The clinical pharmacology of ageing

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The ageing of populations and individuals continues to be as vital, yet to some extent as neglected, a topic in pharmacology and therapeutics as was first realised about 30 years ago. In parallel with the realisation of the predicted demographic shifts in both the developed and developing world, there have since been major developments in the basic biological concepts of ageing, in the physiology of ageing, in the study of pathogenetic mechanisms underlying a variety of age-associated disorders and syndromes, and in the evidence base for therapeutic intervention in elderly patient populations. These all present new challenges both in the practical delivery of effective medical care and in clinical and biological research. The scale of prescribing for an ageing population has continued to rise as anticipated. Whether there has now been any improvement in the quality or rationality of prescribing, or in the previously demonstrated unacceptable level of susceptibility to adverse drug reactions in the (now expanded) older patient population is largely unknown. We urgently need to find out using up-to-date research methods. National and international guidelines for drug development and regulation have more recently been followed by broader policy inititiatives on prescribing for older people, but the impact of these on standards of medication use and on clinical outcome remains to be seen. A new series in this journal on the clinical pharmacology of ageing is timely. The required focus and framework for research have often tended in the past to emerge as afterthoughts behind the merely disease specific, and it is to be hoped that a sequential review of some of the key topics may help to re-ignite a more sound and less short-sighted agenda than previously.

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Introduction: history of the field

The study of ageing as a factor affecting drug response first acquired a degree of prominence in the 1970s and 1980s. The research impetus had two main origins: (i) an awareness of the growing scale of prescribing (and its economic consequences) in parallel with demographic change [1, 2]; (ii) concern over the perceived susceptibility of older people to the unwanted effects of medication [3].

Systematic approaches to the investigation of adverse drug reaction (ADR) susceptibility identified factors extrinsic (notably prescribing patterns and medication management) and intrinsic (drug disposition/pharmacokinetics, and drug effect/pharmacodynamics) to the patient [4]. From the early 1970s onwards, a requirement to incorporate evidence in older subjects where relevant in the four phases of clinical trials in drug development increasingly became part of the pre- and postmarketing regulatory process in Europe and the USA. Several texts, monographs and reviews [5–8] have since been published. Awareness amongst prescribers, the pharmaceutical industry and to some extent consumers has been raised.

It is likely that older people have in general derived some benefit from this activity, although there is no concrete evidence that the original concerns are any less pertinent than 30 years ago. Furthermore, the climate of clinical activity and evidence has continued to change and develop, so that new aspects of the pharmacology and therapeutics of ageing and new research questions now present themselves.

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Why revisit this subject now?

Reasons include the following.

1. *Developments in biological and medical gerontology*

The inadequacy of chronological age as an indicator of ageing in individuals has long been recognized. Human ageing is characterized in individuals by reduced adaptive reserve and in populations by increased heterogeneity. The cellular and molecular basis of these phenomena has probably become best understood in terms of the disposable soma theory [9], which provides a robust contemporary interpretation of the observed biological processes of ageing within and between species in terms of evolutionary pressures. It asserts that in any given species the relative investment (or trade-off) of energy and other resources in either reproductive activity or somatic maintenance (the processes of prevention, detection, repair and replacement which determine longevity) is proportional to the degree of environmental hazard to which the species is exposed.

This trade-off contributes to the marked diversity of lifespan amongst species. In organisms with relative longevity and environmental safety (including humans) in which ageing processes are prominent, these are manifest as essentially random changes at cellular and molecular level (the consequences of a relative disinvestment in somatic maintenance). This debunks previous concepts such as 'programmed self-destruction' and 'wear and tear', both unsustainable in an evolutionary context, in favour of an approach more in tune with current biological thought.

From the standpoint of therapeutics, this is at least of conceptual relevance and at best provides a more coherent scientific basis for clinical research. The concept of cumulative random error is inherently more compatible with the potential for intervention (at any level from the molecular and cellular to the social) and the validity of therapeutic endeavour in the health problems of ageing. As such it constitutes a radical departure from the intractability implicit in the general thrust of previous unsustainable theories.

The framework and taxonomy of the field have also become clearer. Medical gerontology is the study of human ageing (in individuals and populations) as it applies to the science and practice of medicine and therapeutics. In particular it encompasses the following:

- The interface between ageing and diseases
- Organ- or system-specific disorders of high prevalence in ageing populations
- Special clinical problems or 'syndromes' affecting older people (e.g. falls, reversible cognitive deficit, iatrogenesis)
- Population and epidemiological studies
- Service evaluation and health technology assessment.

The clinical pharmacology of ageing is a legitimate and necessary subdiscipline of medical gerontology. Although clinical pharmacology research is usefully represented in each of the above domains, a more systematic and strategic approach to investigation and dissemination is still needed if key issues for the health care of older people are to be adequately addressed.

2. *Important findings using drugs as probes*

As in most aspects of physiology and of research into the pathogenesis of disorders, drugs have been used to good effect as probes into the physiology of ageing and its interface with disease. Recent examples have included the autonomic, cardiovascular and neurocardiovscular basis of syncope and presyncope [10–12] and the influence of age and age-related change on vascular stiffness, with the associated implications and possibilities for intervention [13–16] (see Section 2).

3. *Developments in the evidence for efficacy (but continued exclusion from clinical trials)*

The requirement of regulatory bodies for evidence to support product licence applications and development portfolios for drugs destined for use amongst older recipients has resulted in a significant growth of clinical trials data. In addition, the clinical research community has increasingly recognized the incongruity of developing and prescribing drugs that are predominantly applicable to older patients, but providing evidence only in the young.

The resulting inclusion of representative numbers of older participants in a growing number of large-scale trials has in general supported the view that chronological age *per se* in no way reduces drug efficacy. Older people have been unequivocally demonstrated, for example, to benefit comparably from thrombolysis in myocardial infarction [17], drug treatment of impaired left ventricular systolic function [18] and hypertension [19], cardiovascular risk reduction from lipid-lowering agents [20], and stroke prophylaxis from anticoagulation or antiplatelet aggregating agents in atrial fibrillation [21]. In the latter case there is evidence of widespread underutilization [22, 23]. The era of demonstrable drug efficacy in Alzheimer's disease is now also established [24] (after a long historical track record of the extensive use of 'cognitive enhancers' in Europe and elsewhere with no such supporting evidence [25]) (see Section 3).

These studies have supported the validity of an increasingly interventional approach to disorders common in

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late life. Quite apart from the benefits to individuals, the cost–benefit return from the postponement of disabling disease is beginning to be recognized. The prevention of stroke, for example, has immediate and substantial implications for the consumption of hospital bed days. Health economic modelling is now an essential and rewarding component of efficacy studies involving the management of acute and chronic diseases of older people.

A widely discussed issue, nevertheless, is the applicability (or not) of the growing body of clinical trials data to 'typical' outpatient and inpatient populations of older people, particularly those of very advanced age and those with accumulated co-morbidity. This is a legitimate and essential question, since the major demographic increase in developed countries over the next 30 years will be in this sector of the population. Comparatively few studies include very elderly patients and significant co-morbidity is commonly an exclusion criterion.

Conducting randomized controlled trials in patient populations of sufficient size to redress this problem poses considerable difficulty in both costs and logistics. In situations where a substantial body of conventional clinical trials evidence supports the efficacy of a treatment across a wide age spectrum, it may be that prospective cohort studies of implementation (using historical controls as comparators) might usefully provide such information in so-called typical patient populations. To date, the few studies of this kind that have been undertaken suggest that in the absence of well-defined contraindications the benefit remains comparable to that reported in trials, and that the current scale of under-prescription (and therefore under-treatment) may be unjustified [26].

Examples of continued inappropriate exclusion of older people from clinical trials programmes and continued attempts, particular in some corners of industry, to justify this, frankly beggar credibility. There are, of course, practical constraints, as well as organizational and study design challenges entailed in carrying out the work. There is a strong case for focusing the conduct and co-ordination of such research activity within fewer, more specialist units than formerly. For individual drugs there is legitimate discussion about the need or otherwise for separate studies *vs.* coverage of a sufficiently wide spectrum of age within (for example) a single large scale Phase 3 trial. But the general weight of argument for appropriate inclusion of older subjects in clinical trials can no longer be in dispute and is recognized in international harmonization guidelines [27] (See Section 8).

4. Medication management issues for the future

A consequence of the growth of evidence for efficacy is the logical commitment to long-term multiple medication. 'Polypharmacy' is a pejorative term implying the poorly rationalized and inadequately supervised targeting of multiple drugs at older patients with intractable problems, with the resulting likelihood of both unwanted effects and poor compliance. While such poor clinical practice is wholly unacceptable, it can no longer be identified by a simple count of concurrent medication, because of the increasing numbers of medicines (long- and short-term) with well-attested benefit for older people. Legitimate and beneficial use of multiple agents looks set to be an issue for future medical care, requiring appropriate investment in systems and professional personnel to support medication management. Without this investment the benefits (and expense) of costly medication may be cancelled out by non-compliance with complex long-term regimens.

5. Developments in prescribing audit methodology

Historical concerns with the extent of prescribing for an ageing population, much of it perceived (rightly or wrongly) as inappropriate, have led to a variety of strategies to reduce its scale. These have included mechanisms for regular review of repeat prescriptions in primary care and hospitals, educational approaches to therapeutic self-audit and peer audit amongst clinicians, and at 'management' level the identification of major variation in prescribing expenditure through cost scrutiny (e.g. the Prescription Pricing Authority in the UK). Each of these approaches has been limited by the failure to link routine prescribing data collection with the existing and developing clinical evidence base.

The development of consensus guidelines [e.g. the 1987 Omnibus Budgetary Reconciliation Act (OBRA) in the USA] with monitoring of levels of adherence is an approach pursued in some contexts, but reliable data collection and interpretation continue to present difficulty. A promising method has been the selection and validation of evidence-based markers or indicators of prescribing quality [28, 29]. The characteristics of ideal indicators are as follows: (i) firmly based on the published literature; (ii) amenable to routine data collection with minimal additional cost/effort; (iii) independent of case mix; (iv) quantifiable in terms of reference ranges for comparison.

Such indicators function as screening markers of variation from the norm which can then be fed into self-audit and peer-audit procedures or training interventions. Evaluation of their feasibility and applicability in a range of clinical settings has begun, but their potential to promote rational and optimal prescribing for older people has yet to be fully explored (see Section 7).

6. Evaluation of adverse drug reactions

As stated, hard epidemiological evidence for useful reduction in the incidence of ADRs overall amongst older patients is lacking. Investment in costly prospective ADR surveillance schemes such as the Boston Collaborative Program of the 1970s and 1980s is not seen as a contemporary priority and is unlikely to occur. Both local record linkage systems and national spontaneous reporting systems are ongoing. The former provide useful pointers to change in defined geographical settings. The latter have also been shown to generate robust evidence over the years, despite substantial levels of under-reporting. Strategies to strengthen the reporting of both ADRs and medication errors through more co-ordinated approaches to risk management are in progress, including the involvement of professions allied to medicine.

The principal burden of drug-induced morbidity amongst older people has, however, been predominantly dose-related rather than idiosyncratic, and insidious rather than overtly serious or life-threatening in character. As a result its detection falls outside the main categories of ADR targeted (for example) by the UK Yellow Card spontaneous reporting system. As a result, the scale of ADR amongst older people may not necessarily be accurately identified by current methods. Research and reporting strategies are required to ensure that this important issue remains firmly on the agenda (see Section 6).

7. Developments in the therapeutics of 'ageing syndromes'

Characterization of age-associated physiological change and its contribution to 'ageing syndromes' has led to significant developments in the drug treatment of such 'special clinical problems' of older people. Mechanisms involved in various aspects of the reduction in functional or homeostatic reserve capacity that in general accompanies human ageing are gradually being delineated. These manifestations of reduced adaptability to intrinsic or extrinsic stresses contribute substantially to the most common syndromes, such as falls and syncope, reversible cognitive deficit (delirium) and impaired continence.

The largest body of literature to date comprises changes in cardiovascular and neural mechanisms identified in older people with unexplained falls and/or syncope and the possible relationships between them. As a result, the capacity to delineate (for example) those with the cardioinhibitory form of carotid sinus syndrome most likely to benefit from dual chamber pacing [11, 12] is now greatly enhanced, and there is progress in evaluating the efficacy of various agents, such as α_1-agonists, in vasodepressor carotid sinus syndrome.

Similarly, the more rigorous methods now available for evaluating drugs (such as cholinesterase inhibitors) in Alzheimer's disease are beginning (through modification) to find their way into the evaluation of a wider range of therapeutic indications. These include, for example, a possible role in the management of delirium (see Section 4).

There remains a surprising dearth of data on the precise mechanisms involved in both bowel and bladder dysfunction in late life, and a crying need exists for these to be more systematically explored.

8. Developments in health policy

The costs of medication for an ageing population increasingly bring aspects of prescribing and drug utilization into the policy arena. The England National Service Framework for Older People [30] incorporates an independent subsection on 'Medicines and Older People. Implementing Medicines Aspects of the NSF for Older People'. This is, however, slanted heavily towards pragmatic aspects of medication management with a bias towards the role of pharmacists, rather than embarking on a broader consideration of the implications of the clinical science, clinical pharmacology and therapeutic evidence.

It is as yet unclear how comprehensively the activity of the National Institute for Clinical Excellence in Britain will cover the issues of drugs for an ageing population as part of its programme of evidence analysis for the provision of prescribed medication within the National Health Service.

Issues of standardization in medication for older people are also raised by the progressive organization of more harmonized regulatory procedures for the granting of product licences and for the monitoring of ADRs across the member states of the European Community.

Such policy initiatives need to be underpinned by a more systematic programme of evidence gathering covering the consequences of individual and population ageing for the efficacy and safety of medications.

Conclusion

For all the above reasons this is a good time to revisit the clinical pharmacology of ageing. Topics included in the series of eight articles have been selected to cover a range of developments and particularly to address most of the areas highlighted here. There are strong reasons to review and strengthen the body of evidence. It is important for the future that the research agenda in the field be re-focused and re-vitalized.

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