Editors' review of 2006 and the BJCP prize

Jeffrey K. Aronson, Editor-in-Chief; Martin S. Lennard, James M. Ritter, European Editors; Evan J. Begg, Australasian Editor; Lionel D. Lewis, North American Editor; Michael Schachter, Reviews Editor

In this, the first issue of the *Journal* of 2007, we review some of the papers that caught our attention during 2006 (see Appendix 1).

The BJCP prize 2006

'Everybody has won and *all* must have prizes' was the Dodo's conclusion about the caucus race described by Lewis Carroll in *Alice in Wonderland* (1865). We hope that everyone who had a paper published in the *Journal* last year has indeed won – citations and reputation at least. But the cash prizes, alas, are rationed. In deciding the inaugural BJCP prize the judges had a hard task, as one would expect. They finally agreed to split the prize between two contrasting papers, awarding the prize to Dr JA Clayton, Specialist Registrar in Clinical Pharmacology and Therapeutics in the Queen's Medical Centre, Nottingham, and Dr A Pathak, a trainee in Clinical Pharmacology in the University Hospital of Toulouse.

One would have thought that thiazide diuretics would be regarded with considerable caution and even suspicion, particularly when they are prescribed for elderly patients. But when Clayton et al. reviewed the records of more than 32 000 adults from six UK general practices in the East Midlands, they found that of the 12% or so who had received at least one prescription for thiazide diuretics between 1990 and 2002, only 32% had had their serum sodium and potassium concentrations tested. Of those who had been tested, 21% had concentrations that fell below the reference range. The extent of sodium potassium depletion is probably greater than these figures suggest, since some believe that the threshold concentrations below which we define hypokalaemia and hyponatraemia are too low. Low dosages and frequent monitoring are surely essential. This paper was the subject of widespread press interest when it was published [1] and it surely deserves a share in the BJCP prize, demonstrating as it does the value of simple clinical observations, one of the cornerstones of our trade, but under-rated by many nowadays [2].

In contrast, Pathak et al. demonstrated the different benefits of a careful pharmacodynamic study in a small number of patients. They carried out a double-blind, placebo-controlled, randomized, crossover study of the effects of dobutamine 2.5 and 7.5 micrograms/kg/minute in 17 healthy subjects, and measured ventilation, haemodynamics, and sympathetic nerve activity during normoxia, isocapnic hypoxia, post-hypoxic maximal voluntary end-expiratory apnoea, hyperoxic hypercapnia, and a cold pressor test. Dobutamine dose-dependently increased ventilation during normoxia, enhanced the ventilatory and sympathetic responses at the fifth minute of isocapnic hypoxia, and enhanced the sympathetic response to apnoea performed after hypoxia. Pathak et al. concluded that there is a β_1 -adrenoceptor agonist component in dobutamine-evoked increases in peripheral chemosensitivity, although a contribution of other adrenoceptor subtypes cannot be excluded.

We congratulate Dr Clayton and Dr Pathak on winning the BJCP prize, and all of their respective colleagues for their contributions to these excellent and informative pieces of work.

Problems with diuretics

Jennifer Clayton's work on diuretics found an echo in a paper on the risk of falls in elderly people in last year's *Journal*, in which Ziere et al. showed that polypharmacy is a risk factor only when particular drugs (diuretics, of course, but also, for example, benzodiazepines) are part of the daily regimen. The authors concluded that 'the falls assessment should focus on identifying risk-increasing drugs rather than on polypharmacy *per se*. As a consequence, there is an opportunity for risk-reducing interventions in a frail elderly population, in whom polypharmacy is inevitable, in order to control the underlying comorbidity'. However, studies that have explored the use of, for example, the vitamin D analogues ergocalciferol and colecalciferol in preventing falls have been overall disappointing, and other

interventions need to be tested. Greater care over the use of diuretics and antihypertensive drugs in elderly people might be more productive.

There has been much recent research, including many articles published in the *Journal*, on the role of transporter proteins in the biological fate of drugs. However, for various reasons, little is known about the clinical implications of interindividual variability in transporter function. Vormelde et al. investigated the association between the renal clearance of torsemide, a loop diuretic, and genetic variations in the organic anion transporters OAT1, OAT3, and OAT4, all of which are expressed in the kidney. The large variation in renal clearance was partly explained by genetic polymorphisms in bilaterally expressed OAT4, but not in luminally expressed OAT1 and OAT3. Such information is valuable, but this and many similar studies still do not establish the therapeutic relevance of these transporters in determining drug responses. A much more clinically based approach to defining their role, if any, is needed if this basic science is to become of practical value to prescribers.

On the QT – problems with rhythm

'If the heart trembles, has little power, and sinks, the disease is advancing and death is near.' The Ebers Papyrus (circa 3500 BCE) is believed to contain one of the earliest descriptions of fatal cardiac arrhythmias. Torsade de pointes is an infrequent but potentially fatal adverse effect of some non-cardiac drugs [3]. The publicity surrounding the removal of some such drugs from the market (terfenadine and cisapride, for example) was one of the driving forces that caused regulatory authorities to issue guidance concerning the study of the QT interval in the clinical development of new chemical entities [4].

During 2006 Harrison–Woolrych et al. described a patient who developed torsade de pointes while taking sibutramine (a serotonin and noradrenaline reuptake inhibitor) for the treatment of obesity. This patient had a novel mutation in a cardiac potassium channel subunit gene, KCNQ1, which is likely to prolong cardiac membrane depolarization and increase susceptibility to prolongation of the QT interval. A review of reports to the New Zealand Intensive Medical Monitoring Program identified five other patients taking sibutramine who had bouts of palpitation associated with syncope or presyncope symptoms, one of whom had a QT_c interval at the upper limit of the reference range. Among reports concerning sibutramine in the WHO database there were three reports of QT interval prolongation and one fatal case of torsade de pointes in a patient who was also taking cisapride. Taken together these data suggested

that sibutramine could be associated with prolongation of the QT interval and torsade de pointes in genetically predisposed individuals.

At about the same time, Friberg et al. investigated plasma concentrations of citalopram (a selective serotonin reuptake inhibitor, SSRI) and electrocardiographic data from 52 patients after 62 episodes of citalopram overdose, analysed in WinBUGS using a Bayesian approach. The claimed ingested dose of citalopram ranged from 20 to 1700 mg. A pharmacokinetic–pharmacodynamic model predicted the probability of having an abnormal QT_c interval, which was assumed to be related to an increased risk of torsade de pointes. The data suggested that citalopram caused delayed prolongation of the QT interval.

Meanwhile, in our sister journal, the *British Journal of Pharmacology*, Rajamani et al. reported a case of prolongation of the QT interval by the SSRI antidepressant fluoxetine and correlated this with a dual effect of the drug, and its major metabolite norfluoxetine, on hERG (human ether-a-go-go related gene) channels [5]. Both drugs acutely inhibited the hERG channel by pharmacological blockade but also disrupted normal trafficking of hERG protein to the cell membrane. Mutations in a key component of the drug binding site in the S6 region of the hERG channel greatly attenuated the channel block, but did not impair disruption of trafficking. This suggested that hERG channel blockade and drug effects on trafficking are mediated by different mechanisms. These findings add to the growing evidence that disruption of hERG channel trafficking is a mechanism for drug-induced prolongation of the QT interval. In addition, this study has raised questions about the possible limitations of in vitro hERG blockade assays, which are widely used as front-line screens in cardiac safety testing of novel chemical entities. Further study of this phenomenon in relation to the widely prescribed SSRIs or SNRIs is clearly merited.

Finally, Koo et al. studied the ethnic variability of the genes associated with the long QT syndrome (KCNQ1, hERG, KCNE1, and KCNE2) in Chinese, Malayan, and Indian subjects. They observed a higher expression of known hERG channel variants in the Indian subjects compared with the Chinese subjects. Such ethnic variation could underlie variable ethnic susceptibility to prolongation of the QT interval.

The clinical pharmacologist's expertise and management role in patients with this important adverse effect offer a unique opportunity for studying the relationships among the drug concentration, prolongation of the QT interval, and the underlying genotype that confers susceptibility.

New perspectives on opioid receptor agonists

New uses are constantly emerging for old drugs. We encourage readers to tell us about their favourite examples of this, two of which appeared in the *Journal* last year in relation to opioid receptor agonists.

Detrusor overactivity is not easy to treat. Even in clinical trials, the efficacy of anticholinergic drugs is modest and discontinuation rates are high, particularly because of dry mouth. In everyday prescribing the problem is even worse. So the prospect that at least some of these patients may be helped by tramadol, as Safarinejad & Hosseini have shown, is distinctly encouraging. Tramadol reduced urinary frequency, increased urinary volume, reduced incontinence, and generally improved all aspects of the condition. Apart from the obvious evidence-based appeal of a double-blind randomized controlled trial, this paper pressed a few other buttons. Firstly, idiopathic detrusor overactivity is a modern diagnosis that is controversial. Drug companies have espoused it with aplomb, defining it liberally to include most elderly people. Some have criticized pharmaceutical companies for medicalizing normal variations in this way [6, 7]. However, some people do suffer, and genuine relief, which has so far not been in abundance, is welcome. Those who have believed that the best approach to this problem is through anticholinergic action will have been surprised that μ opioid (OP3, now MOR) receptor activity combined with inhibition of amine reuptake could be effective. The effective dose of tramadol was relatively low (100 mg bd), meaning that adverse effects were minimal, apart from nausea, which occurred in 18% of patients.

It is not surprising that an opioid receptor agonist, such as tramadol, should cause nausea. It was therefore surprising to read that motion sickness could be reduced by loperamide, a peripherally acting μ opioid receptor agonist, accompanied (perhaps mechanistically) by reductions in ACTH and ADH, as Otto et al. have shown. The postulated mechanism was diminution of afferent gastrointestinal signals to the vomiting centre, through stimulation of vagal fibres.

New perspectives on NSAIDs

The possible cardiovascular effects of both non-selective and COX-2-selective anti-inflammatory drugs has generated immense controversy. In our special 75th anniversary issue last year [8], Knights et al. presented a novel angle, the possibility that at least the non-selective drugs inhibit the glucuronidation of aldosterone in the kidney and therefore increase concentrations of the circulating hormone, perhaps by as much as 300%. This is certainly a plausible additional if not principal mechanism for the

deleterious effects of these drugs on cardiovascular outcomes. It is not clear whether the coxibs have similar properties. Elsewhere we highlighted problems with rofecoxib [9] in the light of new Scottish data from Williams et al., who showed that after the withdrawal of rofecoxib there was an immediate increase in the number of prescriptions of celecoxib; the increase, however, was short-lived – after 3 months it fell dramatically. At the same time the numbers of prescriptions of ibuprofen and diclofenac rose. Prescriptions for etodolac and meloxicam also rose – most prescribers probably do not realize that they too are coxibs in all but name. The total number of prescriptions for all the NSAIDs included in this study seems to have fallen by about 10%, perhaps reflecting increased disillusionment with the use of NSAIDs, since the cardiovascular safety of the non-selective NSAIDs has also been questioned.

Disappointment with paracetamol?

TH Huxley once said that the great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact. The use of paracetamol may be such a case, as Bateman et al. have shown. In 1998, UK legislation restricted the amount of paracetamol (and other medicines) that could be sold at any time. Along with other efforts, such as blister packaging, it was hoped that this would reduce the prevalence of self-poisoning with paracetamol and the mortality associated with it. Unfortunately, the latest data, at least from Scotland, seem to show the opposite: little or no change in prevalence and in fact an increase in mortality. One wonders whether over-optimistic expectations have led to complacency and worse clinical outcomes, by diversion from the priority to get patients to hospital quickly to receive early antidote therapy.

Prescribing, prescribing, prescribing

We make no apology for ending with a brief mention of medical education, and in particular how to teach safe and effective prescribing, a topic that occupied much of the attention of the Clinical Section of the British Pharmacological Society during 2006 [10, 11] and will continue to occupy it for some time to come. In a randomized controlled trial of teaching methods, Vollebregt et al. compared two methods of teaching therapeutics, a problem solving paradigm and the normal curriculum in third year preclinical medical students, comparing their knowledge immediately and again 9 months later. The study group scored significantly higher than the control group. This may seem like a small advance, but it shows that an evidence base for teaching methods is possible. Other papers that we published last year, from Maxwell et al.

and Smith et al., showed how a prescribing curriculum can be delivered electronically to medical students.

Without proper training in prescribing, the many important advances that we publish in the *Journal* will not be properly implemented in the clinic.

Appendix 1

References from Br J Clin Pharmacol 2006 highlighted in this review.

- Bateman DN, Gorman DR, Bain M, Inglis JH, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol 2006; 62(5): 573–81.
- Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. Br J Clin Pharmacol 2006; 61(1): 87–95.
- Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic–pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. Br J Clin Pharmacol 2006; 61(2): 177–90.
- Harrison–Woolrych M, Clark DW, Hill GR, Rees MI, Skinner JR. QT interval prolongation associated with sibutramine treatment. Br J Clin Pharmacol 2006; 61(4): 464–9.
- Knights KM, Mangoni AA, Miners JO. Non-selective nonsteroidal drugs and cardiovascular events: is aldosterone the silent partner in crime? Br J Clin Pharmacol 2006; 61(6): 738–40.
- Koo SH, Ho WF, Lee EJ. Genetic polymorphisms in KCNQ1, HERG, KCNE1 and KCNE2 genes in the Chinese, Malay and Indian populations of Singapore. Br J Clin Pharmacol 2006; 61(3): 301–8.
- Maxwell SRJ, McQueen DS, Ellaway R. eDrug: a dynamic interactive electronic drug formulary for medical students. Br J Clin Pharmacol 2006; 62(6): 673–81.
- Otto B, Riepl RL, Otto C, Klose J, Enck P, Klosterhalfen S. Mu-opiate receptor agonists – a new pharmacological approach to prevent motion sickness? Br J Clin Pharmacol 2006; 61(1): 27–30.
- Pathak A, Velez-Roa S, Xhaet O, Najem B, van de Borne P. Dose-dependent effect of dobutamine on chemoreflex activity in healthy volunteers. Br J Clin Pharmacol 2006; 62(3): 272–9.
- Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. Br J Clin Pharmacol 2006; 61(4): 456–63.
- Smith A, Tasioulas T, Cockayne N, Misan G, Walker G, Quick G. Construction and evaluation of a web-based interactive prescribing curriculum for senior medical students. Br J Clin Pharmacol 2006; 62(6): 653–9.
- Vollebregt JA, Metz JC, de Haan M, Richir MC, Hugtenburg JG, De Vries TP. Curriculum development in pharmacotherapy: testing the ability of preclinical medical students to learn therapeutic problem solving in a randomized control trial. Br J Clin Pharmacol 2006; 61(3): 345–51.
- Vormfelde SV, Schirmer M, Hagos Y, Toliat MR, Engelhardt S, Meineke I, Burckhardt G, Numberg P, Brockmoller J. Torsemide renal clearance and genetic variation in luminal and basolateral organic ion transporters. Br J Clin Pharmacol 2006; 62(3): 323–35.
- Williams D, Singh M, Hind C. The effect of the withdrawal of rofecoxib on prescribing patterns of COX-2 inhibitors in Scotland. Br J Clin Pharmacol 2006; 62(3): 366–8.
- Ziere G, Dieleman JP, Hofman A, Pols HA, van der Cammen TJ, Stricker BH. Polypharmacy and falls in the middle age and elderly population. Br J Clin Pharmacol 2006; 61(2): 218–23.

References

- 1 BBC News. Fears raised over diuretic drugs. <http://news.bbc.co.uk/1/hi/health/4603190.stm>.
- 2 Rothwell PM. Funding for practice-oriented clinical research. Lancet 2006; 368: 262–6.
- 3 Kao LW, Furbee RB. Drug-induced q-T prolongation. Med Clin North Am 2005; 89: 1125–44.
- 4 Shah RR. Drugs, QTc interval prolongation and final ICH E14 guideline: an important milestone with challenges ahead. Drug Saf 2005; 28: 1009–28.
- 5 Rajamani S, Eckhardt LL, Valdivia CR, Klemens CA, Gillman BM, Anderson CL, Holzem KM, Delisle BP, Anson BD, Makielski JC, January CT. Drug-induced long QT syndrome: hERG K⁺ channel block and disruption of protein trafficking by fluoxetine and norfluoxetine. Br J Pharmacol 2006; 149: 481–9.
- 6 Payer L. Disease-Mongers. How Doctors, Drug Companies, and Insurers are Making You Feel Sick. New York: John Wiley & Sons, Inc, 1992.
- 7 Moynihan R, Cassels A. Selling Sickness. How Drug Companies are Turning Us All Into Patients. Crows Nest, NSW: Allen & Unwin, 2005.
- 8 Aronson JK. Clinical pharmacology: past, present, and future. Br J Clin Pharmacol 2006; 61: 647–9.
- 9 Aronson JK. The NSAID roller coaster: more about rofecoxib. Br J Clin Pharmacol 2006; 62: 257–9.
- 10 Aronson JK. A prescription for better prescribing. Br J Clin Pharmacol 2006; 61: 487–91.
- 11 Aronson JK, Henderson G, Webb DJ, Rawlins MD. A prescription for better prescribing. BMJ 2006; 333: 459–60.