CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

GUIDELINE FOR THE STUDY OF DRUGS LIKELY TO BE USED IN THE ELDERLY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

NOVEMBER 1989

For further information regarding this guideline, please contact:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I (HFD-100)
5600 Fishers Lane
Rockville, MD 20857
(301) 443-4330

Table of Contents

FOREWORD

The following guideline provides detailed advice on the study of new drugs in older patients. The guideline is intended to encourage routine and thorough evaluation of the effects of drugs in elderly populations so that physicians will have sufficient information to use drugs properly in their older patients. It is hoped that the guideline will serve as a stimulus to the development of this information, encouraging those sponsors who have not yet started to address the issue at all to begin, and suggesting additional steps to sponsors who are already assessing the effects of their drugs in the elderly.

This guideline presents acceptable current approaches to the study of drugs in the elderly. The guideline contains both generalities and specifics and was developed from experience with available drugs. It is anticipated that with passage of time this guideline will require revision.

The recommendations in this guideline should not be interpreted as mandatory requirements for allowing continuation of clinical trials with an investigational drug or for obtaining approval of a new drug for marketing. This guideline, in part, contains recommendations for clinical studies that are recognized as desirable approaches to be used in the development of more and better information than is currently available on the use of drugs in the elderly.

GUIDELINE FOR THE STUDY OF DRUGS LIKELY TO BE USED IN THE ELDERLY

I. INTRODUCTION

A. Other Pertinent Guidelines

"General Considerations for the Clinical Evaluation of Drugs" is an important companion document and should be reviewed prior to reading this guideline. It contains suggestions that are applicable to the evaluation of most classes of drugs in all age groups. That guideline now states that "drugs should be studied in all age groups, including the geriatric, for which they will have significant utility." This guideline expands on this general theme and provides detailed advice on the evaluation of a new drug in elderly patients. It is intended to assure that treating physicians will have the information needed to use drugs properly in the elderly.

In addition, the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," which now recommends analysis of safety and effectiveness data to determine the influence of demographic factors such as age and sex, can be used to anticipate what information will need to be collected and presented.

B. Underlying Observations

The following general observations and conclusions underlie the recommendations set forth in this guideline:

1. Age-related differences in response to drugs can arise from pharmacokinetic differences (that is, differences in the way a drug is absorbed, excreted, metabolized, or distributed) or pharmacodynamic differences (i.e., differences in the response to a given blood, or other tissue, concentration of the drug).

2. Age itself is not the only characteristic of the elderly that could affect pharmacokinetic or pharmacodynamic responses to drugs. Most differences seemingly related to age are probably not related to age itself but to conditions that, although common in the elderly, can occur in patients of all ages, such as diminished renal or cardiac function, concomitant illness, and concomitant treatment, especially concomitant drug treatment. An approach is therefore needed that will detect, better than is done at present, the major patient characteristics that influence response to therapy. Understanding their influence will greatly enhance our ability to treat older patients with appropriate doses.

3. For a number of practical and theoretical reasons, the evaluation of possible differences in response between younger and older people should focus on the evaluation of potential pharmacokinetic differences. Such differences are known to occur and are much more frequent than documented pharmacodynamic differences. Most problems with drugs in the elderly

identified to date have resulted from pharmacokinetic differences related to age itself or to age-associated conditions such as renal impairment, congestive heart failure, or multiple drug therapy.

Moreover, pharmacokinetic differences are relatively easy to discover. Once a reliable assay for a drug and its metabolites is developed (and an assay is now almost always available early in development), techniques exist for readily assessing age-related or other influence-related effects. Aside from the recognized ability of formal pharmacokinetic studies to answer questions about specific subgroups, a screening procedure, a "pharmacokinetic screen," carried out in Phase 3 populations, has the potential for greatly increasing our ability to detect pharmacokinetic differences in sub-populations and individuals, even when these were not anticipated. That is, by obtaining a small number of blood level determinations in each of many Phase 3 patients, it is possible to detect markedly atypical pharmacokinetic behavior in individuals, such as that seen in slow metabolizers of encainide, and also more subtle pharmacokinetic differences in population subsets, such as patient populations of different age, sex, race, or with particular underlying diseases or concomitant therapy.

The relative ease with which pharmacokinetic differences among population subsets can be assessed must be contrasted with the difficulty of developing precise relationships of most clinical responses to drug-dose or the drug-

blood level, a necessary step in attempting to compare two subgroups. New drug applications received by the Food and Drug Administration often do not have excellent dose response or blood level response information for effectiveness or adverse effects. This situation is improving, however, and when there is a readily measured pharmacodynamic endpoint, such as blood pressure or rate of ventricular premature beats (VPB's), it is reasonable to expect dose response data from a variety of different populations, particularly when differences could have an important impact on the safety or effectiveness of the drug. However, where the endpoint is not immediately assessable in small populations (e.g., in treating depression or anxiety), good dose response information is difficult to get at all, much less for a subset of the overall population, such as the elderly. It is possible, of course, to examine the clinical data for effectiveness or adverse effects differences between subgroups. Observed differences could reflect pharmacokinetic differences or pharmacodynamic differences such as unusual susceptibility to the pharmacologic effect of the drug.

A final reason to emphasize pharmacokinetic evaluation is that it must be carried out first to allow intelligent assessment of pharmacodynamic differences or relationships. Assessing pharmacodynamic differences between groups or establishing blood level-response relationships is possible only when groups are reasonably well matched for blood concentrations. Enough pharmacokinetic data must therefore be available to permit the

investigator to administer doses that will produce comparable blood concentrations in the subsets to be compared or, alternatively, to compare subsets that have been titrated to similar blood concentrations.

4. The number of documented age-related pharmacodynamic differences is at this time so small, and the ability to conduct pharmacodynamic studies to detect them in many situations so uncertain, that additional formal studies to seek such differences between the blood level/response curves of younger and older patients are warranted only if differences are suspected for some reason, such as clinical trial results, or appear particularly important (e.g., because of a low therapeutic index). The observations made during clinical trials that include both younger and older patients, if properly analyzed and particularly if accompanied by blood level data for each patient, should allow detection of important pharmacodynamic differences related to age or other influences.

II. DETERMINATION THAT A DRUG IS LIKELY TO HAVE SIGNIFICANT USE IN THE ELDERLY

In many cases it is obvious that a drug will be widely used in the elderly because the diseases that it is intended to treat are characteristically diseases of aging, e.g., coronary artery disease, senile dementia, or peripheral vascular disease. In other cases it is not entirely clear what the age of the ultimate population will be. A sponsor should determine, through estimates of the disease prevalence by age or

through examination of the age distribution for other drugs of a similar type (using the National Disease and Therapeutic Index, for example), whether a drug is likely to have significant use in the elderly.

III. INCLUSION OF ELDERLY PATIENTS IN CLINICAL STUDIES

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. Therefore, for drugs likely to be used in the elderly, older patients should be included in clinical trials in reasonable numbers. Although it is appropriate and necessary to exclude patients on the basis of functional characteristics that make it impossible for them to be safely, ethically, and usefully included (e.g., patients who are too infirm to participate, too medically complicated to permit interpretation of results, too likely to suffer serious intercurrent illness, or unable to provide meaningful informed consent), exclusions should not be arbitrary. Moreover, exclusions deemed prudent in early studies need not necessarily be maintained in Phase 3. There is no good basis for the exclusion of patients on the basis of advanced age alone, or because of the presence of any concomitant illness or medication, unless there is reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study. Attempts should therefore be made to include patients over 75 years of age and those with concomitant illness and treatments, if they are stable and willing to participate.

Ordinarily, elderly patients should be included in the same trials as younger patients. This permits direct comparisons with younger, but otherwise similar, patients in the same studies. In some cases, however, especially for drugs targeted to older patients or where age-related differences or problems are anticipated, trials might be carried out specifically in the elderly. These could include special monitoring procedures, e.g., of cognitive function. An alternative to a separate trial would be a study that includes both young and old patients in the same clinical environment but is stratified by age to allow special care or monitoring of the older patients.

IV. ANALYSIS OF EFFECTIVENESS AND ADVERSE EFFECTS BY AGE

As indicated in the "Introduction" to this guideline, FDA's "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" calls for analysis of effectiveness, adverse effects, dose response, and, if available, blood level response, with respect to the influence of demographic features such as age, sex, and race, and patient characteristics such as renal, cardiac, and hepatic status, concomitant illness, and concomitant drugs, including ethanol and nicotine. These analyses should be carried out both for individual studies and in the overall integrated analyses of effectiveness and safety. The analyses of subsets with particular characteristics can be expected to detect only fairly large age-related differences. This is not a great problem, however, as only reasonably large differences are likely to be important. The results of these analyses may suggest the need for more formal dose-response or blood level

response studies in an elderly population or in other patient subsets. Depending on the significance of the findings, these additional studies might be carried out before or after marketing.

V. DEFINING THE PHARMACOKINETICS OF THE DRUG IN THE ELDERLY AND OTHER POPULATION SUBSETS

Age itself is only one factor, and not the most important one, that can alter the pharmacokinetics of a drug in the elderly. The most important influences, such as renal function for drugs excreted by the kidney, should be assessed directly. The effects of other possible influences, including age, can be assessed by a screening approach, described below in section C. If a screen is not appropriate or not carried out, or if the screen suggests an influence of age, a formal pharmacokinetic study should be performed in the elderly.

Evaluation of the effects of age or age-associated conditions on the pharmacokinetics of drugs should include:

A. Effects of Renal Impairment

Drugs that are excreted (parent drug or active metabolites) significantly through renal mechanisms should be studied to define the effects of altered renal function on their pharmacokinetics. Information should be developed to support dosing instructions that provide appropriate adjustments for varying degrees of renal impairment. Because it is often difficult to obtain accurate direct measures of creatinine clearance without hospitalizing the

patient for urine collections, labeling for such drugs should include a means of calculating creatinine clearance from the serum creatinine, adjusting for weight and age. The following equation, put forth by Cockcroft and Gault [Nephron 16:31-41 (1976)], is probably the most widely accepted:

$$\text{male CCr} = \frac{\text{wt (kg)} \times (140 - \text{age})}{72 \times \text{Cr (mg/100 ml)}}$$

female CCr = 0.85 x above

B. *Effects of Hepatic Impairment*

Drugs subject to significant hepatic metabolism, especially drugs with metabolism by oxidative mechanisms, or that have active metabolites, require particular attention to permit proper use in all patients, including the elderly. Special pharmacokinetic studies should be carried out in these situations to explore the effects of decreased liver function and to look for possible genetic variability in metabolism or drug-drug interactions. There is, unfortunately, no recognized measure of liver function that serves as a predictor of how the excretion of compounds will be altered, as creatinine clearance does for renal function, but the presence of hepatic cirrhosis has sometimes indicated a likelihood of decreased drug clearance (e.g., for theophylline). It may ultimately prove possible, however, as marker compounds like debrisoquin and aminopyrine are studied further, to define liver function in functionally relevant ways and examine the effects of specific metabolic deficiencies on new drugs.

C. *Pharmacokinetic Screen*

It is important to identify as many of the factors that alter pharmacokinetics of a drug as possible, but it is practical to carry out only a limited number of specific interaction (drug-drug, drug-disease) studies, and only suspected potential interactions can be studied. A pharmacokinetic screen is a means of identifying subgroups of patients in whom the drug has unusual pharmacokinetic characteristics even where no such subgroups are suspected.

A pharmacokinetic screen consists of obtaining, for all or most patients in Phases 2 and 3 of a clinical investigation, a small number (one to several) of steady-state blood level determinations in order to determine the variability of blood concentrations of a drug under defined conditions of dosing. Discussions have been published on how such screens could be conducted and analyzed [Sheiner, L. B., and Benet, L. Z.: Clin. Pharm. Ther. 38:481-487 (1985)] and experience will undoubtedly refine their use.

Even a relatively crude screen, consisting of one or two steady-state trough measurements, can answer a number of simple, but important, questions so long as the trials include a full range of patients with respect to age, sex, race, weight, body composition (e.g., degree of obesity or leanness), concomitant illness, smoking and alcohol consumption, and the use of concomitant drugs. It should be possible to determine the extent of inter-

individual variability of blood concentrations of drug and, using multiple linear regression (or other means such as mixed effects modeling), to determine the relationship of relevant clinical features (age, sex, race, weight, lean body mass, etc.) to trough level. Extreme individual outliers would also be readily identifiable; these patients would often require further study.

It should also be possible to learn from these studies whether the elderly differ from others in their blood concentrations and whether the differences are the result of age alone or other age-associated conditions. Under crude screening conditions, only relatively large differences would be detected but, given the variability in blood concentrations experienced with most drugs, only relatively large differences are generally important. Where small differences could be important, e.g., for relatively toxic drugs with a low ratio of toxic to therapeutic blood concentration, a more rigorous screen (Sheiner and Benet, at 14) could detect even small differences. A very important possible finding of a screen would be that for various demographic (e.g., age) or clinical (e.g., use of other drugs) subsets present in adequate numbers, no apparent effect on blood concentrations was seen.

An important virtue of a screen is that it requires no prior hypothesis and can detect the unexpected. It is inherent in the idea of a "screen" that when the screen discovers something unusual and important, further studies may

need to be done. Thus, if a particular sub-population (e.g., people of a certain age or those receiving another drug) were found to have significantly higher or lower blood concentrations, particularly if this would increase toxicity or decrease effectiveness, an attempt to confirm the observation and discover the reason for it might be necessary. The importance of pursuing such differences, and determining when to pursue them (preapproval or Phase 4), would depend on the therapeutic index of the drug and the extent to which toxicity or beneficial effects are blood-concentration related.

The screen may also help to interpret clinical findings in Phase 2 and Phase 3 studies. Unusual effectiveness or adverse reaction responses might be explained in some cases by the patients' blood concentrations of drug. It should be possible to carry out crude concentration-response observations using the clinical data and screening results.

D. *Pharmacokinetic Study in the Elderly*

If the pharmacokinetic screen is not used, a pharmacokinetic study in elderly patients (over 65 years) should be conducted. The patients should be in reasonably good health, but should usually have the condition the drug is intended to treat. A pharmacokinetic study in the elderly might also be needed if the pharmacokinetic screen suggested age-related pharmacokinetic effects.

E. Drug-Disease and Drug-Drug Interactions

Any substantial pharmacokinetic effects of concomitant illness and therapy would be expected to be revealed by the pharmacokinetic screen. In cases where the therapeutic ratio (i.e., ratio of toxic to therapeutic dose) is low, however, and the likelihood of concomitant therapy or illness is great, specific interaction studies should be carried out. The studies needed must be determined case-by-case, but would include:

1. Interaction Studies

a. Digoxin Interaction

So many drugs alter serum concentrations of digoxin, which is widely prescribed in the elderly and is potentially toxic, that evaluation of this interaction is appropriate for most drugs.

b. Drugs That Affect Hepatic Metabolism

For drugs that undergo extensive hepatic metabolism, the effects of hepatic-enzyme inducers (e.g., phenobarbital) and inhibitors (e.g., cimetidine) should be assessed. Of particular note is the inhibition by quinidine and other drugs (propafenone, for example) of the cytochrome P-450 debrisoquin hydroxylase enzyme, causing fast metabolizer patients receiving those drugs to exhibit the slow metabolizer phenotype. For most drugs metabolized by this enzyme, the effect of quinidine should be explored.

c. *Other drugs*

Other drugs particularly likely to be used with the test drug should be studied for possible drug-drug interactions unless the pharmacokinetic screen or the interaction screen (described below) provides adequate assurance that important interactions do not exist.

d. *Protein Binding Studies*

Drugs that are extensively bound to plasma proteins are subject to displacement from binding sites by other drugs (e.g., displacement of warfarin by NSAID's) and other drugs that are extensively bound may be displaced by the new drug. These interactions can be readily and inexpensively explored in vitro. If a clinical interaction has been observed, binding studies can help to elucidate the underlying mechanism.

2. **Concomitant Disease and Concomitant Drugs; Interaction Screen**

If the drug will be used in conditions where specific concomitant diseases are likely to be present, an attempt should be made to include in the treatment population patients with the other diseases. The pharmacokinetic screen will be useful in determining whether the concomitant diseases affect blood levels of the test drug, and clinical observations should permit detection of specific adverse effects associated with the other diseases. Similarly, with respect to other medications that are used concomitantly, the screen will help evaluate

whether the other medications affect the kinetics of the test drug. In some cases, where a concomitant drug is used frequently, formal interaction studies should be carried out. For example, anti-anginal drugs of different pharmacologic classes (nitrate, beta-blocker, calcium antagonist) are commonly combined and should be subjected to formal studies of their combined effectiveness and tolerance.

It is possible that the new drug will have an effect on the kinetics of other drugs. There is almost no limit to the number of studies that could be mounted to explore this question; therefore, a second screening mechanism, an "interaction screen," would be helpful. If Phase 3 clinical trials include patients on a variety of other drug therapies (held stable during introduction of the new agent), trough blood levels of the other drugs can be obtained prior to dosing with the new agent and again after the new agent has reached steady state. It should thus be possible to detect, with relatively little effort, major effects of the new drug on many concomitant medications. The principal impediment to doing so will be lack of availability of reliable blood level assays for the other agents.

VI. PHARMACODYNAMIC STUDIES IN THE ELDERLY

The number of age-related pharmacodynamic differences (i.e., heightened or dampened beneficial or toxic effects at a given blood concentration of drug)

discovered to date is too small to necessitate routine separate pharmacodynamic or clinical studies in the elderly. Observations made during clinical trials that include both young and old patients should make it possible to identify the important differences; indeed, these trials are more likely to detect differences than studies carried out entirely in older populations. Stratifying patients by age may allow more sensitive assessments and provide the best of both approaches.

In some cases, however, most notably sedative/hypnotic agents and other drugs with important CNS effects, separate studies of older populations may be needed. Results of analyses of other trials may also suggest the need for separate studies. These should ordinarily be directed at defining the dose-response relationships for favorable and adverse effects, particularly attempting to define the lowest useful dose and to define the CNS consequences of larger doses. Specific drug and disease interaction studies might also be indicated.

*U.S.GOVERNMENT PRINTING OFFICE:1990-261-215:24706