BMJ

LONDON, SATURDAY 11 JANUARY 1992

Clinical trials in community pharmacies

Too little is known about over the counter drugs

In 1990 sales of over the counter medicines in Great Britain amounted to £650m, equivalent to one quarter of the cost of drugs used by the NHS. Their impact, however, is largely ignored: there is no formal follow up assessing efficacy or safety, and self medication occurs largely without the participation of the general practitioner. But as shown by a recent pharmacy based study which compared astemizole with terfenadine,[1] clinical trials of over the counter drugs are feasible.

The common perception is that drugs bought over the counter are innocuous, but this is not always so—for example, theophylline and insulin may be bought from a pharmacy. Recent years have seen the category of drugs available over the counter expanded by the inclusion of many that were previously available only on prescription. These include loperamide, ibuprofen, hydrocortisone, astemizole, mebendazole, and nicotine chewing gum.

As outlined in its white paper *Promoting Better Health*,[2] the government foresees the community pharmacist's role developing beyond dispensing prescriptions, with more emphasis on treating minor illness. Even now, the average community pharmacist responds to 20 requests a day about the symptoms and treatment of minor illness,[3] and this therapeutic role is likely to become more important as pharmacists are provided with more effective medicines by the deregulation of drugs from prescribed only to available over the counter. Furthermore, the continued emphasis on cost effective prescribing through the provision of prescribing analysis and cost data and indicative prescribing amounts to general practitioners may prompt them to refer more patients to pharmacies to buy their medicines. Some general practitioners already consider that many consultations are for minor complaints that could and should be self treated.[4]

Despite the current consumption of over the counter drugs and the likelihood that this will increase, great ignorance exists of their use, efficacy, and safety. With self treatment being advocated reasonable grounds should exist for believing that the available medicines are safe and effective in the context in which they are used. As the Royal College of Physicians points out, trials in patients are justified not only to evaluate the new but also to assess existing treatments.[5] A good case for clinical trials in pharmacies therefore exists.

How should such trials be conducted? Is aiming for randomised, double blind, placebo controlled trials reasonable, and how should criteria for admission and assessment be applied?

Some pharmacists are already becoming more "hands on" by measuring blood pressure and serum cholesterol concentration. With training they should be able to develop new skills. To participate pharmacists would need adequate facilities, a good relationship with the public, a good relationship with local general practitioners, and strong professional motivation. The lack of privacy in community pharmacies is a potential problem, although some pharmacies have space set aside specifically for counselling.

It is possible to design a pharmacy based trial that conforms to the European Commission's guidelines for good clinical practice.[6] These require approval by an ethical committee and the guarantee of confidentiality and informed consent for subjects and exclude trials that are essentially promotional. In the pharmacy based study comparing astemizole with terfenadine[1] issues such as informed consent, referral to the general practitioner, the risk of drug interactions, and avoidance of other over the counter products were addressed in the protocol. The activities of the 12 participating pharmacies were coordinated by two supraregional centres.

The public normally has access to more than one pharmacy, so one condition of entry must be continued attendance at the trial pharmacy; temporary residents such as tourists and students would have to be excluded. Concurrently prescribed treatment should be recorded; although other methods of recording treatment may be acceptable, subjects would ideally take their prescriptions to the trial pharmacy. In fact, this is not substantially different from everyday practice for many people: in shopping areas in Birmingham nearly half the people interviewed said they always bought over the counter products from one pharmacy and nearly two thirds that they visited only one pharmacy for advice and dispensing services.[7] This proportion is likely to be higher in smaller towns. Experience shows that motivation is high among trial participants and that attendance at the pharmacy for follow up is not a substantial problem: only eight of 179 patients recruited to the pharmacy trial did not attend the pharmacy for their follow up visit.[1]

Randomisation may be achieved provided a subset of patients who strongly prefer one treatment option undergo a separate, secondary, analysis.[8] In the recent pharmacy trial this was achieved by dividing subjects into three groups: those who insisted on buying one product, those who requested one but were open to change, and those who had no preference. The latter two subsets were randomised. A placebo arm in the study is in theory possible, but people who have gone to the

effort of seeking active treatment from a pharmacy may be unwilling to accept anything else. The appropriateness and feasibility of such an approach have yet to be tested. Comparative studies should present no such problems.

Blinding is one way of excluding potential bias. One pharmacy trial chose not to blind because it would require the participation of the general practitioner.[9] The European Commission's guidelines for good clinical practice specify that the person responsible for the trial should be a doctor or dentist, though some customers of pharmacies may be reluctant to accept notification to their general practitioner and his or her involvement as part of the protocol. The value of a non-blinded study of this type is limited, particularly when patients and investigators assess the results without objective measurements.

Complete blinding, with double dummy techniques to overcome differences in formulation, may be unrealistic in a community pharmacy setting, and single blinding should be sufficient if only patients' assessments are used. There seems no reason why potential subjects cannot be persuaded of the need to judge a medicine free of preconceptions, knowing that it is not a placebo. Those who do not accept blinding should not be excluded completely but included in a non-blinded arm, which could be assessed separately for possible bias and could add further useful data on safety. Blinded trials in the community pharmacy require further evaluation.

A thornier problem is defining criteria of symptoms for admission and assessment. Standardisation with appropriate protocols is essential: people attend pharmacies complaining of vague problems, which, for a clinical trial, must be defined. Definitions of diarrhoea—of both frequency and severity—vary. How runny is a runny nose? How bad is a headache? Assessments by both the pharmacist and customer are therefore important. Once admitted to the study, subjects are perfectly capable of assessing their own symptoms with visual analogue scales and symptom diaries. For example, one comparison of cold symptoms by both doctors and subjects at the Medical Research Council's Common Cold Unit recorded a close correlation between the two,[10] suggesting that this methodology is valid.

If health policy is to encourage the public to use community pharmacies pharmacists will need information on the relative efficacy and safety of over the counter drugs. The role of pharmacy based clinical trials is potentially valuable and worthy of further testing.

STEVE CHAPLIN

Drug Information Specialist,
Haydon Bridge,
Northumberland NE47 6HG

ALISON BLENKINSOPP

Director of Pharmacy Postgraduate Studies,
Centre for Pharmacy Postgraduate Medical Education,
University of Manchester, Manchester M13 9PL

1 Quick JM, Blenkinsopp A. A community pharmacy study to compare the control of hay fever symptoms by astemizole 10 mg and terfenadine 120 mg. *Pharmaceutical Journal* 1991;**246**:272-5.
2 Department of Health. *Promoting better health*. London: HMSO, 1987.
3 Smith FJ, Salkind MR. Factors influencing the pharmacist's advisory role in Greater London. *Pharmaceutical Journal* 1990;**244**(suppl):R4-7.
4 Cartwright A, Anderson R. *Patients and their doctors revisited*. London: Tavistock Press, 1981.
5 Royal College of Physicians of London. *Research involving patients*. London: Royal College of Physicians, 1990.
6 Group Working Party on Efficacy of Medicinal Products. *Notes for guidance*. Brussels: Commission of the European Communities, 1988.
7 Milburn LJ, Dunbar PE, Kendall HE. Factors influencing pharmacy practice in the West Midlands. *Pharmaceutical Journal* 1990;**245**:R19.
8 Brewin CR, Bradley C. Patient preferences and randomised clinical trials. *BMJ* 1989;**299**:313-5.
9 Noyelle RM, Crossland DM, Pickvance NJ. Ibuprofen, aspirin, and paracetamol compared in a community study. *Pharmaceutical Journal* 1987;**238**:561-4.
10 Macintyre S, Pritchard C. Comparisons between the self-assessed and observer-assessed presence and severity of colds. *Soc Sci Med* 1989;**29**:1243-8.

Psychiatric symptoms and low blood pressure

More evidence for an association

German doctors apparently have available some 85 preparations for treating low blood pressure (defined as systolic pressure <110 mm Hg or diastolic pressure <60 mm Hg). German medical textbooks attribute symptoms such as mental and physical fatigue, dizziness, depression, and anxiety to hypotension,[1,2] for which one in 20 German women is being treated. Similarly, a survey of French speaking Canadians found that one in 10 of those attending for blood pressure screening was already being treated for hypotension.[3]

The Anglophone medical community currently takes a different view. Hypotension is recognised in its acute stage, after haemorrhage or myocardial infarction; in a chronic form, resulting from persisting cardiac damage or Addison's disease; and as orthostatic hypotension.[4] Constitutional hypotension, however, is not recognised as a disease, being variously described as a "non-disease,"[3] "rarely symptomatic and treatment not indicated,"[5] and the "ideal normal blood pressure."[6] Attention has focused on an apparent excess of psychiatric symptoms associated with hypertension, although such excess is probably secondary to the diagnosis and labelling of the hypertensive state or to treatment with antihypertensive drugs.[7]

How ironic, therefore, that at the time when Britain is so preoccupied with Europeanisation, analysis of data from the first phase of the second Whitehall study found a relation between low systolic blood pressure and complaints of tiredness and responses to a valid measure of psychiatric morbidity (the general health questionnaire) (p 75).[8] The association between low blood pressure and complaints of tiredness, however, disappeared in an analysis that controlled for the questionnaire's score. This is the second paper published in this journal within a year to show the presence of symptomatic hypotension in a British population. An analysis of data from the health and lifestyle survey also showed that complaints of tiredness and feeling faint were increasingly common with lower levels of blood pressure.[9] In contrast to the Whitehall study, however, in the health and lifestyle survey the score on the general health questionnaire did not show any relationship with blood pressure. Both analyses carefully controlled for evident confounders of age, sex, body mass, drugs, smoking, current physical illness, and current level of exercise.

What might explain these associations? A critic might comment on the inconsistency between the studies and ask whether minor psychiatric morbidity or fatigue was the main consequence of hypotension. The two are not necessarily the same. Secondly, as the data were collected for other purposes an unknown confounder is possible. The analyses were carried out on the data from 74% and 82% of the respondents, respectively, so a response bias could, therefore, have operated. But an explanation parallel to that in hypertension