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# PHARMACOKINETIC CONSEQUENCES OF AGING

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## INTRODUCTION

For the purpose of this review we have chosen a rather narrow definition of geriatric pharmacology. We deal with the influence of increasing age on the plasma concentration of a drug and the factors that influence the peak concentration and the rate at which the drug leaves the body. We also discuss what changes in tissue sensitivity occur with age that would affect the overall response to a drug at a given blood level concentration. We do not discuss the extensive literature on the safety and utility of drugs in geriatric patients or the effect of increasing age on the incidence of adverse reactions and altered drug utility. Reviews on these have been published (1–5). Not considered as part of this review is one other aspect of geriatric pharmacology, namely, the effect of drugs on the aging process. Information on this aspect of the subject can be found in other reviews (6,7).

We would like to remark on the progress that has been made in our understanding of the effects of age on how a drug is handled by the body and the implications that these changes have on the utility of pharmacological agents in the treatment of diseases of old age. Until recently, most of the work has concerned the use of drugs in the elderly patient to determine their safety and their efficacy. There have been few comparisons with the response in younger populations. Even when such comparisons have been made, however, there have been few attempts to explain the reason for these differences and the basic biological rationale for them. In the last several years, however, greater attention has been focused on the effect of age on mechanisms responsible for drug disposition, and we are gradually laying the foundation for understanding how drugs may be more effectively used in the treatment of diseases of the elderly patient (8–13). It is our hope that the review of this biological rationale, and more specifically the pharmacokinetic aspects of increasing age, will contribute to this understanding.

## AGE-RELATED CHANGES IN DRUG HANDLING SYSTEMS

Accepting the general principle that pharmacological effects—as well as side effects and toxic effects—are closely related to the circulating level of an administered drug, it is instructive to consider the physiologic processes which influence that level. Pharmacotherapeutic problems encountered in the elderly are due largely to age-related functional changes in the body's drug-handling machinery.

### *Absorption*

Oral dosage forms must initially undergo dissolution, and although the decrease in stomach acid production which accompanies increasing age has sometimes been cited as a factor mitigating against adequate drug absorption, there is no real evidence for such an effect. It is quite possible that the only clinically important aspect of gastric pH as regards drug absorption is that it affects gastric motility, with higher pH values favoring absorption by hastening the movement of stomach contents to the small intestine. The pharmacologic consequence of abnormal gastric motility may not be simply in the timing of the onset of drug action but rather an alteration in the rate at which the drug enters the circulation so that an excessive and adverse physiologic reaction may occur or so that an inadequate blood level is achieved and thus a limited drug effect is developed. Bianchine et al (14) demonstrated the importance of this factor in treating patients whose parkinsonism was unrelieved by L-DOPA therapy.

The effects of increasing age on the drug absorption process per se have not been carefully or thoroughly studied. An early review of this topic (15) cited the general paucity of such information and concluded that there was an overall suggestion of reduced absorption in the elderly. Age-related decreases in the absorption of glucose and calcium (specifically transported substances unlike most drugs which are passively absorbed) are of uncertain significance, but the decreased absorption of xylose (16) and iron (17) in older subjects may indicate some decrease in the efficiency of drug absorption. A possible basis for decreased drug absorption in the aged has been developed (8) and concerns itself with a decrease in intestinal blood perfusion. While circulation to the coronary and cerebral regions is only slightly changed in the older subjects, intestinal perfusion is decreased by 40–50% (18), and this presents the potential for decreasing transfer of a drug across the serosal membrane.

### *Metabolism*

A limitation on the duration of action of many drugs is established by the rate at which they are metabolized by the hepatic microsomal hydroxylating system and converted to (multi)hydroxylated forms and their conjugates and subsequently excreted. Gorrod (19) has reviewed at length the reports on the effects of age on drug-metabolizing ability. Kato and his co-workers (20) found that after the attainment of sexual maturity, rats steadily lose their capacity for the metabolism of a variety of drugs and that this decrease is mirrored by increases in the serum levels of such drugs and by the intensity or duration of their pharmacologic effects. Good

support for the interpretation of this finding was supplied by Kuhlmann et al (21) who found that hexobarbital is metabolized more slowly by older rats and gives a more prolonged effect, whereas barbital (which is not metabolized at all) gave effects of equal duration for old and young rats.

### *Excretion*

The ultimate elimination of a drug or its metabolite(s) from the body is predominantly through the kidneys, mostly by simple glomerular filtration but also by active excretion at the tubule (for organic acids and antibiotic metabolites). This step can limit the pharmacolgic effect for nonmetabolized drugs, and will regulate the elimination of drug metabolites for other drugs. As will be noted in the clinical studies to be described later, renal function is probably the single factor most responsible for altered drug levels in an aging population. The age-related decrease in renal perfusion is estimated at about 1.5% per year after maturity, totaling a decrease of roughly 40–50% from age 25 to age 65. This blood flow decrement is reflected by a 45% drop in both glomerular filtration rate and urea clearance (22) and a corresponding 50% increase in blood urea nitrogen. Even in the absence of any active intrinsic renal disease, creatinine clearance is reduced in the elderly to about half normal (23) and can often be referred to as an index of relative drug clearance capacity. A number of dosage guidelines and nomograms have been developed on the basis of endogenous creatinine clearance (24, 25).

## CLINICAL STUDIES

### *Antibiotics*

The earliest studies depicting differences in drug handling by young and geriatric subjects were concerned with antibiotics. Leikola & Vartia (26) reported on the results of a large study of penicillin levels in patients administered penicillin G and procaine penicillin i.m. A young group of subjects (average age 25 years) had a half-time of 0.55 hr for penicillin G while an older group (average age 77 years) had a 1.0 hr half-time. For the procaine form also, younger subjects displayed more rapid elimination with a half-time of about 10 hr compared with 18 hr for the older group. Extrapolation of the serum level curves to zero time indicated that the effectiveness of absorption of penicillin from the intramuscular site was equal for both age groups. The investigators attributed the group differences in half-time to the reduced renal secretion of the antibiotic through active tubular processes known to decrease with age. It is worth mentioning that all of the subjects were hospitalized throughout the study to minimize other influences on drug handling.

Vartia & Leikola (27) extended their work to include dihydrostreptomycin and tetracycline. For dihydrostreptomycin, the serum half-time of a young group (aged 27 years) was 5.2 hr, and this was extended to 8.4 h
years). A similar situation existed for tetracycline, with the same older group having a 4.5 hr half-time vs 3.5 hr for the younger patients. These age-related decreases in half-time are realized as two- to threefold greater serum levels of these two antibiot-

**Table 1** Age-related pharmacokinetic results

| Drug | Age group (years) | Pharmacokinetic observations | Age-related effect | Reference |
|---|---|---|---|---|
| Penicillin | Avg. 25 | $T_{1/2}$ = 0.55 hr (penicillin-G)<br>$T_{1/2}$ = 10 hr (procaine penicillin) | Decreased renal function (tubular secretion) | 26 |
| | Avg. 77 | $T_{1/2}$ = 1.0 hr (penicillin-G)<br>$T_{1/2}$ = 18 hr (procaine penicillin) | | |
| | Females < 50 | $T_{1/2}$ = 23.7 min | Decreased renal function (tubular secretion) | 28 |
| | Females > 70 | $T_{1/2}$ = 55.5 min | | |
| | Males < 30 | $T_{1/2}$ = 20.7 min | | |
| | Males > 65 | $T_{1/2}$ = 39.1 min | | |
| Dihydrostreptomycin | Avg. 27 | $T_{1/2}$ = 5.2 hr | Decreased renal function (glomerular filtration) | 27 |
| | Avg. 75 | $T_{1/2}$ = 8.4 hr | | |
| Tetracycline | Avg. 27 | $T_{1/2}$ = 3.5 hr | | 27 |
| | Avg. 75 | $T_{1/2}$ = 4.5 hr<br>Elderly have 2–3 × serum level of young | | |
| Kanamycin | 20–50 | $T_{1/2}$ = 107 min | Decreased renal function | 29 |
| | 50–70 | $T_{1/2}$ = 149 min | | |
| | 70–90 | $T_{1/2}$ = 282 min<br>Good inverse correlation with creatinine clearance | | |
| Propicillin | 20–30 | $V_d$ = 28.7 liters | Decreased distribution volume | 30 |
| | 60–80 | $V_d$ = 19.9 liters<br>Absorption and elimination constants are similar for both groups, and serum levels are twice as high in the elderly | | |

**Table 1** *(Continued)*

| | | | | |
|---|---|---|---|---|
| Digoxin | Avg. 27 | $T_{1/2}$ = 51 hr | Decreased renal function | 44 |
| | Avg. 27 | $T_{1/2}$ = 73 hr<br>Blood levels about twice as high in older group. Creatinine clearance = 122 ml/min in young vs 56 ml/min in elderly | | |
| | | Plasma level (on equal maintenance dose) increases 2X from age 60 to 80; highly correlated with creatinine clearance values | Decreased renal function | 62 |
| | | Absorption unaltered with age. Plasma level increased 3X in over 50s compared with young adults | Decreased renal function | 63 |
| | | Toxic states 3 to 4X greater in over 70s and related to excessive serum creatinine levels | | |
| Antipyrine | Avg. 26 | $T_{1/2}$ = 12 hr | Decreased metabolism | 35 |
| | Avg. 78 | $T_{1/2}$ = 17.4 hr | | |
| | 18–39 | $T_{1/2}$ = 12.7 hr | | 36 |
| | 40–59 | $T_{1/2}$ = 13.8 hr | | |
| | 60–92 | $T_{1/2}$ = 14.8 hr | | |
| | 20–40 | $T_{1/2}$ = 12.5 hr | | 37 |
| | 65–92 | $T_{1/2}$ = 16.8 hr<br>Doubling dose did not alter $T_{1/2}$, so metabolism may be limited not by simple enzymatic capacity, but perhaps by splanchnic circulation | | |

**Table 1** *(Continued)*

| Drug | Age group (years) | Pharmacokinetic observations | Age-related effect | Reference |
|---|---|---|---|---|
| Aminopyrine | 25–30 | $T_{1/2}$ = 3 hr | | 38 |
| | 65–85 | $T_{1/2}$ = 10 hr<br>Absorption unaltered by age | | |
| Pethidine/meperidine | | Plasma levels twice as high in over 70s as in the young | | 39 |
| | | Red cell binding of drug is 50% in young vs 20% in elderly | | 41 |
| | | Plasma binding of drug decreased from 75% in young to 35% in elderly | | |
| Phenytoin | | Serum level (equal maintenance dose) increased 2× from 20 to 80 year olds | Decreased metabolism | 32 |
| | 20–43 | Phenytoin clearance = 26 ml/kg/hr | | 31 |
| | 67–95 | Phenytoin clearance = 42 ml/kg/hr | | |
| | | Decrease (18%) in binding by plasma proteins in elderly; binding correlates well with plasma albumin concentration; no affinity change | | |
| | | Clearance not affected by induction of hepatic enzymes | | |
| Amylobarbitone | 20–40 | Urinary metabolite excretion = 14.2%.<br>Plasma drug level = 1.3 μg/ml | Decreased metabolism | 34 |
| | > 65 | Urinary metabolite excretion = 4.3%.<br>Plasma drug level = 1.0 μg/ml | | |
| Phenobarbital | 20–40 | $T_{1/2}$ = 71 hr | | 32 |
| | 50–60 | $T_{1/2}$ = 77 hr | | |
| | > 70 | $T_{1/2}$ = 107 hr | | |

**Table 1** *(Continued)*

| | | | | |
|---|---|---|---|---|
| Lithium | Avg. 25 | Li clearance = 41.5 ml/min | | 64 |
| | Avg. 58 | Li clearance = 16.8 ml/min | | |
| | Avg. 63 | Li clearance = 7.7 ml/min | | |
| | | Dose required to achieve therapeutic plasma level decreases approximately 30% from age 20 to age 80 | | 65 |
| Phenylbutazone | Avg. 26 | $T_{1/2}$ = 81 hr | Decreased metabolism | 35 |
| | Avg. 78 | $T_{1/2}$ = 105 hr | | |
| | Avg. 24 | $T_{1/2}$ = 87 hr | | 43 |
| | Avg. 81 | $T_{1/2}$ = 110 hr | | |
| | | $T_{1/2}$ correlated (inverse) with plasma albumin concentration | | |
| Propranolol | | Plasma level approximately 4× in elderly (avg. age 77) compared to young (avg. age 27) at all time periods after administration (p.o.) | Decreased metabolism (first pass effect) | 46 |
| Practolol | Avg. 27 | $T_{1/2}$ = 7.1 hr | Decreased renal function | 46 |
| | Avg. 80 | $T_{1/2}$ = 8.6 hr | | |
| Diazepam | | $T_{1/2}$ increased linearly with age, from 20 hr at age 20 to 80 hr at age 70 | | 47 |
| | | Distribution volume increased 3× from 20 to 80 yr | | |
| Ampicillin | 21–30 | $T_{1/2}$ = 1.0 hr | | 66 |
| | 60–76 | $T_{1/2}$ = 1.2 hr | | |
| Doxycycline | 20–28 | $T_{1/2}$ = 11.95 hr | | 67 |
| | 42–55 | $T_{1/2}$ = 17.74 hr | | |

ics in older subjects. In contrast to penicillin, both dihydrostreptomycin and tetracycline are removed by simple filtration, and the observed decrease in their removal rates in elderly patients is thought to reflect the known decrease in glomerular filtration rate (GFR) which accompanies aging.

A significant observation regarding antibiotic elimination was reported by Hansen et al (28). In their note on the kinetics of penicillin G in different age groups, they found half-time values of 39 and 55 min in older men and women respectively, versus 21 and 24 min for their younger counterparts. Most important, Hansen et al noted that the serum creatinine concentration was of no value in estimating healthy patients' kidney function, while endogenous creatinine clearance measurements were good (inverse) reflections of intrinsic kidney efficiency and correlated very well with half-time measurements for penicillin. This observation pointed up not only that kidney function may be increased by 50% before it is reflected in an increased serum creatinine level, but also that this age-related functional decrement occurs even in the absence of overt renal disease and will greatly decrease the elimination of many drugs in older patients.

Hansen's group (29) provided more support for the above conclusions with their report on kanamycin half-life values in young (20–50 years), intermediate (50–70 years), and elderly (70–90 year) patients. The kanamycin half-time increased from 107 min to 149 min to 282 min with increasing age and was apparently related to a concomitant decrease in creatinine clearance from 94 to 75 to 43 ml per minute. There was no difference in serum creatinine values for the three groups, and the authors cautioned against drug dosage based on serum creatinine data without consideration of urinary creatinine excretion.

A more formalized kind of analysis of drug pharmacokinetics in different age groups was performed by Simon et al (30) with orally administered propicillin. This study used a computer program to generate kinetic constants for drug handling based on serum propicillin levels. Although the older patient group (aged 60–80) had an area-under-curve twice that of the younger group (aged 20–30), both groups had comparable values for the absorption rate and for the drug serum half-life. Nevertheless, peak concentration was twice as high in the older group and the computations indicated a similarly higher initial serum concentration (hypothetical). The investigators concluded that the drugs must be distributed through a smaller circulatory and tissue volume in the older subjects, and this view was supported by calculated distribution volumes of about 29 liters in the younger group and 20 liters in the aged subjects.

### *Phenytoin and Barbiturates*

Hayes et al (31) observed that plasma binding of phenytoin was decreased by about 20% in people over 65 as compared to those under 45. This difference was due not to an altered affinity for the drug but to reduced albumin concentration. Apparently related to this binding difference was an increased phenytoin clearance in the older group presumably reflecting the greater "available" drug circulating in the older subjects. Since Hayes et al did not include serum level data in their report, it is unclear how older subjects' serum phenytoin concentrations compared with the

levels in younger subjects. Other clinical results with phenytoin (32) indicate that serum levels are in fact increased in older patients. This increase amounts to approximately a doubling of phenytoin levels over the range 20–80 years. It is possible that the two reports may well be in harmony since more rapid metabolism of phenytoin in younger subjects would lead to both lower serum levels and a lower drug clearance value. Phenytoin is of course extensively metabolized and it is unfortunate that neither of these groups included estimates of this factor in their investigations. It is not possible from the data supplied to determine whether the differences reported are due to age-related alterations in drug binding, renal function, or drug metabolism.

The serum half-life of phenobarbital was found by Traeger et al (33) to increase from 71 hr in a 20–40 age group to 77 hr in 50–60 year olds and to 107 hr in those subjects over 70. Somewhat more information was gathered by Irvine et al (34) who found that oral amylobarbitone gave significantly higher plasma levels in an elderly patient group than in a 20–40 year old group. Furthermore, the older subjects excreted only one third to one half as much of the drug as its primary metabolite, 3-hydroxyamylobarbitone, as did the young group. Irvine et al concluded that an age-related decrease in hepatic drug metabolism was responsible for the higher drug levels in the elderly. Because of the known deficit in renal function in the elderly, one cannot assume that urinary metabolite excretion reflects metabolism accurately. In this instance the conclusion of decreased metabolism is probably correct (especially because none of the subjects had greatly reduced creatinine clearance values), but without plasma metabolite levels or urinary drug estimation to complete the picture, this verdict is uncertain.

### *Antipyrine and Aminopyrine*

Because of its minimal binding by proteins and its clearance from the plasma almost solely by hydroxylation, antipyrine is a favorite for drug metabolism studies. A paper of significant impact on clinical pharmacokinetics is that of O'Malley et al (35) who studied the plasma half-life of antipyrine and phenylbutazone in different age and sex groups. These investigators recorded a substantial increase in the antipyrine plasma half-time for the elderly (average 78 years) group, 17.4 hr, as compared with 12 hr for a group averaging 26 years of age. Some sex differences in metabolism rate were noted for antipyrine, and there were some suggestions of age differences in drug distribution volumes, but these were not impressive or of the importance of the other findings. An elaborate project designed to evaluate the separate and collective effects of age, smoking, caffeine, and alcohol on antipyrine metabolism [Vestal et al (36)] arrived also at a longer plasma half-life for elderly subjects, albeit a modest 16% increment compared to young subjects. The investigators cautioned that smoking habits could account for much of even this small difference, however, and that other factors should be considered when estimating age-related changes in pharmacokinetics. Results similar to those of O'Malley et al were obtained by an Australian group (37). They found that the elderly displayed a 16.8 hr plasma half-life for antipyrine with a 12.5 hr value for younger subjects. The half-time differences were not the result of altered distribution volumes. A similar study by Jori et al (38) led

to the same conclusions as the O'Malley group with the plasma half-life of aminopyrine prolonged from about 3 hr in 25–30 year olds to about 10 hr in a geriatric group aged 65–85.

### *Analgesics and Anti-Inflammatory Agents*

Plasma levels of pethidine were consistently twice as high in a geriatric group as in a younger group (39). While much of this difference seemed to be related to a comparably decreased urinary excretion of pethidine, there was also the strange observation that the elderly excreted larger amounts of pethidine metabolites (40). It was also observed that approximately 50% of any level of pethidine was bound to the red cells of the younger subjects whereas only 20% was bound to the red cells of the geriatric subjects. If the bound drug is protected from metabolism, the elderly of course experience more rapid metabolism and excrete more metabolites than does a younger group. While Mather et al (41) did not find the same age effect as Chan et al on the half-life of pethidine (meperidine), they did find a striking decrease in plasma binding of the drug. A linear decrease in binding occurred with increasing age, proceeding from 75% bound at age 25 to only 35% bound at age 75. It is an interesting contrast to consider that a minimally bound drug such as antipyrine is less metabolized in older than in younger subjects, while highly bound drugs such as pethidine may be more rapidly metabolized if their binding decreases with age.

It has been reported (42) that indomethacin has a slightly greater half-life in the elderly (104 min) than in the young (92 min), but that the difference is not significant. The data indicated nevertheless that the younger control group excreted much more unchanged drug than did the elderly and that serum levels of indomethacin were higher in the latter. Again, because of incomplete information on comparative metabolite levels and excretion, it is impossible to ascribe the differences to any specific component of the drug-handling apparatus.

Phenylbutazone administered to the O'Malley groups of patients showed a more modest age effect than did antipyrine, but still showed a longer plasma half-time (104.6 hr) in the geriatric group than in the controls (81.2 hr). These values are very similar to those obtained by Triggs et al (43) who reported 110 hr for the elderly versus 87 hr for the young. They calculated this difference to be of little statistical significance. They did report, however, that the half-life of phenylbutazone, which is highly bound by plasma proteins, correlated well (and inversely) with the plasma albumin concentration, suggesting that if the elderly do indeed have reduced albumin levels they will experience a prolonged half-life for this drug.

### *Digoxin*

Few drugs are as well known to the geriatric practitioner as digoxin. There is a great familiarity with the problem of establishing an effective but nontoxic regimen of digoxin therapy for cardiac patients. Ewy et al (44) showed that a given i.v. dose of digoxin gave rise to higher blood levels and longer blood half-life in the elderly. They established that this was due to reduced renal function as reflected by creatinine clearance values approximately half those of young patients and that digoxin clearance bore a linear relationship to creatinine clearance. Chamberlain et al (45)

extended the pharmacokinetic observations of Ewy et al to show that in patients with good renal function, plasma digoxin levels were roughly proportional to daily dosage and that plasma level was positively correlated with ventricular rate. This latter observation showed that the elderly have in fact essentially the same sensitivity to digoxin as younger patients but need a lower dose to achieve the proper serum level.

### *Miscellaneous Drugs*

Two β-blocker drugs, propanolol and practolol, have been administered orally to elderly and young groups and the plasma levels monitored by Castleden et al (46). Propanolol, which is eliminated almost exclusively by the hepatic route, gave plasma levels approximately five times as great in the elderly as in the younger subjects. Since this included also the peak level, it appears that propanolol's first-pass effect is the primary site of the age-related difference; the sustained constant ratio of serum levels in the decay phase indicates no significant renal influence on this difference. Conversely practolol gave similar plasma levels in both groups until near the peak level, after which the elderly group levels approached levels twice that of the young group, suggesting primarily a difference in renal elimination.

In a concerted study of three drugs—sulphamethizole, paracetamol, and phenylbutazone—Triggs et al (43) compiled a number of pharmacokinetic measurements on young and geriatric subjects. The phenylbutazone results were mentioned above. Both sulphamethizole clearance and the elimination rate constant for sulphamethizole were linearly related to creatinine clearance as might be expected for a drug eliminated by renal excretion. Half-lives of 181 min and 105 min were reported for the geriatric and young groups respectively. Similar results were found for paracetamol although with a smaller difference in half-time (130 min vs 109 min).

Both of these drugs have relatively short half-lives although paracetamol is eliminated predominantly by metabolism. For all three drugs no difference in absorption was noted with age nor was there any age-dependent variation in drug distribution volumes.

The β-phase half-time for diazepam shows a pronounced (and linear) age dependence, increasing from about 20 hr at age 20 to 70 hr at age 70. Klotz et al (47) reported that plasma and red cell binding of the drug was independent of age. Computer analysis of their data also implied that there is a linear increase in distribution volume with increasing age.

## PLASMA PROTEIN BINDING

Once they enter the circulation, many drugs are bound to circulating plasma proteins, and it is for the most part the concentration of the free drug (in equilibrium with the drug that is bound) that determines the drug response interaction with receptor site. Drugs are ordinarily bound to plasma albumin, but other plasma proteins can also bind certain drugs. The binding involves a reversible bonding of the ionic, hydrogen, or van der Vaals type. Not all drugs are equally bound. Some may be bound to a major extent (up to 98% for phenylbutazone) or only very

slightly as with barbital, or for all practical purposes not at all as is the case with antipyrine.

Our immediate concern in this review with drug binding is twofold. First, we are concerned with the effect of increasing age per se on the binding of drugs by plasma albumin and the interaction of one drug on the binding of another; and second, on the effect that various diseases have on the binding of drugs.

### *Plasma Binding and Age*

With increasing age there is a decrease in the plasma binding of some drugs, which in some cases can be explained on the basis of lower serum albumin concentrations in the elderly. The character of the binding to plasma protein seems qualitatively the same as in healthy subjects, however. Studies by Bender et al (48) suggest that age per se is not associated with a defect in drug-binding proteins or the presence of endogenous materials that would compete with a drug for binding sites on the albumin molecule. Additionally, Hayes et al (49) have found that the strength of warfarin binding is uninfluenced by age. In a separate study the same investigators have ruled out any change in liver function that might influence the plasma binding of drugs in normal, healthy elderly subjects (31).

Bender et al (48) reported no change with age in the plasma binding of phenytoin, penicillin G, and phenobarbituric acid. In this study the serum albumin for normal, healthy subjects less than 50 years of age was 4.0 g/100 ml and for subjects over 50 years of age the serum albumin concentration was 3.4 g/100 ml. Klotz et al (47) also reported no change in plasma binding of diazepam with age; however, in this study serum albumin levels were not given. In another study, Wallace et al (50) compared drug binding in young and old healthy subjects who had serum albumin levels of 4.2 and 3.6 g/100 ml respectively. In this study they found that the binding of phenylbutazone was significantly reduced in the elderly; however, the binding of sulfadiazine and salicylate was unchanged. The binding of these two drugs was not as dependent on serum albumin levels as was the binding of phenylbutazone. Other authors have reported a consistent decrease in plasma binding with increase in age, and in these studies a large and rather significant drop in the concentration of serum albumin has been reported. For example, Hayes et al (31) found a significant reduction in plasma binding of phenytoin when data for subjects less than 45 years of age were compared to the binding for patients over 65 years of age. The serum albumin level in the two groups was 4.1 and 2.9 g/100 ml respectively. In this study the decrease in the maximum binding capacity paralleled the decrease in plasma albumin. A similar finding has also been recorded by Hooper et al (51). A decrease in the binding capacity of elderly people for warfarin (49) and carbenoxolone (52) has been reported and the decrease correlated with a fall in plasma albumin concentration. A decrease in meperidine binding with age has also been reported (41).

The question of drug-drug interactions with regard to the level and extent of binding of drugs in the elderly has not yet received a great deal of experimental attention. One study concerning this was carried out by Wallace et al (50) who studied the binding of three drugs—salicylate, sulfadiazine, and phenylbutazone—

to plasma protein in young and elderly subjects who previously had not been taking any drugs and in subjects who had received prior drug therapy with one or more drugs. They found that the presence of one or more drugs significantly decreased the binding of salicylate, sulfadiazine, and phenylbutazone to plasma proteins. They found the reduction in plasma binding to be greatest in a group of elderly patients who at the time the study was carried out were receiving one or more drugs. The authors suggest that because of their low albumin levels elderly patients may be more susceptible to the effects of multiple drug therapy on drug binding and that this effect is of particular importance for highly bound drugs like phenylbutazone.

### *Plasma Binding and Disease*

Decreased drug binding has been observed in certain disease states (53), and as opposed to what we have just reviewed as changes occurring in normal elderly subjects, the changes that occur in drug binding in various disease states cannot be explained simply in terms of hypoalbuminemia. It has been postulated from various studies that abnormal or "damaged" albumin and/or the accumulation of endogenous materials apparently contribute to the decrease in drug binding. When considering the use of drugs in the treatment of diseases commonly found in elderly people, the prescribing physician must be alert not only to the potential for decreased drug binding per se because of lowered serum albumin levels and the interaction of one drug on the binding of another but also to the influence that specific disease states will have on the drug-binding capacity of the patient.

To cite the work of a single investigator, Andreasen (54) found in a series of in vitro experiments that the protein binding of acetylsalicylic acid, salicylic acid, phenylbutazone, phenytoin, sulfadiazine, and thiopental was decreased in the plasma of ten surgical patients with acute renal failure. The decreased binding of these drugs could only partly be explained by the lower concentration of serum albumin. In a follow-up study (55) the author conducted a series of experiments using dialyzed plasma samples and concluded that the reduced binding capacity in patients with acute renal failure may be explained only in part by a decrease in the serum albumin level and may be due to a structural change in the plasma protein itself and in part to the accumulation of competitively or noncompetitively bound substances.

## CHANGES IN TISSUE RESPONSIVENESS

The response to a drug is a reflection first of the drug's concentration at its site of action, and second the ability of a given amount of drug to affect the receptor and to translate the effect on the receptor to a responsive tissue or tissue system. Decreases in response may occur specifically with an increase in the threshold of a receptor to the effect of a drug, to a decrease or a change in the number of receptor sites, to a decrease in available enzymes that help translate the effect of the drug, to structural changes in the tissue itself which could be rate limiting with respect to the response of a specific tissue, and finally to an alteration in the interrelationship of various organ systems as they change in response to the primary effect of the drug.

A number of changes have been reported to occur in old experimental animals and in elderly human subjects which cannot be explained merely by a change in the plasma concentration of a drug; it has been inferred from these studies that the tissue itself is modified in some way. It is not our intent to review here in exhaustive detail all of these examples but to outline a few as they reflect various possible changes in the status of the receptor site and its behavior.

In rats, amphetamine was on the one hand less effective in increasing spontaneous motor activity in older animals (56) while on the other hand the depressant effect of amphetamine on food intake was enhanced in older animals (57). This response is explained on the basis of a reduced number of cells in the central nervous system, creating a situation where it is more difficult for stimulants to exert an effect but easier for the depressant actions of a drug to be expressed.

A reduction in the number of target cells has also been used to explain the increased activity of alloxan in older rats (58). In this study alloxan administered to young and old rats produced a far larger increase in serum glucose levels in older rats; this was attributed to a decrease in the number of $\beta$ cells in the pancreas of older rats. An increase in protein and collagen in aortic strips has been cited by Tuttle (59) to explain a decreased response of aortic smooth muscle strips in response to norepinephrine. With increasing age there is a change in the innervation of the heart which is reflected in a decreased response to atropine, suggesting a reduction in the number of receptor sites (60).

In a more recent study, Hewick et al (61) found a difference in the sensitivity to warfarin in young and old rats and humans and stated that the difference appears to be due to a greater depression of hepatic clotting factor synthesis by warfarin in elderly rats and humans.

Table 1 summarizes the clinical results we have presented.

## CONCLUSIONS

On balance, the clinical pharmacokinetic studies we have reviewed lead us to these simple generalizations:

1. Changes in absorption with increasing age are not very significant but may be an occasional cause of ineffective therapy in the aged.
2. Drug metabolism changes may be significant in the elderly either because of decreased hepatic enzyme levels or because of reduced hepatic circulation.
3. Plasma binding of drugs is often decreased in the elderly giving rise to higher blood levels.
4. Renal performance is always decreased in the aged and leads frequently to increased blood levels and prolonged drug half-life.

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