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. *Anästh 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