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DRUG-PROTEIN BINDING IN OLD AGE

John G. Kelly and Kevin O'Malley

INTRODUCTION

The elderly may differ from the young both in the manner in which a drug is distributed and eliminated and in their intrinsic sensitivity to the drug. Pharmacokinetics and pharmacodynamics in the elderly have been fields of increasing interest in recent years. It is now recognized that the elderly require a significant proportion of health care resources, including drug therapy. It is also recognized, however, that new and even established drugs should be proven safe and effective in the elderly. The pharmacokinetic profile of a drug likely to be used in the elderly is incomplete without specific study of the effects of ageing on its handling by the body. However, study of the specific pharmacodynamics of a drug in the elderly is equally important.

As a general rule, drugs eliminated mainly unchanged by the kidney have their elimination slowed with advancing age. The pattern is not so consistent for mainly metabolized drugs (O'Malley et al. 1980). Less attention has been paid to the effects of age on sensitivity to drugs. Carefully documented studies are still not common. It is apparent, however, that ageing can result in either increases or decreases in sensitivity to drugs (Wood and Feely 1984). There are theoretical grounds for effects of alterations in protein binding on either pharmacokinetics or pharmacodynamics. An increase in the unbound fraction of a drug might increase the amount of drug eliminated or might increase the amount of free drug available to interact with receptors. Relationships between drug binding and clinical effects are complex, and practically no information is available regarding such relationships in the elderly.

PROTEIN CONCENTRATIONS IN OLD AGE

Albumin

Serum concentrations of albumin are lower in the elderly. For example, Bender and colleagues (1975) reported a mean serum albumin concentration of 3.4 g/100 ml in a group of ten people aged greater than 50 years, and a mean concentration of 4.0 g/100 ml in a group of 14 people aged less than 50 years. Greenblatt (1979) examined results from 11,090 hospitalized medical patients as part of the Boston Collaborative Drug Surveillance Program. These excluded patients with diseases likely to be associated with abnormal serum albumin concentrations. Serum albumin concentrations fell with each decade of advancing age. The mean serum albumin concentration in patients less than 40 years was 3.97 g/100 ml, falling to a value of 3.58 g/100 ml in patients aged 80 years or greater.

Alpha-1-Acid Glycoprotein

Knowledge of the importance of this protein with respect to drug-binding is much more recent than for albumin. Correspondingly, studies in the elderly have been much fewer, details of the physicochemical aspects of the drug-protein interactions are not available, and indeed, a definitive study of variations in alpha-1-acid glycoprotein concentrations is still awaited. Those studies which have been carried out suggest that alpha-1-acid glycoprotein concentrations increase with age. Braithwaite, Heard, and Snape (1978) found a mean concentration of 0.73 g/l in 14 young people and a mean of 1.37 g/l in 25 geriatric patients. A more recent report by Hayler and Holt (1983) described similar results. A group of 13 adults had a mean alpha-1-acid glycoprotein concentration of 0.69 g/l and a group of 24 geriatrics had a mean concentration of 1.4 g/l. Davis and colleagues (1980) reported a significant but weak positive correlation between serum alpha-1-acid concentration and age.

Age Versus Disease

One consistent problem associated with studying effects of age is the separation of age effects from effects of concomitant disease. The elderly are more likely to have chronic disease. This is compounded by carrying out studies in which hospitalized elderly people are compared with healthy young people. In addition, selective mortality may mean that a young group is compared with a group of elderly people who are a "biological elite." This bias is further

increased when groups of very old people (aged greater than 80 years) are studied. Studies of protein binding are subject to these potential artifacts in the same way as other studies.

Albumin concentrations fall with immobility in elderly people (Woodford-Williams et al. 1964). Study of a hospitalized group of subjects then may not relate well to a group of "fit" elderly people. Another complication is that concentrations of alpha-1-acid glycoprotein rise with inflammatory disease, which is more likely to be present in elderly subjects.

STUDIES OF DRUG-PROTEIN BINDING IN THE ELDERLY

Knowledge of the alterations in concentrations of drug-binding proteins in the elderly allows formulation of hypotheses regarding the likely consequences on protein binding of specific drugs. Thus, acid drugs binding to albumin might be expected to show diminished protein binding with advancing age. Basic drugs binding to alpha-1-acid glycoprotein might be expected to increase with advancing age. Some drugs, for example, propranolol, bind to both albumin and alpha-1-acid glycoprotein. In general, these hypotheses have validity although it must be stressed that there are exceptions, and there are cases where no agreement has yet emerged.

Drug binding to albumin has been most extensively studied and includes oral anticoagulants, non-steroidal anti-inflammatory drugs, phenytoin, and oral hypoglycaemic drugs.

Hayes, Langman, and Short (1975a) compared warfarin plasma protein binding in a group of people aged between 21 and 45 years, and in a group between 65 and 90 years. Plasma binding of warfarin corresponded to a mean of 561 μmol/l in the young group, and 451 μmol/l plasma in the elderly group ($p < 0.002$). This decrease in binding in the elderly correlated with a decrease in plasma albumin concentrations. However, Shepherd and colleagues (1977) found no difference in warfarin protein binding between a group of young and elderly people, and suggested that pharmacokinetic factors were not important in altered pharmacodynamics of warfarin in the elderly. The correlation between warfarin-binding and albumin concentration is a point in favor of the study by Hayes et al., but as was pointed out by Shepherd and colleagues, the former used a range of plasma concentrations larger than those found therapeutically.

Hayes, Langman, and Short (1975b) also examined the protein binding of phenytoin in the elderly. A group of 17 young people aged 20 to 38 years displayed a mean maximum binding capacity of 727 μmol/l against a value of 595 μmol/l in 19 elderly people aged 65

to 90 years. Patterson and colleagues (1982) found a modest but significant decrease in phenytoin plasma protein binding in elderly people and suggested that this was due to decreased albumin concentrations in the elderly. Again, there are conflicting findings. Bender and colleagues (1975) found no difference in protein binding of phenytoin, penicillin, and phenobarbital between young and elderly people. Gal, Oles, and Baird (1984), while finding a significant inverse correlation between percentage unbound phenytoin and serum albumin concentration, did not find an age-related decrease in phenytoin binding in elderly people.

Wallace, Whiting, and Runcie (1976) studied plasma protein binding of salicylate, sulfadiazine, and phenylbutazone in young and elderly subjects and found that elderly subjects had significantly lower albumin concentrations than subjects under 40 years of age. Correspondingly lower degrees of protein binding were observed in the elderly for all three drugs studied. However, the decreases were more marked in older people receiving multiple drug therapy.

Upton and colleagues (1984) compared the pharmacokinetics of naproxen in 10 males aged between 66 and 81 years with 10 males aged from 22 to 39 years. The fraction of naproxen unbound in plasma was doubled in the elderly subjects at both peak and trough concentrations of drug.

A similar picture exists for both warfarin and phenytoin as for diazepam with studies showing either decreased protein binding in the elderly (Greenblatt et al. 1980) or no change (Klotz et al. 1975).

For drugs which bind to both albumin and alpha-1-acid glycoprotein, it is difficult to carry out meaningful studies. In the case of propranolol, for example, binding to albumin might decrease with advancing age, while binding to alpha-1-acid glycoprotein would be expected to increase. The resultant of these two changes would perhaps be zero change but, of course, the individual effects are masked. Much more sophisticated studies requiring measurement of binding to individual proteins would be required to elucidate these processes.

In recent years there has been an increase in interest in binding of drugs to alpha-1-glycoprotein.

Lignocaine is an example of such drugs and has been examined by several groups. Cusack et al. (1980) compared the protein binding of this drug in six young people aged 20 to 34 years, and in six elderly patients aged between 73 and 78 years. In the concentration range 1-2.2 μg lignocaine/ml the young bound a mean of 48.1 percent against 69.5 percent for the elderly. Davis et al. (1980) examined the binding of diazepam and lignocaine. While both are basic drugs, diazepam binds to albumin and lignocaine to alpha-1-acid glycoprotein. While binding of diazepam showed a continuous decrease with age, that of lignocaine increased with age.

Verbeeck and Cardinal (1983) examined the binding of the basic drugs chlorpromazine, perphenazine, desipramine, propranolol, and meperidine in plasma from 47 people aged between 18 and 98 years. The percentage of free drug was significantly inversely related to age for chlorpromazine, perphenazine, and meperidine. Alpha-1-acid glycoprotein concentrations increased with age. Similar increases in plasma protein binding in the elderly have been described for maprotiline (Braithewaite, Heard, and Snape 1978) and for disopyramide (Hayler and Holt 1983).

A general summary of these results suggests the occurrence of modest decreases in plasma protein binding in the elderly for drugs binding to albumin and these changes roughly parallel the decrease in serum albumin concentrations. The age-related changes in protein binding may be more marked at high concentrations of the drugs. For drugs binding to alpha-1-acid glycoprotein, significant increases in protein binding with old age are seen. These parallel the increases in serum alpha-1-acid glycoprotein concentrations.

CLINICAL SIGNIFICANCE OF ALTERATIONS IN PLASMA PROTEIN BINDING IN OLD AGE

No definitive studies of this exist. Some groups have suggested possible consequences of results which they report, and it may be possible to make tentative extrapolations from studies in younger subjects, or in other patient groups. Theoretical consequences include:

Pharmacokinetic
- —increased clearance of some acidic drugs as a result of a larger unbound fraction in the elderly
- —decreased clearance of some drugs binding to alpha-1-acid glycoprotein concentrations as a result of a decreased unbound fraction in the elderly

Pharmacodynamic
- —increased intensity of action of drugs binding to albumin
- —decreased intensity of action of drugs binding to alpha-1-acid glycoprotein

Convincing evidence is lacking of the clinical importance of all these points. As a general rule, one might expect alterations in protein binding to be most important for the highly protein bound drugs. Yacobi, Undall, and Levy (1976) have shown a significant correlation between warfarin and the proportion of free drug in

plasma. If this were pertained in elderly people, a modest increase in clearance in these people might be expected. However, this has to be balanced against possible age-related decreases in metabolic clearance of drugs. The net result for a given drug cannot be accurately predicted, but no studies have been reported showing increased clearance of drugs in the elderly. Shepherd et al. (1977) found no age-related changes in the pharmacokinetics of warfarin. The same authors suggested that increased sensitivity to warfarin in the elderly was not due to any changes in elimination or protein binding, but to a greater sensitivity of the clotting factor synthesis mechanism to warfarin.

Houghton, Richens, and Leighton (1975) suggested that for phenytoin, genetic differences, exaggerated by enzyme saturation are more important in determining steady-state phenytoin concentrations than are age, weight, and height. Correlations between the free fraction of phenytoin, and any alterations in sensitivity in the elderly, have yet to be shown. At least one group (Wallace, Whiting, and Runcie 1976) have suggested that changes in protein binding of drugs is likely to be a special problem in the elderly.

For drugs binding to alpha-1-acid glycoprotein, it is even more difficult to put findings in a clinical context, even though fairly marked increases in protein binding with age have been described. Lignocaine and propranolol, while widely studied, introduce complications since their hepatic elimination is flow limited, and decreases in hepatic blood flow with age may be the major factor determining changes in their elimination. One study by Magowan and colleagues (1983) has shown correlations between protein binding of verapamil and alpha-1-acid glycoprotein concentrations in 15 patients (of unspecified ages) with a history of paroxysmal supraventricular tachycardias. The correlation between plasma concentrations of verapamil and its effects on P-R intervals was stronger for free verapamil than for total verapamil.

Few, if any, such studies have been carried with other drugs binding to alpha-1-acid glycoprotein, and there are no studies in the elderly. Assessment of the importance of this aspect of pharmacokinetics in the elderly awaits.

SUMMARY AND CONCLUSIONS

1. The protein binding of drugs which bind mainly to albumin decreases modestly with advancing age in parallel with decreases in albumin concentrations. Several studies, however, show no changes with age.

2. The clinical significance of this is probably slight. Other changes in rates of elimination, or in responsiveness to drugs are more important.

3. For drugs binding mainly to alpha-1-acid glycoprotein, consistent increases in binding with advancing age have been shown. These changes may parallel age-related increases in alpha-1-acid glycoprotein concentrations. Alpha-1-acid glycoprotein concentrations increase with inflammatory disease, however, and it may be that the presence of concomitant disease accounts for a significant proportion of the age-associated increase in concentrations of this protein.

4. The clinical significance of these increases in protein binding is as yet unknown.

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