Buspirone studies in primary care; ACE inhibitors in cardiac failure; when do migraines occur?

**Buspirone in primary care**

Preliminary data from a recent double-blind multicentre study in 410 patients with major depressive disorders and accompanying anxiety have shown buspirone to be significantly superior to placebo in both the melancholic and non-melancholic sub-groups. The median final dose of buspirone was 50 mg/day in responding patients — about twice the usual anxiolytic dose. Ten studies in primary care show that buspirone has favourable efficacy and tolerability. Retrospective analyses of these and other studies have shown no adverse clinical interactions with a wide variety of co-prescribed medication, including tricyclic and tetracyclic antidepressants, antihistamines, bronchodilators, H2 antagonists, oral contraceptives, NSAIDs, hypnotics, cardiac glycosides, antihypertensives or oral hypoglycaemics. Both double-blind and open studies in more than 800 elderly patients show a safety and efficacy profile comparable to that in younger patients during either acute treatment (four weeks) or chronic treatment (up to one year). Except for adverse interactions with monoamine oxidase inhibitors and haloperidol, no other unexpected toxic effects have occurred. More than 3 million patients have been treated with buspirone since it became available for clinical use. Patients have taken up to 3 000 mg — 150 times the average anxiolytic dose — in overdose and up to 2 400 mg a day in clinical studies. Unlike experience with the benzodiazepines and other CNS depressants, retrospective analysis of several studies has shown that buspirone (2%) induced no more depression than placebo (2%) and significantly less than lorazepam (11%), diazepam (7%) or clorazepate (7%). Studies of long-term safety (up to one year) have shown no delayed toxicity.

**ACE inhibitors in cardiac failure**

Seven hundred cardiologists from 27 countries gathered in Montreux, Switzerland, recently for the meeting “Heart Failure Management in the ’90s”, sponsored by ICI Pharmaceuticals. Professor Lars Ryden, Professor of Cardiology at the Karolinska Institute, Stockholm, Sweden, presided. He commented that, over the past few years, important information has emerged which indicates that ACE inhibitors should be used to reduce mortality from heart failure. “We need to use them from mild to moderate heart failure, as demonstrated by the SOLVD study, right through to the later stages of severe heart failure, as demonstrated by the CONSENSUS 1 study,” he said. Focusing on the evolution of heart failure, Professor Victor Dzau of
Stanford University, California, pointed out that, in recent years, it has become apparent that the development of heart failure involves not only structural adaptations of the myocyte, collagen and vascular components of the heart, but of the peripheral vasculature and renal tissue as well. Continuing the focus on abnormal growth mechanisms in cardiovascular disease, Professor Detlev Ganten of the German Institute for High Blood Pressure Research, Heidelberg, Germany, presented current concepts on the role of plasma versus tissue renin-angiotensin-aldosterone systems (RAAS) in local control of cardiovascular function. Experimental data, he said, indicate that the RAAS has a role in target organ damage: administration of an ACE inhibitor at a dose which failed to affect blood pressure still successfully reversed ventricular hypertrophy in the rat model. Such experimental data, he concluded, may help us to determine whether other tissue systems participate in the development of target organ damage, and help us predict the best treatment to use, so that we not only reduce blood pressure but influence target organ damage as well. Turning to the post MI potential for ACE inhibitors, Dr Norman Sharpe (Auckland, New Zealand), said that following MI various changes occur in the infarcted ventricle, which together have been termed ventricular remodelling. Changes in the tissue of the heart, including myocyte hypertrophy and abnormal deposition of collagen matrix, form the basis for ventricular dilatation, he said. Cardiopreparation, a new concept in heart failure, was introduced by Dr Jean-Pierre Ollivier (Paris, France), who outlined the adverse structural changes that occur in the heart during the evolution of heart failure.

Migraines occur in morning, timing similar to MIs

Over one-half of all migraine headaches occur in the morning, says Glen Solomon, MD. He and colleagues analyzed the time of their onset in 15 patients who had a history of migraines. Over 20 weeks, the patients suffered 211 migraines. Of these, 111 occurred between 06:00 and 12:00; 59 between 12:00 and 18:00; and 41 between 18:00 and 06:00. A few patients who had migraines at night often went to bed with them but were seldom awakened by migraines. Dr Solomon says that the similar 24-hour circadian rhythm observed in nonfatal myocardial infarctions, sudden cardiac death, platelet aggregation, and plasma catecholamines suggests that migraines may be vascular in origin. Consider treating a migraine sufferer with drugs that have peak efficacy during hours when the patient is at highest risk for headaches, he adds. Dr Solomon is director, the Headache Training Programme, The Cleveland Clinic. He presented his data at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics in San Antonio.
Anaphylaxis — a margin of safety

The treatment of anaphylaxis should address the emergency situation and the prevention of recurrence, and adrenaline (epinephrine) is the drug of choice. Soon, it will be possible to provide susceptible patients with personal protection against anaphylaxis. Bayer-Miles Pharmaceuticals are shortly introducing an on-the-spot, patient-administered emergency treatment in the form of a dose-controlled, pre-filled adrenaline syringe, to be carried on the person of susceptible individuals at all times. These syringes will prove useful not only to those patients receiving medical treatment which could predispose to anaphylaxis, but also to those patients with known allergies to substances encountered in everyday life. Any health care worker involved in the administration of medication or care of patients — whether doctor, dentist or paramedic, is ethically obliged to be able to appropriately manage the potential consequences of his actions — the anaphylactic reaction. Each syringe contains two 0.3 ml doses of adrenaline (epinephrine), for those occasions when one dose is insufficient. This eliminates not only the loss of valuable time in drawing up the drug, but also the possibility of dosage error. Patients and doctors may never need to use it, but the mere presence of such a facility will provide a margin of safety which both will appreciate.

Top medical researcher honoured

Professor Michael Kew of the University of the Witwatersrand has won the 1991 Wellcome Medal for Medical Research. He received this honour for his investigative work into the role of the hepatitis-B virus in the pathogenesis of liver cancer. In a research programme conducted over the past 20 years on two continents, Professor Kew has been investigating the high incidence of cancer of the liver in the black population. Primary cancer of the liver occurs more commonly in the black people living in Africa south of the Sahara than in population groups in any other region of the world with the possible exception of parts of the Far East. The incidence of the tumour is particularly high in South Africa. This tumour carries an especially grave prognosis in black patients: it is rarely amenable to surgical resection, it responds very poorly to non-operative treatment, and the average survival time is only 11 weeks from the onset of symptoms. Professor Kew’s research has shown a very close association between chronic infection with the hepatitis-B virus and the development of liver cancer. The great majority of black patients either are or have been infected with the virus. The virus is present in the patient’s blood and can also be detected in the liver and cancer cells. In the cancer cells, the viral DNA is almost always integrated into the human DNA. If it could be proved that the hepatitis-B virus causes liver cancer this would greatly strengthen the need for a nation-wide programme in which all newly-born black babies and all young black children are vaccinated against the virus.
The Systolic Hypertension in the Elderly Programme (SHEP) tested the hypothesis that, if isolated systolic hypertension causes cardiovascular events, antihypertensive treatment might be beneficial. Thus 4736 subjects aged 60 years or more with systolic blood pressure between 160 and 219 mm/Hg but with diastolic blood pressure below 90 mm/Hg were randomized to active treatment or placebo. Mean age of the participants was 72 years. Active treatment was with low-dose thiazide (chlorthalidone 12.5 to 25 mg daily) with the addition of atenolol 25-50 mg daily, if necessary. The goal of treatment was a systolic pressure below 160 mm/Hg, or a reduction of 20 mm/Hg if the baseline systolic value was less than 180 mm/Hg. Patients were followed for an average of 4-5 years. Treatment significantly reduced the incidence of stroke by 37% and of all cardiovascular events by 32%. The effect of treatment on coronary heart disease was particularly interesting. Myocardial infarction was reduced significantly by 33%, fatal coronary events non-significantly by 20% and all coronary events significantly by 25%. Editorial in THE LANCET observed that, although the patients studied in SHEP are not typical of all hypertensive patients, the results nevertheless drive a stake through some fondly held hypotheses. For example, it has been suggested that excessive reduction of diastolic blood pressure in patients with pre-existing coronary disease may actually cause coronary events — the so-called J relation. The highly significant 25% reduction in coronary events with blood pressure reduction shown in SHEP argues strongly against the J hypothesis. A second suggestion is that the metabolic effects of beta-blockers and thiazides on lipids or insulin resistance will increase coronary risk. In SHEP, patients with average initial serum cholesterol of 6.1 mmol/l were treated with low dose chlorthalidone and addition of atenolol when required. The significant reduction in coronary events with these treatments speaks for itself.

Finally, the hypothesis that thiazide treatment may predispose to coronary death in those with abnormal electrocardiograms initially was put to test within SHEP. In these patients, thiazide-based treatment significantly reduced the rate of myocardial infarction and coronary death by 31%. THE LANCET editorial poses the question: “Is it too much to hope that these hypotheses will now be given a decent burial?”, and concludes by saying: “Low dose thiazides and beta-blockers should be accepted unreservedly as suitable first-line therapy for the vast majority of hypertensive patients.” Commenting on another trial which has also proved treatment of hypertension in the “old” elderly (70-84 years) to be worthwhile [Morbidity and Mortality in the Swedish Trial in Old Patients with Hyperten-
Family, personal history raise risk for colorectal cancer

Patients with a family history or those who have been successfully treated for colorectal cancer are at higher risk for developing the disease, according to studies presented at the 90th annual convention of the American Society of Colon and Rectal Surgeons in Boston.

- Malcolm Stuart, BSc(Med), studied 600 patients with a family history of colorectal cancer. Colonoscopy detected neoplasms in 45%. The incidence of neoplasms in patients with more than one first-degree relative with colorectal cancer was 67%; the rate among asymptomatic patients was 36%; and in patients aged 30 to 39, the incidence was 20%. Dr Stuart recommends colonoscopy every 4 years for patients 30 and older with a family history of colorectal cancer and every 3 years if two first-degree relatives have been affected. Dr Stuart is a fellow of the Royal Australian College of Surgeons, Sydney.

- Patients successfully treated for colorectal cancer have a much greater risk of again developing the disease than reports based on crude rate would indicate. Rebecca LCali, MD, and colleagues reviewed the records of 5,476 colorectal cancer patients. The cumulative risk for developing a second incidence increased at a yearly rate of 0.35% and reached 6.3% at 18 years. Dr Cali says the crude rate, which was 1.5% in this study, is inaccurate because it does not consider a number of factors, such as patients who die of other causes 1 or 2 years after treatment. Cumulative risk is calculated by summing the rates for the population at risk yearly after diagnosis of the primary lesion. Dr Cali is a fellow in colorectal surgery, Creighton University, Omaha, USA.