in thrombocytopenic patients with immune thrombocytopenic purpura. *Blood* 2005; **106:**68A.

Cotreau MM, Stonis L, Strahs A, Schwertschlag US. A multiple-dose, safety, tolerability, pharmacokinetics and pharmacodynamic study of oral recombinant human interleukin-II (oprelvekin). *Biopharmaceutics & Drug Disposition* 2004; **25:**291–6.

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 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*. Human embryonic stem cells 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. Human embryonic stem cells 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):**111–7.

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 rest well alone!

G Masterton

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

Mood disorder and poor quality of life following first MI

A prospective, observational cohort (n=260) study adds further weight to the importance of recognising and treating abnormal anxiety and/or depression following an MI. While mood disorder at the time of the MI had no predictive value, depression and anxiety identified at six months was a strong predictor of impaired health-related quality of life at one year, explaining more of the variance than cardiac and other medical factors even after these had been accounted for. Fatigue appeared to be the main mediating factor. Affected patients were rarely identified and treated appropriately.

G Masterton

From Dickens CM, McGowan L, Percival C *et al.* Contribution of depression and anxiety to impaired health-related quality of life following first myocardial infarction. *Br J Psychiatry* 2006: **189:**367–72.

SEPSIS

Don't miss infection in hypothermia

This prospective observational study included 88 patients attending Bellevue Hospital, New York, on 96 occasions with rectal temperatures ≤ 35°C (86°F). External re-warming was either passive or active, and core re-warming used inspired warm humidified oxygen or warmed peritoneal saline. Re-warming intensity increased as admitting temperature fell, but in uninfected patients the re-warming rate was independent of the method used. Seven patients died within 14 hours; all had severe underlying conditions (seizures, renal failure, hepatic failure, ethanol intoxication) and six died of infection. Re-warming < 1°C /hour, hypotension, bradycardia and albumin < 27 g/l suggested a poor outcome. Treating underlying illness, especialy infection, is important in these patients.

N Finlayson

From Delaney KA, Vassallo SU, Larkin GL, Goldfrank LR. Rewarming rates in urban patients with hypothermia: prediction of underlying infection. *Acad Emerg Med* 2006; **13(9):**913–21.

NEUROLOGY

The use of longterm low dose aspirin is safe following intracerebral haemorrhage

In a recent 'Reflection and Reaction' in *Lancet Neurology,* Donnan and Ly argue that it is safe to use aspirin in patients who have earlier suffered a haemorrhagic stroke. Since the survival rate in some studies is as low as 50%, this is a clinically important observation. Indeed, Viswanthan and colleagues have shown survivors of primary intracerebral haemorrhage on aspirin not to suffer a recurrence. Interestingly, 17–20% of the cohort had either a prior ischaemic stroke or heart disease, 13% atrial fibrillation, and 6% diabetes mellitus; all good candidates for ongoing antiplatelet treatment to prevent recurrent ischaemic events. Donnan and Ly are a bit more coy about how long after an event aspirin therapy should be resumed and simply state that 'it seems prudent to wait at least one month'.

JS Kelly

From Donnan GA, Ly J. Aspirin after intracerebral haemorrhage: probably safer than we thought. *Lancet Neurology* 2006; **5:**288–9.
Viswabathan A, Rakich SM, Engel C *et al.* Antiplatelet use after intracerebral haemorrhage. Neurology 2006; **66:**206–9.

Standard therapy in migraine for 24 weeks is no better than verum and sham acupuncture for six weeks

In a randomised, blinded, adequately powered clinical trial in migraine patients, standard therapy for 24 weeks, or

verum (genuine) or sham acupuncture for six weeks, at the end of 26 weeks reduced the number of migraine days over four weeks by about 50% in 40 to 50 percent of the patients. Since, statistically, acupuncture was more effective (47% verum acupuncture, 39% sham acupuncture and 40% standard therapy) the authors claim that, in the absence of adverse side effects or contraindications, acupuncture is a reasonable alternative to standard therapy with beta blockers, flunarizine and valproic acid. However, the large drop-out of patients on standard therapy who had expected to received acupuncture, and the results from other studies of acupuncture on pain, must raise the possibility that the greater or lesser efficacy of all three treatments is a placebo effect.

JS Kelly

From Diener H-C, Kronfeld K, Boewing G *et al.* Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurology* 2006; **5:**310–6.

VASCULAR DISEASE

Endarterectomy favoured for carotid stenosis

The endarterectomy vs angioplasty in patients with symptomatic severe corotid stenosis (EVA-35) trial randomised 262 patients to endarterectomy and 265 patients to stenting. All patients had ≥ 60% carotid stenosis. Primary outcomes were stroke or death 4·2% of endarterectomy patients and 10·2% of stented patients (p 0·008) had a stroke or death at 30 days plus or ipselateral stroke at 31 days to 6 months. 6·1% of endarterectomy patients and 11·7% of stented patients had any stroke or death within six months (p 0·02). Endarterectomy causes fewer strokes and deaths within 30 days and six months. Longer follow-up will be needed to assess sustained benefits.

N Finlayson

From Mas JL, Chatellier G, Beyssen B *et al.* Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006; **355(16):**1660–71.

CLINICAL PHARMACOLOGY

Problems with medicines in the community

This study was carried out in 63 representative US hospitals. Adverse drug events (ADEs) caused 21,298 outpatients to attend emergency departments, and 3,487 (1·6%) required hospital admission. This translated into 701,547 patients annually in the US unwell, leading to 117,318 hospital admissions; 48·9% of patients were ≥65 years old. Approximately 85% of ADEs caused skin, GI, neurological, metabolic, or coagulation problems or altered mental status; one third were due to unintentional overdose usually by drugs needing regular monitoring (e.g. insulin, warfarin, digoxin). Adverse drug events were caused by relatively few drugs; insulin or warfarin caused 1 in 7 ADEs, and antibiotics caused 1 in 8. Adverse drug events are common in outpatients as well as inpatients, and prevention should focus on better drug overview, and on elderly patients.

N Finlayson

From Budnitz TZ, Pollock DA, Weidenbach KN *et al.* 2006; *JAMA* **296:**1858–66.

GASTROENTEROLOGY

COX-2 inhibition and the prevention of colorectal adenomas

Most cases of colorectal cancer are preceded by colorectal adenomas. High levels of COX-2 enzymes are expressed in both colon cancers and adenomas suggesting that COX-2 inhibitors may be chemoprotective agents. In this study, the investigators gave either a placebo or celecoxib (400 mg once daily) to patients who had undergone colonoscopy and polypectomy at baseline. The primary outcome was detection of adenomas at year one or year three by colonoscopy. At three years, the cumulative rate of adenomas detected was 33·6% in the celecoxib group and 49·3 % in the placebo group (P<0·001). However, serious cardiovascular events occurred in 2·5% of the celecoxib group and 1·9% of the placebo group. Therefore this trial suggests that COX-2 inhibitors do reduce the occurrence of colorectal adenomas but with an increase in cardiovascular risk that may outweigh any benefit.

J Ferguson

From N Arber, CJ Eagle, J Spicak *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355(9):**885–95.

Advanced colorectal neoplasia isdetected at a higher rate in men during colorectal screening

Screening in colorectal cancer can lead to a decreased incidence and mortality. In this study, the investigators performed a large cross-sectional analysis of a colonoscopy-based screening programme from Poland. Advanced neoplasia was detected in 5·9% of participants aged 50–66. Interestingly, on regression analysis, male sex was independently associated with advanced neoplasia. This suggests that recommendations for screening programmes may in the future need to be refined to include sex as well as age and family history.

J Ferguson

From Regula J, Rupinski M, Kraszewska E, *et al.* Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006; **355(18):**1863–72.