Therapeutics 1995

A joint conference on therapeutics with the Faculty of Pharmaceutical Medicine was held at the Royal College of Physicians on 28 June 1995, organised by Professor M C L'E Orme. A wide variety of topics was covered ranging from management of acute poisoning to the treatment of myocardial infarction, as well as the teaching of therapeutics in the new undergraduate medical curriculum. The aim of the conference was to provide an overview of the most recent therapeutic developments and controversies in the specific subject areas covered.

Recent advances in the therapy of acute poisoning

Dr J A Vale (National Poisons Information Service, Birmingham City Hospital) reviewed the role of gastric lavage, syrup of ipecacuanha, and activated charcoal in reducing drug absorption following acute overdose. Regardless of treatment, the mortality following overdose remains low (less than 1%). Studies evaluating the role of gastric lavage in overdose have been poorly designed and involved only small numbers of patients. There is no good evidence to support the routine use of gastric lavage in overdose except if it is known that a life-threatening amount of the toxic substance has been taken within one hour before admission to hospital. Similarly with ipecac, few studies have assessed the outcome of using it later than an hour after the ingestion of a drug; giving it sooner than that provided no evidence of significantly reduced drug absorption. Together with the fact that the use of ipecac is sometimes associated with aspiration pneumonia and Mallory-Weiss tears, Dr Vale suggested that its use should be abandoned. The efficacy of single doses of activated charcoal in the treatment of paracetamol poisoning has been compared with that of gastric lavage or ipecac [1]. Charcoal produced a greater percentage fall in plasma paracetamol concentration than the other two treatments. Using multiple doses of activated charcoal in the treatment of overdoses is simple, inexpensive, safe and may make dialysis unnecessary. This form of treatment is particularly effective in adsorbing toxic material from slow-release preparations and drugs which reduce gastric emptying. The use of activated charcoal may also interrupt both the enterohepatic and enteroentero circulation of certain drugs, thus reducing their absorption. It also shortens the half-life and increases the clearance of drugs such as phenobarbitone and carbamazepine [2-4].

Management problems following ingestion of street drugs

Dr J A Henry (Guy's Hospital, London) started his talk with the sobering statistic that 25% of children in the UK have tried drugs by the age of 16, and that the drugs trade has an estimated annual turnover of about £3 bn. Heroin kills about 200 people a year as a result of experimentation, taking heroin of high purity or from a loss of tolerance after withdrawal, for example in prison, followed by re-exposure to the drug. Death is primarily due to respiratory depression, aspiration or pulmonary oedema. Using citric acid to dissolve the drug is called ‘chasing the dragon’ and may result in encephalopathy.

Cocaine abuse is more common in the USA than in the UK, and may lead to agitation, paranoia, confusion, aggression, hallucinations, convulsions, cerebrovascular accidents, chest pain, palpitations, dyspnoea and myocardial infarction. The effects on the heart include premature atherosclerosis, intimal hyperplasia and coronary artery spasm. Cocaine abuse should be suspected if a patient below 30 years old presents with a myocardial infarction. Cocaine may be smoked (crack), sniffed (rocks) or injected. Inhaled cocaine can cause pneumonitis. There is no antidote, and care after taking an overdose is largely supportive.

LSD (lysergic acid diethylamide) is a hallucinogen which causes perceptual distortion and flashbacks. ‘Bad trips’ may cause depression, acute paranoia and anxiety; death frequently results from suicide or violence.

Amphetamines produce a rush of energy and confidence, diminish fatigue, and suppress appetite through a sympathomimetic effect. They may cause convulsions, hyperthermia, rhabdomyolysis and renal failure. In animal studies there is evidence that amphetamines produce a group effect: mice become hyperactive only if given amphetamines in a group. Ecstasy or MDMA (3,4-methylenedioxyamphetamine) kills about 25 people a year. It is mainly used in clubs to improve the ‘dance experience’ by creating a feeling of boundless energy. The main danger is death from overheating caused by frenetic dancing. Heat production increases but sweating is reduced, so body temperature may rise dramatically. Other known effects are trismus, muscle spasms, tachycardia, paranoia, hepatotoxicity and cerebral haemorrhage. Clinical management requires resuscitation, rehydration and treatment of convulsions. Dantrolene may be effective if the temperature is over 40°C. At rave parties, dancers often chew gum to reduce jaw stiffness, inhale ‘Vicks’ to increase hallucinations and drink plenty of sugary drinks such as lucozade to maintain hydration. Ecstasy abusers do not usually take alcohol or cannabis which are considered ‘downers’.

Drug couriers who act as ‘body packers’ and swallow condoms or plastic bags containing drugs, or insert them vaginally or rectally, may collapse if the drug
becomes absorbed. Treatment is supportive and surgery not indicated. In the USA, whole gut lavage with an isotonic solution is sometimes used.

Finally, Dr Henry mentioned some other drugs of abuse, including injected temazepam which is a particular problem in Scotland, and phencyclidine or ‘angel dust’ which leads to aggressive behaviour and violence. *Khat* is a problem in Somali refugees who may chew it in large amounts and develop paranoid psychosis. The active substance is methcathinone which is like cocaine.

**Treatment of peptic ulceration**

**Professor C J Hawkey** (University of Nottingham) discussed the modern treatment of peptic ulceration; extensive experience with drugs such as the H₂-receptor antagonist agents and the proton pump inhibitors have shown that simple acid suppression is not enough to effect a cure of peptic ulcers. The discovery that *Helicobacter pylori* is associated with 95% of duodenal ulcers and over 80% of gastric ulcers suggests that it has an important role in the pathogenesis of peptic ulceration. However, how it does this is not fully understood; the mechanism is complex and involves an interplay between bacterial-derived cytotoxins, transporter proteins and cytokine secretion which ultimately leads to mucosal damage. Should all patients receive treatment aimed at eradicating *H pylori* [5]? Professor Hawkey pointed out the increasing evidence for the use of eradication therapy, not least the much lower relapse rates (0–3% annually) than with continued H₂-receptor antagonist treatment (10–30%). He suggested that eradication therapy should be used in all patients with peptic ulceration not associated with the use of non-steroid anti-inflammatory drugs (NSAIDs). Many regimens have been used to eradicate *H pylori*. Recently, a 93% eradication rate has been reported with a one week course of omeprazole, clarithromycin and tinidazole. The nitroimidazole is poorly tolerated, so Professor Hawkey’s favoured regimen is omeprazole 20 mg bd, amoxycillin 1 g bd and clarithromycin 250 mg bd for one week. The mode of action of proton pump inhibitors in *H pylori* eradication is unclear, but may be due to their intrinsic antibacterial activity which has been demonstrated *in vitro* and/or an enhancement of the bioavailability of the concomitantly used antibiotics.

The other major cause of peptic ulceration is the use of NSAIDs. The rise in NSAID use runs parallel with an increase in peptic ulcer complications, particularly in the elderly. The risk of ulceration varies with the individual compounds, azapropazone and piroxicam having the highest rates of gastrointestinal toxicity [6]. The concomitant administration of misoprostol, a synthetic prostaglandin analogue, reduces endoscopically defined ulceration by 50%; more recently, the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) study [7] has shown that it also reduces by a similar amount significant gastrointestinal adverse events such as haemorrhage. Misoprostol, however, is poorly tolerated, causing diarrhoea in a significant percentage of patients. H₂-receptor antagonists or omeprazole, given in high dosage, may also prevent NSAID-induced peptic ulceration.

**The use of bisphosphonates in metabolic bone disease**

**Dr W D Fraser** (University of Liverpool) reviewed the use of bisphosphonates in the treatment of metabolic bone disease. These drugs are highly charged and poorly absorbed (oral bioavailability of 1–10%), but are rapidly taken up into bone where they bind to hydroxyapatite. Their half-life in bone is about five years. Bisphosphonates decrease the ability of osteoclasts to resorb bone, thus restoring the balance between osteoblastic and osteoclastic activity [8]. They are used to treat hypercalcaemia of malignancy, Paget’s disease of bone and osteoporosis. In all three conditions, they not only relieve symptoms such as bone pain, but also reduce long-term complications, for example, fractures in Paget’s disease and osteoporosis. For the treatment of hypercalcaemia, these drugs are usually given intravenously, which occasionally has to be followed by oral treatment. Serum calcium levels usually return rapidly to normal, particularly when parathormone-related peptide is not elevated. The treatment of Paget’s disease and osteoporosis usually involves the administration of multiple courses of bisphosphonates. Although many complex treatment protocols have been described, a simplified regimen which involves a 4–6 hour infusion every three months is as effective as the more complex regimes, and is routinely used in Dr Fraser’s unit.

Many bisphosphonates are now available; although the newer generation compounds such as alendronate are pharmacologically more potent than the older compounds such as etidronate, they have not been shown to be clinically more effective. The exception seems to be with steroid-induced osteoporosis in which pamidronate was found to be more effective than cyclical etidronate in increasing bone mineral density.

Bisphosphonates are generally well tolerated, although they can sometimes cause bone pain and hypocalcaemia. Demineralisation leading to osteomalacia is perhaps the most serious adverse effect. It is dose-dependent and more likely to occur with the older drugs than with the new generation compounds which are relatively more potent in inhibiting resorption than in inhibiting mineralisation. However, to minimise the risk of osteomalacia, treatment of osteoporosis with these drugs should not be continued for longer than three years.

**Management of patients with myocardial infarction**

**Professor K A A Fox** (University of Edinburgh) gave an overview of the currently available evidence regarding
the optimal use of thrombolytics in acute myocardial infarction. Following the publication of large studies such as ISAM [9], GISSI-1 [10] and ISIS-2 [11], which clearly demonstrated the beneficial effect of streptokinase in reducing mortality from myocardial infarction, the use of thrombolytics has rapidly increased. Benefit is seen in patients presenting with ST elevation or bundle branch block but not in patients with a typical history but who have a normal ECG, non-specific ST segment changes or ST depression [12].

There is no doubt that the earlier the treatment after the onset of chest pain, the greater the benefit to the patient. In fact, every hour of delay is associated with a reduction in the benefit by about 1.6 lives per 1,000 patients; there is little benefit in those presenting 24 hours after the onset of chest pain [12]. To minimise the delay to treatment, some clinicians have advocated the use of pre-hospital thrombolysis. Professor Fox feels that although the time to thrombolytic treatment is significantly shortened when anistreplase is given at home (eg in the EMIP study [13]), the benefit in terms of fatality rates is not great. Furthermore, about 60% of general practitioners are opposed to giving thrombolysis at home, and only 32% own an ECG machine. An alternative approach may be a ‘fast track’ triage system within a hospital whereby patients with myocardial infarction are rapidly identified and directly assessed by the cardiac care team. Such a system can halve the delay to thrombolytic treatment without affecting diagnostic accuracy [14]. Age should not be considered a contraindication to thrombolysis [12]. Fibrinolytic therapy shows greater benefit among high-risk patients presenting with tachycardia and/or hypotension.

Which thrombolytic agent should be used? ISIS-3 [15] has shown no difference between the three currently available agents, but the more recent GUSTO trial [16] suggests that accelerated alteplase (recombinant tissue plasminogen activator) may be slightly more beneficial than streptokinase, particularly in patients with extensive infarcts, at the expense of a slightly higher risk of haemorrhagic stroke.

Professor Fox ended his review by stating that streptokinase (in combination with aspirin) should be the drug of first choice in all patients fulfilling the criteria for thrombolysis unless they have previously received streptokinase, are hypotensive or have an extensive myocardial infarct, in which case accelerated alteplase and aspirin should be used together with intravenous heparin. Despite the overwhelming evidence of benefit obtained by thrombolytic treatment, only 35–50% of eligible patients routinely receive thrombolytics [17].

Dr K L Woods (University of Leicester) reflected on the factors affecting the impact of a positive trial on usual clinical practice. Wide variations have been observed across Europe in the use of different treatment strategies in acute myocardial infarction, despite the good evidence of the benefit of certain forms of treatment. For example, there is a 100-fold difference in the use of intravenous β-blockers between the UK and Sweden. To determine the factors affecting clinical practice, Dr Woods felt that the paradox of whether trials are generalisable to the real clinical population has first to be resolved. Different trial designs may lead to completely different outcomes despite investigating the same intervention. For example, in meta-analysis, the pooling of the results of small trials may lead to bias towards the positive trials, and differences in the entry criteria between the different trials often make it difficult to interpret the pooled estimate effect.

In contrast, the large prospective trials with their strict entry criteria often give rise to data of high quality, but which may lack statistical power. However, the increase in statistical power obtained in the mega-trials is often at the expense of a reduction in data detail and validation. Furthermore, a mega-trial often has minimum restrictions on recruitment and the use of non-trial medications, both of which may affect trial outcome.

To illustrate these points, Dr Woods considered the use of nitrates and magnesium in myocardial infarction. Randomised trials have demonstrated that short-term nitrates may reduce mortality in acute myocardial infarction by one-third, yet ISIS-4 [18] showed no effect on mortality of oral mononitrate. He speculated that the high non-trial use of nitrates in ISIS-4 could have obscured a true treatment effect.

Similarly, in nine small trials and in LIMIT-2 [19] magnesium was beneficial in myocardial infarction whereas, in contrast, no benefit was demonstrated in ISIS-4. The discrepancy between LIMIT-2 and ISIS-4 may have arisen because in the former study magnesium was given either before or during reperfusion rather than after reperfusion as in ISIS-4. Dr Woods concluded that:

- for the results of a trial to be generalisable, the trial conditions must be clear
- large, simple trials may give inadequate guidance in heterogeneous clinical populations
- adequately powered conventional trials may be better in certain circumstances than mega-trials.

The most important factors in ensuring that trial results are generalisable is adequate randomisation to ensure that the groups being compared are similar in all respects apart from the specific treatment being tested.

Dr Woods ended his talk on the positive note that mortality from myocardial infarction has been falling since the early 1980s, particularly since the mid-1980s publications of the various interventional trials. Thus, the public health gain of intervention in acute myocardial infarction is now becoming visible.
Recommended changes in the undergraduate medical curriculum

Professor C F George (University of Southampton) reviewed the recommendations on undergraduate medical education issued in 1993 by the Education Committee of the General Medical Council (GMC) [20], which has responsibility for 'promoting high standards of medical education and coordinating all stages of medical education'. The medical curriculum is already overloaded. Students have become progressively more disenchanted with the emphasis on the passive acquisition of knowledge rather than on the discovery through curiosity. Until the introduction of provisional registration in 1953, newly qualified doctors were legally entitled immediately after graduation to undertake any form of medical practice without supervision and without any requirement for further training. It was therefore considered essential for the medical graduate to have a comprehensive knowledge of medicine sufficient to meet all contingencies. With the advent of postgraduate training, there is no longer a case for such a 'complete graduate'.

The GMC document outlines a series of goals and objectives for undergraduate medical education which fall into three basic categories:

1. The acquisition of knowledge of health and disease in the context of the whole individual.
2. The acquisition of basic clinical skills including history taking and physical examination, and the performance of basic technical procedures.
3. The acquisition of attitudes necessary to achieve high standards of medical practice.

The principal recommendations outlined in the document to reach these goals and objectives are as follows:

1. The burden of factual information imposed on students in undergraduate medical curricula should be substantially reduced.
2. Learning through curiosity, the exploration of knowledge, and the critical evaluation of evidence should be promoted and ensure a capacity for self-education.
3. A 'core curriculum' encompassing the essential knowledge and skills, and the appropriate attitudes to be acquired at the time of graduation should be defined.
4. The 'core curriculum' should be augmented by a series of 'special study modules' which allow students to study in depth areas of particular interest to them, that provide them with insights into scientific method and the discipline of research, and engender an approach to medicine that is questioning and self-critical.
5. The 'core curriculum' should be system-based, its component parts being the combined responsibility of basic scientists and clinicians integrating their contributions to a common purpose, thus eliminating the rigid pre-clinical/clinical divide and the exclusive department-based course.

A template for such a core curriculum was published in 1990 by the Council for Medical Student Education in Clinical Pharmacology and Therapeutics [21] which comprises representatives from four academic societies in the USA. The core curriculum should include 17 items of factual knowledge (including clinical pharmacokinetics, therapeutic drug monitoring and adverse drug reactions), 16 core skills whereby the student learns to use the factual knowledge, and five core attitudes including a balanced approach to drug prescribing.

In order to assess attitudes to this core curriculum, all 27 UK medical schools were sent a list of items and asked to grade them in terms of importance [22]. Replies were received from 21 medical schools. Areas identified as particularly relevant were prescribing for the elderly and patients with renal failure, the treatment of the acutely poisoned patient and adverse drug reactions (particularly following intravenous drug administration). The process of new drug development was felt to be of less importance.

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Recent advances in rehabilitation medicine

Rehabilitation is aimed at minimising the disadvantage experienced by an individual as a result of functional impairment or disability following disease. It also addresses the impact of the social and environmental consequences of disease. Rehabilitation medicine is a new specialty although the concept of rehabilitation is not. Previously this work was undertaken within the fields of rheumatology, physical medicine, neurology, and orthopaedic, general medical and limb fitting services. In some patients, primarily those with neurological and musculoskeletal disease, the interaction of impairments with social and environmental dimensions can be complex. Effective management requires coordination between the patient, carers, and the medical, therapy, nursing, psychology and social services. The management of patients with complex disabilities is undergoing change with the introduction of new treatments, awareness of needs of patients and carers, and new models of care. This conference, entitled ‘Medical priorities in the rehabilitation of adults with complex disabilities’ given at the Royal College of Physicians on 2 February 1995, reviewed these changes. It dealt with medical priorities in rehabilitation for patients with specific diseases, and recent advances in areas pertinent to rehabilitation medicine.

Medical priorities during recovery

Stroke (Dr Derick Wade, Rivermead Rehabilitation Unit, Oxford)—A stroke rehabilitation service has to respond to the needs of patients and their families and demonstrate effective use of resources. Accurate diagnosis, identification of causative factors, documentation of impairments and identification of coexisting diseases is paramount. Acute interventions such as anticoagulation, thrombolysis or the use of neuroprotective drugs to minimise damage may be possible in the future. Common problems such as dysphagia and adverse effects of drugs on the central nervous system should always be identified. It is important to determine as early as possible what the patient was able to do before the stroke and the individual’s social situation. Standardised assessments of physical function (Barthel Index), cognitive function (Short Orientation and Memory Assessment) and speech (Frenchay Aphasia Screening Test) should be made as well as

Correction: Jacobson G, Hals A. Medical investigator’s views about ethics and fraud in medical research. September/October 1995, pages 405–9. On page 407, second paragraph of the left hand column, the sentence beginning on line 4 should read: ‘Whereas one in ten agreed that they found the evaluation and comments from the committee to be of little use or benefit...’

Correction: Benatar SR. Change and coping with change. September/October 1995, pages 436–41. Reference 13 should, instead, read: Ray JL, Global politics, 4th edn. Boston: Houghton Mifflin, 1992—and reference 18 should be replaced by: Rosenblum N (ed). Liberalism and the moral life. Cambridge: Harvard University Press, 1992.

Rapporteurs:
CAROLINE VAUGHAN, MRCP, Lecturer in Rehabilitation Medicine, Southampton General Hospital
BIPIN BHAKTA, MRCP, Senior Registrar, Rheumatology and Rehabilitation Research Unit, University of Leeds

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