Monographs in the *Drug and Therapeutics Bulletin*

Seem to be biased

EDITOR,—The *Drug and Therapeutics Bulletin*, published by the Consumers' Association, gives the impression that its (unsigned) monographs are unbiased and accurate. Thus when I am well informed about the topic it comes as a shock to find every appearance of bias. A recent issue includes a monograph on tramadol, which has been available in the United Kingdom since last June but in use elsewhere since 1977 and registered in 45 other countries.¹ Yet the monograph says that "experience is limited."

What I mainly object to, however, are the weasel words in the monograph—for example, the insertion of "clinical" in the phrase "we can find no clinical evidence for the claim that it has a 'dual' action." There is convincing evidence in volunteers that both naloxone and yohimbine can each only partially reverse the analgesia produced by tramadol.^{2,3} Is the Consumers' Association suggesting that experimental pain and pathological pain are mediated by different pathways?

"Tramadol possibly causes less respiratory depression... than other opioid analgesics for equivalent pain relief" is another example. This is the first time my published results (which the bulletin references) have been impugned. A similar conclusion follows from a study on mean postoperative arterial oxygen saturation (K N Bakhshin *et al*, poster presentation, 7th world congress on pain, 22-27 August 1993, Paris) as well as from the two other studies.

When a drug becomes a market leader, as tramadol is in Germany, there must be a strong presumption that both patients and practitioners find that it has worthwhile advantages and acceptable safety. The clue to the generally denigrating attitude that this publication takes to virtually every new drug is clear from the final sentence: "It is more expensive than standard opioids." These are more weasel words. Nothing will ever be cheaper than morphine; the real question is whether the drug has sufficient advantages to justify the cost.

Reducing prescribing costs may be a legitimate aim of the Consumers' Association. It certainly is of the Department of Health, which pays for copies of the bulletin for all clinicians. Even if this is just coincidence, doctors should regard the *Drug and Therapeutics Bulletin* as surrogate government propaganda and take it not with a pinch but with an emetic dose of sodium chloride—BP (the cheapest on the market).

M D VICKERS*

Professor of anaesthetics

University of Wales College of Medicine,
Cardiff CF4 4XN

1 Tramadol. *Drugs Ther Bull* 1994;32:85-7.

2 Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antinociceptive effect by naloxone in man. *Proceedings of the British Pharmacological Society* 1992;35:73P.

3 Desmeules J, Piguet V, Collart L. Contribution of monoaminergic modulation in tramadol analgesic effect. *Clin Pharmacol Ther* 1994;55:151.

*Professor Vickers has received research grants from Searle, acted as clinical expert for the initial submission of tramadol for registration, and has spoken about this drug at meetings sponsored by Searle.

Bulletin editor's reply

EDITOR,—The *Drug and Therapeutics Bulletin* aims to promote the rational use of treatments by publishing independent articles researched with scientific rigour and interpreted through consensus. We rely on data from well controlled trials published in full in peer reviewed journals. We also put great store on monographs in the *British*

National Formulary and (for newly licensed drugs) information in the datasheet. Finally, we look to data on clinical outcomes when determining advice. We are wary of information gained from studies in vitro or in healthy volunteers or that use surrogate end points. To achieve consensus, drafts are developed through at least three versions and are circulated to 30-40 reviewers, who normally include manufacturers, specialists, groups of patients, representatives of the Department of Health, and our advisory council and editorial board. As with any consensus, a single author cannot be identified so articles are published anonymously.

The bulk of our correspondence is done before publication. Nevertheless, letters are received after publication (under two per article in 1994), and when a response is published it is the product of close scrutiny, appears unsigned, and reflects the views of the bulletin.

Now to tramadol. We know of no evidence from studies in patients with pain that analgesia produced by tramadol depends on effects other than those it would have as an opioid receptor agonist. We would not have relied on the abstract referred to by M D Vickers. We quote two studies showing that in (anaesthetic) patients given tramadol "the likelihood of respiratory depression is less" than with other opioids.^{1,2} We were cautious, however, because we had no comparable data from patients with airways disease, the selection of doses for comparison in at least one study seemed to favour tramadol,¹ and we were aware of the advice in both the *British National Formulary* and the datasheet indicating that tramadol can cause respiratory depression. We would not use data from the company "on file." We quote a study suggesting that tramadol was less likely than morphine to cause constipation,³ but the study had limitations: it lasted only four days, and on at least two days the pain relief from tramadol was less than that from morphine. We were not concerned with the statistical assessment but rather with the suggestion that the doses of the two drugs did not produce equivalent analgesia. It would be inappropriate, and possibly irresponsible, not to compare the price of tramadol with that of standard drugs.

Finally, the bulletin's relationship with the government needs to be clarified. The department buys copies of the bulletin and arranges for its distribution. The editorial process is independent. The notion that we provide surrogate government propaganda is mischievous.

JOE COLLIER
Editor

Drug and Therapeutics Bulletin,
Consumers' Association,
London NW1 4DF

1 Fechner R, Racenberg E, Castor G. Clinical investigations on the effect of morphine, pentazocine, pethidine, piritramide and tramadol on respiration. *Anaesth Intensivmed* 1985;26:126-32.

2 Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992;47:291-6.

3 Wilder-Smith CH, Schimke J, Osterwalder B, Senn H-J. Oral tramadol, a μ -opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* 1994;5:141-6.

Treating heart disease

Benefits of thrombolysis were overstated

EDITOR,—John McMurray and Andrew Rankin's review of thrombolytic treatment in myocardial infarction does not present a balanced précis of current knowledge.¹ The authors state that "initiating thrombolysis . . . 30-60 minutes earlier . . . will . . . save about 15 extra lives for each 1000 patients treated" and that "initiating treatment 30-60 minutes earlier can save as many or more lives as substituting accelerated alteplase for conventional streptokinase." This is not true and is not backed up by the references given.

The Fibrinolytic Therapy Trialists' analysis of 35 day mortality showed that, compared with control, thrombolysis saved 35 lives per 1000 in those randomised in the first hour, 25 lives per 1000 in those randomised two to three hours after the onset of symptoms, and so on.² Although this shows a substantial benefit of thrombolysis over control, the loss of benefit per hour of delay was only 1.6 lives per 1000, as shown by the graph that is reproduced in McMurray and Rankin's article. This mega-meta-analysis of nine large randomised trials did not include GUSTO, a large randomised trial of more than 40 000 patients, in which 30 day mortality was 7.2% with streptokinase and subcutaneous heparin (7.4% with streptokinase and intravenous heparin) compared with 6.3% with tissue plasminogen activator and intravenous heparin—a saving of an additional nine lives per 1000 patients.³

Notwithstanding the above, McMurray and Rankin fail to comment on a widely held and logical view—namely, the open artery hypothesis that speed and extent of lysis leading to early reperfusion are important factors in terms of morbidity and mortality in addition to the time from the onset of symptoms to treatment. By comparing benefit from early treatment with benefit from a given agent the paper implies that the doctor is faced with a choice of whether to treat early or whether to use the most effective agent, while in reality these are separate issues which, when combined, produce the most favourable outcome.

Finally, the authors state that the real question is "what is a worthwhile benefit?" This needs to be put into perspective. A benefit of 1% represents a saving of 10 lives per 1000 patients treated. This is a true benefit for those patients whose lives are saved, and the cost per patient is small when compared, for example, with the price of angioplasty or many other treatments that have been adopted into routine clinical practice.

ANTHONY HALL

Medical adviser

D M HUMPHREYS

Medical director

Boehringer Ingelheim,
Bracknell,
Berkshire RG12 8YS

1 McMurray J, Rankin A. Cardiology. I: Treatment of myocardial infarction, unstable angina, and angina pectoris. *BMJ* 1994;309:1343-50. (19 November.)

2 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22.

3 GUSTO Investigators. An international randomised trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.

Nicotine patches may not be safe

EDITOR,—In their first article on recent advances in cardiology John McMurray and Andrew Rankin imply that the use of transdermal nicotine patches is completely safe in patients with coronary heart disease.¹ Serious, sometimes fatal cases of atrial fibrillation and myocardial infarction have, however, been reported after using such patches in patients with and without a history of heart disease, particularly when patients have smoked while using the patch.² Two such cases were reported recently to the Dutch Bureau of Drug Side Effects.³ In one case myocardial infarction occurred in a 39 year old man without a history of heart disease and in the other fatal atrial fibrillation occurred in a 60 year old man with a three year history of atypical chest pain. Both cases occurred shortly after the patient had started wearing a patch to stop smoking.³

The American multicentre study that McMurray and Rankin cited in support of their statement was designed to prove the safety of

transdermal nicotine patches before marketing them. The patients with heart disease who participated were kept under strict cardiovascular control. Many cases of angina pectoris and arrhythmias were reported, which led to patients being withdrawn from the study, being admitted to hospital, and even undergoing angioplasty. The study concluded that patches are safe only in patients with stable cardiovascular disease.⁴

The pharmacological effects of nicotine (regardless of its source) on the cardiovascular system are well known.

(1) Nicotine increases blood pressure and heart rate directly, because it has sympathomimetic effects on the heart, and indirectly, because it stimulates catecholamine release. These effects increase myocardial oxygen demands, risking the development of angina pectoris due to reversible myocardial ischaemia, especially in patients with coronary stenosis.

(2) It causes vasospasm in coronary vessels because of its sympathomimetic effects and because it stimulates the local release of prostaglandins.

(3) It may cause platelets to hyperaggregate and increase blood fibrinogen concentrations, which increase the risk of coronary thrombosis and myocardial infarction.

In addition, the drug interactions of propranolol and the contraceptive pill with nicotine should be considered as they might increase nicotine blood concentrations unexpectedly.⁵

The pharmacological effects of nicotine on the cardiovascular system need to be carefully investigated in patients with heart disease who use transdermal nicotine patches. Currently, the safety of such patients using them depends on continuous supervision by a physician, especially in those with coronary stenosis or a history of myocardial infarction.

MAY R ARNAOT

Resident, accident and emergency medicine

Ten Bosch Hospital,
Willebroek,
Belgium

1 McMurray J, Rankin A. Recent advances in cardiology. I. Treatment of myocardial infarction, unstable angina, and angina pectoris. *BMJ* 1994;309:1343-50. (19 November.)

2 Warner JG, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994;120:695.

3 Cardiale problemen bij toepassing van nicotine pleisters. *Geneesmiddelen Bulletin (prik board)* 1994;28(8):28. (In Dutch.)

4 Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine placement therapy for patients with coronary artery disease. *Arch Intern Med* 1994;154:989-95.

5 Benowitz NL. Pharmacological aspects of cigarette smoking and nicotine addiction. *N Engl J Med* 1988;319:1318-30.

Authors' reply

EDITOR,—As discussed by John Rawles and us,^{1,2} analysis of the "early thrombolysis" trials, and not just the Fibrinolytic Therapy Trialists' overview, suggests that giving thrombolysis 60 minutes earlier, a generally feasible time saving, will probably save at least 15 additional lives per 1000 patients treated. This conclusion is much less controversial than how the results of the GUSTO trial (global utilisation of streptokinase and tissue plasminogen activator for occluded arteries) should be interpreted. This controversy was reviewed by us, but two points should be emphasised.

Firstly, Anthony Hall and D M Humphreys fail to point out that the GUSTO trial was not just a comparison of two drugs. It was also a trial of strategies, in which one thrombolytic agent was given rapidly (accelerated alteplase) and the other (streptokinase) at the usual rate.

Secondly, the analysis reported by Hall and Humphreys puts streptokinase at a disadvantage. Accelerated alteplase (currently not licensed in the United Kingdom) is compared with the combined

Numbers of patients who need to be treated to prevent one event

Treatment	Event prevented	No of patients who need to be treated to prevent one event
Of hypertension*	Death, cerebrovascular accident, myocardial infarction	3
Coronary artery bypass grafting for left main stem stenosis	Death	3
Aspirin for transient ischaemic attack	Death, cerebrovascular accident	6
Warfarin for atrial fibrillation	Cerebrovascular accident	7
ACE inhibitor for mild heart failure	Death, admission to hospital	8
After myocardial infarction:		
HMG CoA reductase inhibitor	Death, myocardial infarction, cardiac arrest	11
Aspirin	Death, myocardial infarction, cerebrovascular accident	12

*Diastolic pressure 115-129 mm Hg.
ACE=Angiotensin converting enzyme.

HMG CoA=Hydroxymethyl glutaryl coenzyme A.

streptokinase groups. When given with intravenous heparin (a non-standard treatment), streptokinase caused more strokes and bleeding complications; these complications were less frequent when streptokinase was combined with subcutaneous heparin. It would be more valid to compare the combined death rate and rate of non-fatal disabling stroke (the stroke rate was increased by alteplase) in the accelerated alteplase group with that in the streptokinase and subcutaneous heparin group (6.9% v 7.7%, $P=0.03$).

Even if we accept the analysis of Hall and Humphreys the number of patients that need to be treated to save one life by using alteplase rather than streptokinase is around 100 (though the 95% confidence limits are as high as 240).³ In other words, the cost per extra life saved is of the order of £67 000 but could be as much as £160 000. To this must be added the not inconsiderable cost of an extra disabling stroke. The opportunity cost of routinely switching from streptokinase to alteplase would, consequently, be significant. We cannot agree, therefore, that the cost of the extra benefit from alteplase is small compared with other treatments, even angioplasty (table). We believe that it is entirely appropriate to place these issues in the context of the extra benefit that could be obtained, at no extra cost, by improving current practice to ensure that thrombolysis is given as early as possible.

We did not wish to imply that transdermal nicotine replacement treatment is completely safe in patients with coronary heart disease. Instead we concluded that the role of nicotine replacement in helping patients to stop smoking after a myocardial infarction should be explored further. We still think that this is the case. The study we cited is a double blind placebo controlled five week trial in 156 patients and is, therefore, of considerable value. May R Arnaot, however, cites only individual case reports as evidence against the safety of nicotine replacement treatment. Few such cases have been reported to the United States Food and Drugs Administration.⁴

Arnaot summarises the well known effects of nicotine on the cardiovascular system. Nicotine itself, however, has less pronounced effects than smoking on some of these variables.⁴ Concomitant smoking should ideally be avoided and only patients whose condition is stable should be considered for treatment. We think, however, that the role of nicotine replacement as an aid to smoking cessation in survivors of myocardial infarction should not be dismissed without fuller evaluation.

JOHN McMURRAY
Consultant

Department of Cardiology,
Western General Hospital,
Edinburgh EH4 2XU

ANDREW RANKIN
Senior lecturer

University Department of Medical Cardiology,
Royal Infirmary,
Glasgow G3 7ER

1 Rawles J. Treatment of myocardial infarction and angina. *BMJ* 1995;310:465. (18 February.)

2 McMurray J, Rankin A. Treatment of myocardial infarction and angina. *BMJ* 1995;310:465. (18 February.)

3 Farkouh ME, Lang JD, Sackett DL. Thrombolytic agents: the science of the art of choosing the better treatments. *Ann Intern Med* 1994;120:886-8.

4 Orleans CT, Resch N, Noll E, Keintz MK, Rimer BK, Brown TV, et al. Use of transdermal nicotine in a state-level prescription plan for the elderly. *JAMA* 1994;271:601-7.

GPs accept patients' vote on fundholding

EDITOR,—My partners and I were interested to read of the ballot of patients in a practice in Oxfordshire over whether their practice should become a fundholding practice.¹ Our patient participation group, in association with Leicestershire Family Health Services Authority, funded and carried out a similar exercise in 1991. I write not to claim a first but to compare the outcome.

The fundholding facilitator of the family health services authority and the patient participation group's committee agreed a foreword to the voting paper, explaining the pros and cons of fundholding. No indication of the general practitioners' views was given. The voting papers were sent to a 10% random sample (chosen by the family health services authority) of our adult patients. All voting papers were anonymous and were returned in prepaid envelopes.

Altogether 850 papers were distributed; 372 were returned. The number of patients in favour of the practice becoming a fundholding practice was 108, with 262 against (two spoilt papers)—that is, 70% of the respondents were against fundholding for the practice. The commonest reason against fundholding was the problem of patients' confidence in their doctors' decisions once money had entered into the equation.

Our practice did not become fundholding, and we have seen no reason since then to change our minds.

OREST MULKA
Principal in general practice

Measham Medical Unit,
Leicestershire DE12 7HR

1 Leaver M. GPs accept patients' vote on fundholding. *BMJ* 1995;310:349-50. (11 February.)

Reductions in defence medical services

EDITOR,—While fully understanding the concern expressed by the BMA's armed forces committee over the proposed changes in the medical defence services, I cannot accept that the changes will have an "adverse effect on the quality of care which will be offered to serving personnel in the future."¹ In addition, the statement that doctors are unlikely to be recruited on short career commissions in the future is not correct. There will be a full and rewarding career in the, albeit smaller, armed forces medical service of the future, and short term commissions will, as at present, form the bedrock of our recruiting policy.