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Gerontokinetics – A reappraisal

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Pharmacokinetics (UK) is an informal group of about 70 scientists from academia, the pharmaceutical industry and the hospital environment who have a common interest in the application of pharmacokinetic principles to drug research, development and utilisation. The group has met annually for the last 5 years, and meetings comprise a series of topics with one or two keynote speakers and three to four presentations for each topic. At the meeting of Pharmacokinetics (UK) in November 1990, one session was devoted to a reappraisal of 'gerontokinetics' in the light of current demands for pharmacokinetic studies in the elderly during the early phase of drug development. This article presents the consensus view of the group on this subject.

Interest in pharmacokinetics in the elderly was stimulated by problems encountered with benoxaprofen (Opren), a drug with serious adverse effects which proved fatal to a number of elderly patients. Subsequently, more clinically-relevant studies were demanded when it became clear that some drugs targeted at elderly patients were getting onto the market supported by data derived predominantly from young, healthy volunteers. As a result the UK Committee on Safety of Medicines indicated that suitable dosage recommendations and information on pharmacokinetics in elderly patients should be available for all new drugs. However, with regard to pharmacokinetic aspects, the emphasis of this response may not have been entirely appropriate. The metabolism and kinetics of benoxaprofen are complex. Thus, the problem in the elderly is probably related to impaired renal excretion of its acyl glucuronide followed by hydrolysis back to the parent drug and its accumulation. For the majority of drugs the extent of pharmacokinetic changes with ageing is much less dramatic and the mechanisms are less subtle. One factor that does change consistently with age is renal clearance. However, it seems inappropriate to perform detailed pharmacokinetic studies in elderly patients of all compounds that are excreted largely unchanged by the kidneys just to show yet another correlation between drug and creatinine clearance.

A major concern in studies of the elderly is the selection of subjects. The elderly population represents a continuum from 'fit' to 'frail', yet many studies in the elderly provide no information on the functional status of the subjects. Others are limited to 'normal healthy subjects' from the elderly population who are relatively young (under 75 years of age), do not smoke, receive no other drug therapy, have no clinically relevant disease, are not overweight and have normal ECGs and blood pressure. These elderly 'supersubjects' are physiologically and pharmacokinetically closer to younger people than to their geriatric peers. What then are the ethics of studying healthy elderly patients when the findings may have little relevance to the realities of clinical practice? It may be argued that pharmacokinetic studies in the elderly should concentrate on the 'frail' patient. One problem is to define 'frailty'. Should patients be classified on the basis of disease, drug therapy, in functional terms or in social terms? Furthermore, there are considerable problems in enrolling 'frail' patients into studies, and practical difficulties with sampling and their ability to comply with a study protocol if significant disease, mental impairment, limited mobility or polypharmacy are present. Thus, studies in 'frail' elderly patients also raise ethical issues.

Apart from special circumstances, such as the development of a new cytotoxic agent, there seems little justification for inflicting rigorous pharmacokinetic studies on geriatric patients in early drug trials, nor is there any virtue in investigating healthy elderly volunteers at this stage. Studies in the healthy elderly during Phase 2 may be necessary to give some reassurance on safe dosage in the elderly before progressing to patients. However, Phase 3 provides the ideal platform to define the effects of age on pharmacokinetics.

As regards study design, the observational or 'pharmacokinetic screen' approach seems the most appropriate. This involves taking a few blood samples for drug analysis from as many patients as possible in all trials performed in Phase 3. The data analysis concentrates on singling out patients with relatively high drug concentrations. This initial screen can then be followed up with a classical pharmacokinetic study where appropriate. This approach is more relevant and free of ethical objections because the drug is being used and investigated in the population of patients who actually require it. The data analysis need not be complex, and algorithms such as NONMEM (Beal & Sheiner, 1989) are not always necessary. A simple inspection of the data would have flagged out the problem with benoxaprofen, and familiar multiple regression techniques are likely to pick out the important pharmacokinetic differences, which generally have to be 'barndoor' to cause toxicity. The attraction of this approach is that the data base and optimum sampling time can be

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updated continually as more information becomes available. One valid concern at present is what power the population approach will have to detect differences. Nevertheless, it seems the logical path to follow if clinically relevant information on altered pharmacokinetics in the elderly is to be obtained, and merits investigation.

At present most regulatory agencies have developed no clear strategy or consensus for dealing with drug evaluation in the elderly. A typical 'guideline' is that 'particular consideration should be given to the need for pharmacokinetic studies in the elderly'. What is meant by 'elderly' – healthy, free-range subjects or institutionalised geriatric patients? The FDA has published explicit guidelines for evaluation of drugs which might be used in the elderly, with particular emphasis on those drugs suspected of having adverse central effects. The first step is to determine whether the drug is likely to be used to an important extent in geriatric patients. If it is, elderly patients who require treatment with the drug should be included in the Phase 3 programme. Patients should be stratified according to age and the data analysed to ascertain whether age, disease or a combination of both has any influence on safety and efficacy. A 'pharmacokinetic screen' should also be performed at this stage to identify any age-related changes. If this is not performed or the results suggest an age effect, a classical pharmacokinetic study should be performed using elderly patients in whom the drug would actually be used.

In conclusion, it appears that many inappropriate pharmacokinetic studies are being carried out in healthy elderly volunteers as a result of perceived pressure from regulatory authorities. The knowledge that can be derived from such studies is limited because the subjects and the circumstances do not reflect the realities of clinical practice. The time has come to investigate alternative approaches. Although the 'pharmacokinetic screen' is not without its problems in studying elderly patients, from an ethical viewpoint it may be argued that it is the only way to proceed – a view that was endorsed by Pharmacokinetics (UK).

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Reference

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