Medicine in the Elderly

Clinical trials in elderly subjects

Paul Turner

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE, UK.

Why should drug trials be carried out in the elderly?

It is now generally recognized that age is a major source of variation in response to drugs in man.^{1–3} There are several factors involved in this variation with respect to elderly subjects (Table I) including changes in ratio of muscle to fat mass, hepatic extraction and metabolism, renal clearance, and regional blood flow. Changes in receptor number and affinity are also thought to occur, although their contribution to variation in response is controversial.¹

Table I Some factors which influence drug response in the elderly

Age-related changes in	body composition hepatic extraction and metabolism renal clearance regional blood flow receptor number and affinity homeostatic responses
Compliance	
Disease	
Polypharmacy	

A variety of important changes in homeostatic responses occur in elderly subjects (Table II), which render them more vulnerable to the adverse effects of drugs on autonomic activity, temperature regulation, body stability in the erect position, and glucose tolerance. In addition to these general factors, there are important contributions to drug response produced by disease processes which occur with increasing frequency in the elderly,⁴ and by polypharmacy to which many of them are exposed.⁵ Not all this polypharmacy is doctor-prescribed, but includes a considerable amount of self-prescribed medication purchased over the counter from pharmacies, health shops and general stores. In fact, there is evidence⁶ that the greater drug consumption in elderly patients may

Table II Changes in homeostatic responses in the elderly

Tachycardia response to exercise and posture
Baroreceptor function
Body temperature regulation
Bowel and bladder function
Maintenance of upright posture, body stability
Glucose tolerance

(Based on Caird and Scott³)

be a major factor responsible for their apparent higher rate of adverse reactions.

This recognition of the importance of the vulnerability of the elderly to drugs has led to marked changes in attitudes to clinical trials in the elderly, and in requirements of some licensing authorities for special studies of new drugs in old age. As Caird⁷ has succinctly commented on the situation in the United Kingdom, 'For new drugs likely to be a risk for the elderly there are stringent requirements for testing in old age, and close monitoring. Thus, what has for years been immoral and unethical has suddenly become compulsory.'

The question arises, of course, as to which new drugs are 'likely to be a risk for the elderly'. Caird's list of criteria for at risk drugs used by the Licensing Authority included those with a low therapeutic index, those whose clearance is likely to be reduced, where interactions are likely with other drugs commonly used in the elderly, where kinetic or dynamic effects may occur due to ageing of organs or common disease processes, or where the drug belongs to a therapeutic class with a bad record in the elderly. This list might in reality be thought to include most if not all new drugs. Furthermore, because drugs differ, even within a particular therapeutic class, in their physiochemical properties, their extent and routes of metabolism, and their detailed mechanism of action, there is a lack of uniformity in their dependence on age as a predictor of efficacy and adverse effects. The pharmacokinetic profiles of some drugs show little, if any, difference in elderly compared with younger subjects,⁸ often reflecting lack of clear information on the metabolites

Correspondence: Professor P. Turner, B.Sc., M.D., F.R.C.P.

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produced in the case of extensively metabolized compounds.⁹ It is necessary therefore, in the interests of prudence, to study the absorption and fate, as well as efficacy and safety, of all new drugs in the elderly as well as in younger subjects, before they receive approval for general use. It has, furthermore, been argued⁷ that many drugs already marketed should also be examined in this way.

Who should be included in studies in the elderly?

A general criticism that is sometimes made of many pharmacokinetic studies is that the subjects employed do not represent the population of patients to be treated.³ Very often they are healthy young ambulant volunteers rather than the older, sick, infirm patients who will receive the drug for treatment. This same problem must, therefore, be addressed in considering studies in the elderly. The following groups of patients should probably be considered for inclusion in such studies:

1. 'Normal' elderly subjects, aged 65 or above, who are drug-free and show no evidence of systemic disease on clinical examination, electrocardiography and routine tests of haematological, liver and renal function. It is recognized that the use of 65 years as a cut-off point is arbitrary, and that some important age-related changes occur before this age. For example, renal blood flow and glomerular filtration rate fall by about 1% per annum after the age of 30 years, and organic brain disease increases from the age of 60 years. In general, however, it is convenient to use 65 years as the lower age limit in defining the population group for such studies.¹

2. Because there is an inevitable association of chronic disease with increasing age, there is a strong case against excluding patients with such conditions from study, provided that they are clearly recognized as a well-defined cohort of patients, separate from the 'normal' group already defined. Such patients would be chosen according to the type of drug under evaluation, but might include patients with stable hepatic or renal impairment, musculoskeletal or joint disease, hypertension, and controlled heart failure. Patients whose condition is unstable should be excluded from such studies.

3. Many elderly patients take drugs chronically, particularly non-steroidal anti-inflammatory drugs or compound analgesic preparations,⁵ and it is desirable that kinetic or dynamic interactions which might occur in the elderly should be recognized as early as possible. Patients who are stabilized on such long-term treatment with other drugs may, therefore, be considered for inclusion in studies, provided that they are clearly defined as a subgroup distinct from those groups of subjects discussed in groups 1 and 2 above.

4. Finally, the drug should be examined in detail in patients suffering from the condition for which the drug is indicated.³ This group will probably be relatively heterogeneous when compared with the other groups above, but nevertheless the effects of the disease process, both on presentation and during its response to treatment, on the drug's kinetics and action must be determined.

Organization of studies in the elderly

Although several eminent professional bodies such as the Royal College of Physicians have made recommendations on the principles which should govern prescribing for the elderly,¹⁰ and there are a large number of codes of practice for research in volunteers and patients in general, it has not been possible to find any published guidance specifically designed for studies in elderly subjects, either volunteers or patients. The following considerations may be regarded as self-evident, but nevertheless should be stated:

- (a) All clinical trials, including those in the elderly, should be subjected to scrutiny and approval by an impartial, properly constituted ethics committee before they are commenced. Where elderly subjects may be used, the committee should include a clinician with a special interest in, and experience of geriatric medicine. If the committee does not usually contain such a person, then he/she should be coopted for that particular decision.

- (b) A badly designed experiment is unethical in itself. Because of the heterogeneity of the elderly patient population, it is essential that studies designed to investigate them should have appropriate advice in their preparation from a statistician experienced in clinical trial design and data analysis. Too many studies in the literature involve small and inadequate numbers of patients, so that their conclusions are invalid.

- (c) It is important for the public perception of clinical research, as well as for the assured well-being of the subjects, that investigations in the elderly should be supervised by a physician experienced in, or specializing in geriatric medicine as well as in clinical research. It is encouraging to see the growing number of physicians who have dual training in clinical pharmacology and geriatric medicine.

- (d) Another factor which is important for public acceptance of the need for research in elderly subjects is the assurance that 'informed consent' will be freely obtained before inclusion in a study, even though it is recognized that ability to understand the nature of the study may well be less in the elderly than in younger subjects. The prior approval of an ethics committee, and involvement of younger relatives in the agreement

to participate will also help to safeguard the interests of the volunteers.

(e) It is desirable that the results of all prospective clinical trials in the elderly should be published and become part of the public domain. This principle applies, of course, ideally to all well conducted human investigations, but particularly to studies in the elderly because of the relative paucity of good information on the factors influencing their drug response.

Conclusion

The average age of the population is increasing, and a greater proportion is reaching the age range of 65

years and over. We cannot, therefore, ignore the need for information on the clinical pharmacology of drugs in the elderly. At present the general attitude to such studies is defensive, despite the change of requirements of some licensing authorities, and a campaign of education is necessary to demonstrate to the medical profession and the public at large that a better understanding of drug kinetics and action in the elderly will lead to improved patient care and quality of life.

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