New Drugs

Prescribing in old age

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The growth of information about drugs and prescribing in the elderly over the past 15-20 years has been stimulated by three main factors, which still, in general, retain their validity.

Firstly, there are the demographic trends, particularly the continually expanding number of people aged over 75, who present a complex range of requirements for health care, including drug treatment.

Secondly, expenditure on drugs for the elderly is proportionately greater. Figures from the Association of the British Pharmaceutical Industry for 1984 showed that of 315 million prescriptions, 77.6% were for people exempt from prescription charges, of whom about half were elderly. Thus 35-40% of drug expenditure is on the elderly (these figures relate to those of pensionable age), who constitute 15-16% of the total population.

Thirdly, there is a disturbing apparent increase with age in susceptibility to adverse drug reactions. This has been more difficult to show historically but is an undoubted fact of life, particularly with certain drug groups such as several acting on the central nervous system, those with autonomic effects, and a variety of cardiovascular compounds. Information has been derived from anecdotal reports, expensive drug surveillance programmes in hospitals, detection systems for adverse drug reactions (such as the yellow card system of the Committee on Safety of Medicines), and reports on samples of selected patients, such as those being admitted to psychiatric units or departments of geriatric medicine.

Underreporting and exploitation

The extent to which age is perceived as conferring increased vulnerability may be positively weighted by the greater extent of prescribing but negatively weighted by a widespread failure to detect and diagnose iatrogenic disease in the elderly and by the underreporting of adverse reactions to regulatory bodies. Such underreporting is particularly likely where the adverse effect can be readily explained as an exaggeration of the drug's main action or one of its known side effects—that is, a type A or dose related effect. Many older people, particularly those who are disabled, tend to become reconciled to less than optimal health; hence neither they nor their carers complain readily, and the more subtle, if debilitating, consequences of iatrogenic disorder are readily overlooked unless prescribers remain alert.

The rapid growth in the numbers of new drugs means that special steps must be taken to protect the interests of this vulnerable and potentially exploitable section of the population, particularly as much pharmaceutical innovation is directly aimed at the relief of longstanding disorders prevalent within the age group rather than at radical short term cure.

This paper will first, for completeness, outline the main areas of importance that have emerged from research into drugs in the elderly, though there are numerous recent reviews of the topic.¹⁻⁷ Secondly, the possible implications for future prescribing, drug research, and drug development will be discussed.

Defining the problem

Though the issues mentioned above emphasise drug safety, adverse reactions, and what amounts (as far as patients collectively and individually and indeed the health service as a whole are concerned) to rather poor value for money, it is the more positive objectives of rational and effective drug treatment for older people that should be uppermost. The problems are usually subdivided into two categories—namely, “extrinsic” factors (that is, prescribing and drug compliance) and “intrinsic” factors (that is, pharmacokinetics and pharmacodynamics).

PRESCRIBING PATTERNS

Several prescribing difficulties have been highlighted.

Excessive amount—Several studies have identified large numbers of elderly patients each receiving far more drugs than they can reasonably be expected to cope with in a practical way. Equally, the risk of drug interactions causing unwanted effects is positively correlated with the numbers of drugs prescribed.

Inadequate clinical indication—In the context of multiple problems with symptoms, not all require a pharmacological solution, particularly as the risk-benefit ratio is higher in old age. Treatment without using drugs is often insufficiently explored. Extrapolating clinical indications from younger age groups may also be inappropriate. The particular difficulties of accurate diagnosis in the elderly have already been alluded to. In defence of the prescriber, however, reliable data from clinical trials on drug use in the elderly have been scarce.

Excessive duration of treatment—The withdrawal of drug treatment once the initial indication has resolved often requires greater initiative and discipline than initial prescribing. A reliable “prompting” process is usually needed, together with the necessary time to counsel the patient in order to explain and reach agreement on the drug being withdrawn. Excessive repeat prescribing without review has come in for much justifiable criticism. The stockpiling of drugs is more or less universal in all households, and every geriatrician has a favourite photograph of the vast private pharmacies encountered in the homes of older people. There is now evidence that long term drug treatment with many compounds is not necessary for many patients; examples include hypnotics and other psychotropic drugs, diuretics, digoxin, and non-steroidal anti-inflammatory compounds.

Inappropriate dose regimens—Sufficient information now exists for most drugs to enable prescribers to decide on the best regimen for the elderly. Often the dosage is reduced. The message has probably got through for digoxin, but inappropriately high doses of many

compounds (for example, antiparkinsonian drugs, β blockers, hypnotics, antidepressants) are still commonly prescribed. Complex dose regimens are also given when a simple once or twice daily dosage would be satisfactory and far more manageable.

DRUG COMPLIANCE

Problems of drug compliance are in fact not primarily related to age and are also considered later in this series. Doctors dealing with all age groups are becoming increasingly conscious of the problems and are taking the necessary steps to reduce them. These include the following:

- (1) Prescribing the minimum number of drugs with the simplest possible regimen;
- (2) Improving packaging, labelling, and instructions;
- (3) Identifying patients at high risk: factors include social isolation, severe illness, psychiatric disorder, and long duration of treatment. There is little point in prescribing at all for a patient who has impaired cognitive function or memory unless specific steps are taken to ensure supervision by a third party; and
- (4) Improving communication: several studies have highlighted the discrepancy between the prescriber's perception of what patients are receiving and their actual drug intake. A simple policy measure at all ages would be to ensure that at every consultation each patient is required to bring all drug supplies along to show the doctor. Such an inspection is probably as important as the clinical examination of the patient.

Absolute compliance could never be achieved, and the benefits of "intelligent non-compliance" in some cases have rightly been defended. The goal of rational treatment, however, requires as sensible a contract of agreement as possible between the prescriber and the patient. To achieve this requires time and patience, and the role of mechanical aids to compliance or counselling independent of the prescriber (for example, pharmacists or district nurses), or both, is undoubtedly worth exploring further.

PHARMACOKINETICS

Table I summarises the principle changes in drug handling in the elderly. These broad generalisations represent the main thrust of research to date, but the scale of change, the degree of variability among patients, and the degree of clinical importance differ appreciably among compounds.

TABLE I—Main changes in drug handling in elderly patients

Absorption and bioavailability	Drug absorption by passive diffusion is substantially unaltered with age, though may be marginally slower for some compounds Oral bioavailability of some drugs may be increased by reduced first pass metabolism in liver or gut
Distribution of drugs	Distribution volume of water soluble compounds decreases Distribution volume of lipid soluble compounds increases until extreme age Binding to albumin may decrease, especially in ill health Reactant phase protein binding shows little change with age per se
Metabolism of drugs	Microsomal oxidative (phase I) metabolism exhibits variable decrease with age Non-microsomal, non-oxidative (phase II) metabolism is comparatively unaffected by age
Renal excretion of drugs	Renal elimination of drugs is slower in elderly whether by glomerular filtration or tubular secretion

Absorption and bioavailability

Clinically important changes in passive absorption have not so far been described for any compounds, despite the physiological changes (reduced gastric pH, delayed gastric emptying, reduced blood flow in the small intestine) that might be expected to influence this. The reduction in first pass metabolism for some drugs,

however, by allowing increased peak plasma concentrations to occur after oral administration, might contribute to an increased effect after a single dose. This was undoubtedly the case in the early period of levodopa treatment, when the threefold increase in oral bio-availability of the compound, owing to reduced gastric dopa-decarboxylase activity, accounted for the large number of reports of severe side effects in the elderly and the widely voiced conclusion that the drug was unsuitable for use in this age group.

Drug distribution

The reported changes in drug distribution are readily explained by the reduction in lean body mass and body water, the increase in body fat, and the reduction in plasma albumin (more especially in the context of ill health) that are known to occur in the elderly. For many drugs such changes seem to be of little immediate clinical importance, save that they may have some effect on the extent and duration of response to a drug after a single dose or, in the case of reduced protein binding, may devalue the interpretation of total plasma concentrations used in therapeutic drug monitoring (for example, with sodium valproate). Where an increase in the free fraction occurs in conjunction with other complex changes in pharmacokinetics it may assume greater importance (see discussion of acetazolamide below).

Drug metabolism

Reduced blood flow in the liver and reduced size of the liver with age may be the main contributory factors in the reported reduction in the hepatic clearance of some oxidatively metabolised compounds. The apparent sparing of some metabolic pathways, however, remains unexplained by these mechanisms.

The interpretation of age related changes in drug metabolism has been somewhat confounded by the scale of variability among patients. Thus though in the case of many drugs studied the changes are significant, the 95% confidence interval is extremely wide, making quantitative prediction from age alone unrealistic.

It is now widely stated that these changes are unimportant. From a practical point of view what they in fact imply is a measurable increase in the relative risk of accumulated toxic steady state drug concentrations in elderly patients. To ensure safety it is therefore prudent—almost invariably—to begin treatment with half the normal adult dosage and to titrate upwards only if absolutely necessary and with particular vigilance.

Renal excretion

The parallel decline in both glomerular filtration and tubular secretion with age is in keeping with the "intact nephron" loss hypothesis of renal changes related to age. It is therefore usually possible to correlate reduced renal clearance with estimated or measured creatinine clearance in healthy elderly subjects, irrespective of whether the drug is eliminated predominantly by tubular secretion or glomerular filtration. This is found to be the case with acetazolamide, for example, but only when allowance is made for the reduction in binding of acetazolamide to albumin. The result of the reduced binding is in effect to alter the dynamic balance of distribution and elimination of the drug. The increased concentrations of free acetazolamide are available not only to the kidney for active tubular secretion (resulting in a comparative increase in the total clearance of the drug to concentrations similar to those in a young adult) but also for uptake by red cells (giving increased concentrations of acetazolamide in the red cells). Because the side effects of acetazolamide have been related to the effects of carbonic anhydrase inhibition in the red cell it has been suggested that a complex pharmacokinetic mechanism exists to explain the poor tolerance of this drug by elderly recipients.

In general terms, however, the need for a reduced dose of renally eliminated compounds in the elderly is straightforward where there

is any likelihood that accumulation may give rise to clinically important toxicity.

PHARMACODYNAMICS

Table II shows some of the more important changes in specific aspects of drug sensitivity and in homeostatic mechanisms with age. Elucidating the precise mechanisms in man presents difficulty

TABLE II—*Drug sensitivity in elderly patients*

Cardiac β_1 adrenergic responsiveness is reduced
α_1 adrenergic responsiveness is unchanged
α_2 adrenergic responsiveness is reduced
Responsiveness to benzodiazepines and warfarin is increased
Homeostatic mechanisms may be impaired—for example, postural stability, orthostatic responses, thermoregulation, reserve of cognitive function, mechanisms of bowel and bladder function

for ethical and methodological reasons. Accordingly, some of the data have been derived from animal experiments, while elsewhere the information has been derived indirectly from concurrent measurements of indexes of drug response and plasma drug concentrations. Some of the changes are of direct, clear cut clinical importance, as in the case of the benzodiazepines and anticoagulants, while the consequences of the varying changes in autonomic function are often more difficult to pinpoint because of interaction with other autonomic pathways connected with physiological adaptive mechanisms. Pharmacodynamic changes may, however, be at least as important as alterations in drug handling in modifying the response to drugs in old age; further basic research in these areas is important.

The loss of homeostatic reserve increases the susceptibility of older people to a whole range of side effects of drugs, which feature predominantly in medical reports. These include falls due to postural imbalance and postural hypotension, hypothermia and confusional states induced by drugs, retention of urine, faecal impaction, and urinary and faecal continence problems.

New drugs and the elderly

The lessons of the past and the increased knowledge now available should do much to ensure better results from drug treatment for elderly patients in the future. The basic ground rules of rational prescribing include the following:

- (a) Care in diagnosis, requiring improved detection, accuracy, and definition based on a knowledge of modified presentation of disease in the elderly and a firm clinical indication before starting any course of drug treatment;
- (b) Use of the minimal possible number of preparations, exploring non-pharmaceutical options wherever possible;
- (c) Appropriate dose regimens, adjusted where indicated by pharmacokinetic or pharmacodynamic changes with age; and
- (d) Defined duration of treatment, supported by an automatic mechanism for review or withdrawal and measures to remove stockpiled and outdated drugs.

Computerised record systems offer the opportunity to monitor prescribing performance and perform simple therapeutic audit procedures. Some districts, departments, or practices operate their own drug formularies, which should inter alia reflect the needs of the elderly. Informal peer review sessions to discuss prescribing can be very effective, and it is important that the therapeutics of old age is well represented in undergraduate and postgraduate teaching programmes.

The regulatory requirements for new drugs now have built in safeguards for the elderly. The Committee on Safety of Medicines requires pertinent recommendations for drug dosage in the elderly, based on hard evidence, for all new compounds that have a

prospective market among older patients. Such information is particularly sought when: the drug has a low therapeutic ratio; a reduced rate of elimination is likely; other aspects of drug handling or response are likely to change with age or disease; interactions may be anticipated; or the drug belongs to a class of drugs that has a history of hazardous effects.

In general, data on pharmacokinetics in the elderly are requested, and the efficacy and safety of each compound must be attested at least by a considerable participation of elderly patients in clinical trials over a reasonable period. Though these requirements clearly constitute a safeguard, some possible disadvantages include a prolonged premarketing process, with correspondingly aggressive marketing drives after a licence has been granted, and a rather mechanical flow of data emerging from regulatory studies conducted in contract houses, possibly obscuring some of the more important findings that could emerge from critical studies undertaken in academic departments. The content of regulatory requirements for new drugs to treat the elderly accordingly requires periodic and careful review.

There are still many unanswered questions concerning the basic mechanisms that may modify drug handling or response, or both, in old age, and it is vital that ongoing research in this area continues to receive support. There is also a need for well conducted studies into the practical aspects of presenting and administering drugs to elderly patients, including possible strategies for ensuring appropriate compliance.

Innovations in drugs over the past 10 years have undoubtedly brought benefits for the elderly, particularly in terms of compounds that have fewer side effects—for example, some of the “second generation” antidepressant compounds. In the future a better understanding of pharmacokinetic and pharmacodynamic mechanisms in old age may well provide a basis for developing innovative compounds specifically targeted at this age group.

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For how long may steroids be used in treating temporal arteritis?

The natural course of temporal (cranial or giant cell) arteritis is poorly understood. There is some evidence that for most people it is a self limiting disease lasting about two and a half years, but one third of those affected may show a chronic relapsing course.¹ The risk of relapse, however, must be balanced against the potential hazards of prolonged steroid treatment. The maintenance dose should not only reduce the erythrocyte sedimentation rate and alleviate the head pain but give total protection against loss of vision and thrombotic events. I introduce azathioprine 50 mg twice a day once the response to steroids has been established. Opinions differ on the length of treatment: some doctors will attempt to withdraw treatment after six months, others will continue indefinitely. A reasonable approach is that of Pryse-Phillips and Murray, who stop steroids after two years but continue to observe and monitor the erythrocyte sedimentation rate for at least a further year.² Anderson *et al* followed up 90 patients for nine to 16 years after diagnosis.³ The mean duration of steroid treatment was 5.8 years. Five years after diagnosis 41 of the patients were receiving steroids, and after nine years 15 of 60 survivors were still being treated.—E M R CRITCHLEY, consultant neurologist, Preston.

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