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Review

When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly

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Abstract

The age-related changes in the functions and composition of the human body require adjustments of drug selection and dosage for old individuals. Drug excretion via the kidneys declines with age, the elderly should therefore be treated as renally insufficient patients. The metabolic clearance is primarily reduced with drugs that display high hepatic extraction ('blood flow-limited metabolism'), whereas the metabolism of drugs with low hepatic extraction ('capacity-limited metabolism') usually is not diminished. Reduction of metabolic drug elimination is more pronounced in malnourished or frail subjects. The water content of the aging body decreases, the fat content rises, hence the distribution volume of hydrophilic compounds is reduced in the elderly, whereas that of lipophilic drugs is increased. Intestinal absorption of most drugs is not altered in the elderly. Aside of these pharmacokinetic changes, one of the characteristics of old age is a progressive decline in counterregulatory (homeostatic) mechanisms. Therefore drug effects are mitigated less, the reactions are usually stronger than in younger subjects, the rate and intensity of adverse effects are higher. Examples of drug effects augmented is this manner are postural hypotension with agents that lower blood pressure, dehydration, hypovolemia, and electrolyte disturbances in response to diuretics, bleeding complications with oral anticoagulants, hypoglycemia with antidiabetics, and gastrointestinal irritation with non-steroidal anti-inflammatory drugs. The brain is an especially sensitive drug target in old age. Psychotropic drugs but also anticonvulsants and centrally acting antihypertensives may impede intellectual functions and motor coordination. The antimuscarinic effects of some antidepressants and neuroleptic drugs may be responsible for agitation, confusion, and delirium in elderly. Hence drugs should be used very restrictively in geriatric patients. If drug therapy is absolutely necessary, the dosage should be titrated to a clearly defined clinical or biochemical therapeutic goal starting from a low initial dose.

Keywords: Aging; Pharmacokinetics in the elderly; Pharmacodynamics in the elderly; Drug dosage; Gerontopharmacology; Drug metabolism; Renal drug excretion; Pharmacokinetic dosage guidelines; Antiaging drugs

1. Introduction

Most of us want a long life, but that implies getting old. Aging is associated with many disconcerting problems, not the least of which concerns the efficacy and safety of drug therapy. The increase in life expectancy over the past decades makes this issue more acute, survival to old age seems to be more and more the norm.

The beginning of senescence is insidious. Although this process commences after maturation, it manifests itself prominently and progressively in the post-reproductive stages of live. Society has agreed, rather arbitrarily, to define elderly as individuals aged 65 years and older.

This review deals with the principles of drug use in the elderly and the age-related alterations in drug disposition and response, changes that result from the modifications of the functions and composition of the body associated with aging. The literature on the topic is vast, so this article makes no attempt to be comprehensive.

2. Biology of aging

Survival to old age requires a protected habitat, as wild animals usually die early from extrinsic hazards such as infection, predation, starvation, or cold

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(Kirkwood and Austad, 2000). Aging entails a gradual decrease in physiological fitness and reduced ability to respond to environmental demands. The reduction in homeostatic capablities is a fundamental feature of senescence, but the decline in functional reserve varies markedly between elderly persons (Lamy, 1991; Troen, 2003; Turnheim, 1998). Very old individuals tend to become frail, a syndrome that includes loss of skeletal muscle mass (sarcopenia) as well as neuroendocrine and immune dysfunctions (Walston and Fried, 1999). Because of these changes, the elderly are increasingly prone to diseases and multimorbitity.

The structure of many proteins is altered in old age, for example there is increased crosslinking of extracellular matrix proteins such as collagen, elastin, and the lens protein. Other age-related modifications of proteins are glycation and oxidation (Troen, 2003). Many disturbances of old age have been linked to the occurrence of structurally modified proteins (Gafni, 1997). Protein-protein interactions may be responsible for the increased rigidity of practically all tissue in elderly. For instance, between the ages of 20 and 80 years there is a 90% loss of blood vessel distensibility, which together with enhanced intimal thickness and endothelial dysfunction appears to be responsible for the increase of systolic blood pressure and work load of the left ventricle. Renal, hepatic, and to a lesser degree cerebral blood flow declines. The increased stiffness of the left ventricle, that is a consequence of loss of myocytes with subsequent hypertrophy of the remaining cells, slows diastolic filling, cardiac output decreases. Further, normal human aging is associated with a reduction in baroreflex-mediated heart rate response to hypotensive stimuli (Verhaeverbeke and Mets, 1997; Pugh and Wei, 2001; Lakatta and Levy, 2003).

Other age-related changes include reduction of the diffusing capacity of the lung, the maximum O_2 consumption declines, resulting in a steady decline in arterial pO_2 (Turnheim, 1998).

In the endocrine system, the responsiveness to and the serum levels of many hormones are decreased. The prevalence of hypothyroidism increases in the elderly (Canaris et al., 2000). In men and women there is age-related hypogonadism, the serum levels of estradiol and testosterone, respectively, are decreased as are the concentrations of growth hormone and dehydroepiandrosterone (DHEA). These changes may contribute to defects of the muscular, skeletal, cardiovascular, and other organ systems (Nelson, 1995). But hormone replacement therapy, which has long been considered to be beneficial, is associated with an increased risk of neoplasms (Chen et al., 2002; Li et al., 2002).

The susceptibility for infectious diseases and the emergence of tumors is increased in the elderly, possibly because of a decline in the function of the immune system. While reactivity against foreign antigens drops significantly in old age, autoimmune reactions paradoxically increase (Wick and Grubeck-Loebenstein, 1997).

The effect of age on other organs will be discussed in the appropriate sections of this article.

The mechanism of aging is unresolved, many theories have been proposed that can be generally divided into two categories, stochastic and developmental-genetic. The stochastic theories stipulate that aging events such as damage of macromolecules by background radiation, free radicals or other environmental toxins occur randomly and accumulate with time, resulting in the decline in physiological fitness. The developmental-genetic theories, on the other hand, propose that aging is genetically predetermined as part of the continuum of birth, growth, maturation, and death. Support for the developmental-genetic theories comes from the evidence that the maximal life span of animals is highly species-specific and that several genetic diseases in humans are known that display accelerated aging, for instance the Hutchinson-Gilford syndrome (classical early onset progeria in children), Werner's syndrome (adult progeria), and Down's syndrome (Troen, 2003). The limited proliferative capacity of cells in culture, which is termed 'replicative senescence', also has a strong genetic component (Young and Smith, 2000). The notion that there is an internal clock or counting mechanism for cellular replication has gained interest from the observation that there is shortening of telomeres, the repeated sequences found at the ends of chromosomes, as cells age and loose the ability to divide. The replicative block that occurs in cells from patients with Werner's syndrome also appears to be telomere-based. At least some cells that express telomerase, which prevents telomere shortening, have extended life spans. Activation of this enzyme has the same effect in fibroblasts (Troen, 2003; Butler et al., 2002).

It appears that multiple genes influence the aging process, with 'mutation accumulation' over time or selection of genes which serve the youthful organism but have deleterious effects later on, a phenomenon termed 'antagonistic pleiotropy' (Kirkwood and Austad, 2000; Campisi, 2003). Tissue calcification, for example, is beneficial in early life as it is important for bone formation, but this process may be responsible for atherosclerosis in later years. Other age-related disorders that are explained along these lines are Alzheimer's disease and prostate hypertrophy (Wick et al., 2003).

3. Pharmacokinetics

All stages of the journey of a drug through the human body may be affected by aging, the most important pharmacokinetic change in the elderly being the reduction in renal drug elimination.

3.1. Drug absorption

Although the overall surface of the intestinal epithelium, gut motor function, splanchnic blood flow and possibly gastric acid secretion decrease with age, absorption of most drugs that permeate the gastrointestinal epithelium by diffusion is not diminished in the elderly. An age-dependent reduction of the extent or rate of absorption was shown for only a few drugs (indomethacin, prazosine, digoxin). Agents that impede propulsive gut motility (antimuscarinic drugs, antihistamines, tricyclic antidepressants, opioids) retard intestinal absorption to a greater extent that does aging. Compounds that permeate the intestinal epithelium by carrier-mediated transport mechanisms may be absorbed at a lower rate in the elderly, examples are calcium, iron, and vitamins. Gabapentin and some nucleoside drugs are also absorbed by mediated transport, but it is unclear if their absorption is retarded in old age (Turnheim, 1998).

Although there is atrophy of the epidermis and dermis in the aged with a reduction in barrier function of the skin, the rate of transdermal drug absorption may be diminished in elderly because of reduced tissue blood perfusion (Trautinger, 2001). This holds also true for absorption from the subcutaneous and muscular tissue. Intramuscular injections should be avoided generally in this age group because of erratic absorption and the high risk of sterile infiltrates.

3.2. Drug distribution

The plasma concentration of a drug is inversely related to its volume of distribution, which in turn is dependent on the size of the hydrophilic and lipophilic spaces of the body. The lean body mass, especially the skeletal muscle mass, declines with age, total body water content falls by 10–15% until the age of 80. The volume of distribution of hydrophilic drugs therefore decreases, equal doses as in younger individuals will result in higher plasma concentrations. This, for instance, is the case for aspirin, tubocurarine, edrophonium, famotidine, lithium, but also ethanol (Turnheim, 1998). Use of diuretics may reduce the extracellular space even further, leading to accentuation of toxic drug effects.

Total body fat, on the other hand, increases from 18 to 36% in men and from 33 to 45% in women (Vestal, 1997). Thus, although the fat content is higher in women than in men, the relative change in the volume of distribution for lipophilic drugs is more marked in men than in women. Examples for drugs with increased volumes of distribution in old age are amiodarone, diazepam, teicoplanin, and verapamil (Turnheim, 1998).

It should be remembered that the plasma half-life of a drug changes directly with its volume of distribution. Therefore, a higher volume of distribution implies an increase in half-life and in the time necessary to reach the steady-state serum concentration during repeated drug administration. In other words, it takes longer in these cases until a drug effect can be evaluated.

Very old individuals loose weight and become frail, the proportion of fat decreases so that the volume of distribution for lipophilic drugs again decreases and the serum concentrations increase. The frailty of very old individuals tends to be overlooked, low weight patients on average receive higher doses per unit bodyweight than heavier patients. Hence low bodyweight, in addition to advanced age, constitutes a risk factor for overmedication (Campion et al., 1987).

An important mechanism for removing drugs from the intracellular space is the P-glycoprotein transporter, the expression of which is associated with multidrug resistance (Robert, 1999). There is evidence that patients older than 56 years and afflicted with acute myeloid leukemia are more often positive for the multidrug resistance-associated protein-1 (mrd-1) than younger patients. Mdr-1 gene expression and age are the strongest predictors for failure of cytotoxic treatment (Schaich et al., 2002). This finding has to be confirmed for other malignomas.

Drugs in blood may be bound to plasma proteins with only the unbound fraction being pharmacologically active. Plasma albumin levels are decreased somewhat in the elderly, the concentrations of α_1-glycoprotein, which binds primarily alkaline drugs, are either increased or unchanged. In general, the age-dependent changes in plasma protein binding are not clinically relevant, as drug elimination increases when the free (unbound) drug concentration is enhanced. A decrease in plasma protein binding may therefore obscure an age-related decrease in drug clearance (Turnheim, 1998).

Small reductions in plasma protein binding in the elderly have been observed with acetazolamide, benazeprilat, clomethiazole, diazepam, diflunisal, enalaprilat, etomidate, naproxen, salicylic acid, theophylline, and valproate. These changes are attributed predominantly to renal or hepatic dysfunctions (Grandison and Boudinot, 2000). In malnourished patients with advanced cancer, serum albumin can be quite low so that free drug concentrations may increase causing unexpected drug toxicity (Walter-Sack and Klotz, 1996).

3.3. Renal drug excretion

After the age of 40 there is progressive development of glomerulosclerosis in the kidney, the number of functioning glomeruli is reduced. Renal blood flow decreases by approximately 1% per year, among other factors increased angiotensin-II and endothelin levels and decreased prostaglandin concentrations may contribute to this effect. Glomerular filtration rate declines by 25–50% between the ages of 20 and 90. Tubular secretion falls in proportion to the loss of glomeruli, so that

the glomerulotubular balance is preserved (Lindeman, 1995; Mühlberg and Platt, 1999). There are reports that the progression of kidney damage in old age may be retarded by angiotensin converting enzyme (ACE) inhibitors (Ferder et al., 2003).

Because of these changes, an age-dependent decline of total clearance is to be expected for all drugs that are predominantly eliminated by the kidneys. Disregarding the reduction in drug elimination by the kidneys in the elderly will result in increased drug serum levels. In fact, the decline in renal function is closely related to the incidence of adverse drug reactions (Lindeman, 1995; Mühlberg and Platt, 1999).

For drugs with linear pharmacokinetics, the reduction in renal drug excretion in old age can be compensated by correcting the maintenance dose, D_m, by the factor Q :

$$D'_m = D_m k'_e / k_e = D_m Q, \quad (1)$$

where k_e is the elimination rate constant. The prime, $'$ designates the values in old age. Renal elimination of most drugs is closely correlated with the endogenous creatinine clearance, CL_{CR}, therefore the individual dose adjustment factor Q can be calculated from:

$$Q = Q_0 + (1 - Q_0)\frac{CL'_{CR}}{CL_{CR}}, \quad (2)$$

where Q_0, the extrarenal elimination fraction, represents the Q-value for anuric patients (Turnheim, 1991). Alternatively Q can be obtained from convenient nomograms that relate CL_{CR} and Q_0 (Dettli, 1974; Spring, 1975). Values for Q_0 can be found in appropriate reference handbooks (for instance Dettli (1996) and Fichtl (2001)).

If CL'_{CR} of an individual elderly patient is not available, an average estimate of this parameter as a function of age and serum creatinine concentration, C_{CL} (in mg/dl), may be obtained from the equation of Cockroft and Gault (1976):

$$CL'_{CR} = \frac{(140 - \text{age})\cdot\text{bodyweight(kg)}}{72\cdot C_{CR}}. \quad (3)$$

This equation gives a value for the creatinine clearance in men, that for women is obtained by multiplication with 0.85 to account for the lower skeletal muscle mass in women. Although the Cockroft and Gault equation is reported to overestimate the glomerular filtration rate and modifications have been published (Oo and Liu, 2002), for routine clinical use the Cockroft and Gault equation is practical and user friendly. It should be noted that judging renal function from the serum creatinine concentration alone can be misleading because the input of creatinine into the circulation is diminished in the elderly as muscle mass is reduced. Hence serum creatinine concentration may not change although the glomerular filtration rate is decreased.

The fundamental importance of kidney function for drug elimination is generally recognized, but dosing guidelines based on the creatinine clearance are often neglected in elderly patients (Papaioannou et al., 2000).

3.4. Drug metabolism

Despite significant research efforts, the effect of age on hepatic drug metabolism continues to be a controversial issue. The reduction in liver size in old age is of the order of 25–35%, the endoplasmic reticulum is diminished, the hepatic extracellular space increases. Liver blood flow declines by about 40%, bile flow is reduced as is the rate of synthesis of proteins, lipids, and glucose. But routine clinical tests of liver function do not change significantly with advancing age, although the serum albumin concentration may decrease slightly (Schmucker, 1985; Durnas et al., 1990; Le Couteur and McLean, 1998).

In vitro, no consistent relationship has been found between age and the activity of microsomal cytochrome P_{450} enzymes (CYP) that are responsible for phase-I metabolism (Le Couteur and McLean, 1998). Under in vivo conditions, on the other hand, the metabolic clearance of some drugs is decreased by 20–40%, whereas that of others is unchanged, apparently irrespective of which CYP enzyme is involved (Table 1).

Whether the metabolic clearance of a drug is decreased or unchanged in old age has been attributed to the property of high or low extraction of the drug by the liver. Hemoperfusion of the liver declines in elderly, drugs exhibiting high extraction therefore display an age-related decrease in metabolic clearance as blood which flows through the liver is more or less completely ‘cleared’ from these compounds. Hence we speak of ‘blood flow-limited’ metabolism in these cases (Table 2). The metabolic clearance of drugs with low hepatic extraction, on the other hand, is in most cases not reduced, since it is not dependent on hepatic blood flow but on the total tissue content of metabolizing enzymes (‘intrinsic clearance’). This type of metabolic clearance is termed ‘capacity-limited’ (Le Couteur and McLean, 1998). However, changes in hepatic blood flow and intrinsic clearance do not provide a satisfactory explanation for the age-dependent reduction of hepatic metabolism of all drugs in the elderly, for instance antipyrine and theophylline (Table 2).

In general, the interindividual variation in metabolic drug clearance by CYP enzymes or phase-I reactions exceeds the decline caused by aging.

Phase-II or conjugation reactions usually are unchanged in old age, the activities of glutathione transferase and UDP glucuronyltransferase are not altered (Le Couteur and McLean, 1998).

Thus far, no effect of age on the frequency distribution of slow and rapid metabolizers, i.e. the prevalence of genetic polymorphisms, has been identified (Vestal, 1997).

The nutritional status of a patient has a marked effect on the rate of drug metabolism. In frail elderly, drug

Table 1
Effect of age on the metabolic clearance of various drugs. Indicated are also the major enzymes or reactions responsible for a drug's metabolism

Metabolizing enzyme or reaction	Metabolic clearance in old age	
	Decreased	Not changed
CYP 1A2	Theophylline (Turnheim, 1998), ropinirole (Kaye and Nicholls, 2000)	
CYP 3A4, 3A5	Amiodarone, amitriptylin, carbamazepin, triazolam (Turnheim, 1998), cyclosporine (Fahr, 1993), diltiazem, fentanyl, lidocaine, nifedipin (Durnas et al., 1990), felodipin (Dunselman and Edgar, 1991), zolpidem (Salva and Costa, 1995)	Alfentanil, diazepam, sertraline (Turnheim, 1998), paracetamol (acetaminophen) (Durnas et al., 1990)
CYP 2C9	Naproxen (Durnas et al., 1990), warfarin (Loebstein et al., 2001)	Celecoxib, diclofenac (Brenner et al., 2003), citalopram (Gutierrez and Abramowitz, 2000), irbesartan (Marino and Vachharajani, 2002), phenytoin (Durnas et al., 1990)
CYP 2C19	Imipramin (Sallee and Pollock, 1990)	
CYP 2D6		Fluoxetin (Altamura et al., 1994), nortriptylin (Jerling et al., 1994), propranolol (Colangelo et al., 1992), risperidone (Turnheim, 1998), venlafaxin (DeVane and Pollock, 1999)
Various CYP	Antipyrine (phenazone), clomethiazole, imipramine, pethidine, verapamil (Durnas et al., 1990)	Caffeine (Durnas et al., 1990), ibuprofen (Turnheim, 1998), mexiletin (Labbé and Turgeon, 1999)
Glucuronidation	Morphine (Durnas et al., 1990)	Salicylic acid (LeCouteur and McLean, 1998)
Acetylation		Isoniazid (Durnas et al., 1990)
Glutathion conjugation		Paracetamol (Durnas et al., 1990)

metabolism is diminished to a greater extent than in elderly with normal body weight (Walter-Sack and Klotz, 1996; Vestal, 1997).

The dose adjustment to account for a decline in metabolic clearance (or in total clearance in general) can be obtained from

$$D'_{\mathrm{m}} = D_{\mathrm{m}} \frac{f\ CL'}{f'CL}, \tag{4}$$

Table 2
Effect of age on 'blood flow-limited' or 'capacity-limited' hepatic drug metabolism (data from Le Couteur and McLean (1998))

	Metabolism in old age	
	Reduced	Unchanged
Blood flow-limited metabolism	Amitriptylin, imipramine, lidocaine, morphine, pethidine, propranolol, verapamil	
Capacity-limited metabolism	Antipyrine (phenazone), theophylline	Diazepam, digitoxin, phenytoin, salicylic acid, valproic acid, warfarin

where f is the drug bioavailability and CL the total clearance that is equivalent to $V{\cdot}k_{\mathrm{e}}$. Average values for f, V, k_{e}, and CL/f for a number of agents in old and young adults have been published previously (Turnheim, 1998). It should be noted that Eq. (4) takes into account age-dependent changes of V and f in addition to k_{e}, whereas Eq. (1) compensates only for altered k_{e}.

Using mean clearance values for the calculation of dosage with Eq. (4) will give *average* adjustments. *Individual* dosages can be obtained from the clearance in a given patient by measuring the area under the plasma concentration–time curve (AUC) and using the equation

$$CL' \text{ or } CL'/f' = \frac{D}{AUC'}, \tag{5}$$

where D is the dose administered. Alternatively, the individual clearance of a drug can be obtained form the steady-state drug serum concentration, C^{ss} :

$$CL' \text{ or } CL'/f' = \frac{D_{\mathrm{m}}}{C^{ss'}} \tag{6}$$

where CL and CL/f stand for the clearance after intravenous or peroral drug administration.

4. Pharmacodynamics

The pharmacokinetic guidelines for dose adjustment in the elderly given above disregard changes in the sensitivity to an agent. Aside from its concentration at the site of action, the magnitude of a drug effect depends on the number of receptors in the target organ, the ability of the cells to respond to receptor occupation (signal transduction), and on counterregulatory processes that tend to preserve the original functional equilibrium. Thus, in addition to pharmacokinetics, the pharmacodynamics of a drug may be altered in the elderly. An increase in drug sensitivity has to be assumed when the response to a given serum concentration is enhanced.

Age-related changes in pharmacodynamics may occur at the receptor or signal-transduction level or homeostatic mechanisms may be attenuated.

4.1. Receptor properties

A reduction in response to β-adrenoceptor agonists has been reported for the elderly, the sensitivity of the myocardium to catecholamines is lower. Apparently β-adrenoceptors are downregulated in old age by increased serum noradrenaline levels, possibly because of diminished presynaptic α_2-adrenoceptor activity and augmented noradrenaline release. The decreased antihypertensive effect of β-adrenoceptor blockers may be related to the lower renin levels in the elderly. Responsiveness of adenosine A_1-receptors, which mediate cardioprotective effects, is also reduced as is the activity of heart muscarinic receptors (Hämmerlein et al., 1998; Swift, 1990; Turnheim, 1998).

In contrast to effects mediated by β-adrenoceptors, responses to nitrates do not appear to change with age (Verhaeverbeke and Mets, 1997).

In the central nervous system the number of dopaminergic neurons and dopamine D_2 receptors decreases in the elderly, leading to extrapyramidal symptoms when a certain threshold of neuronal loss is reached (Wong et al., 1997). The number of cholinergic neurons and receptors, that are thought to be involved in cognitive functions, is also decreased.

The decrease in cell proliferation in old age may be attributed to defects in growth factor receptor and signal transduction mechanism (Obeid and Venable, 1997).

4.2. Homeostatic mechanisms

As mentioned, one of the fundamental characteristics of aging is a progressive reduction in homeostatic mechanisms. Hence, following a pharmacological perturbation of a physiological function, more time is required to regain the original steady-state as counterregulatory measures are reduced. Therefore, drug effects are attenuated less in the elderly, the reactions may be stronger than in young individuals and the incidence of adverse drug effects is higher, despite the general decline in receptor number or responsiveness.

A typical example for the consequences of the decrease in homeostatic mechanisms is the increased susceptibility of elderly patients to postural hypotension in response to drugs that lower the arterial blood pressure (Turnheim, 1998). Drug-induced orthostatic reactions, that are estimated to occur at a frequency of 5–33% in geriatric patients, contribute to the risk of syncope and falls. When assessing orthostatic hypotension in the elderly, drug treatment should always be reviewed. Eleven percent of cases of syncope in the elderly are reported to be drug-induced (Verhaeverbeke and Mets, 1997). In addition, peripherally acting antihypertensives such as calcium-channel blockers or loop diuretics may by associated with lower intellectual scores in the elderly (Turnheim, 1998). But untreated, elevated blood pressure may also be associated with cognitive impairment (Amenta et al., 2002).

Do the aged benefit from antihypertensive therapy? At the present time, it would appear reasonable to treat elderly patients with hypertension, particularly those with evidence of target organ damage (Duggan, 2001). According to the recently published ALLHAT study (2002), thiazide diuretics are superior to calcium channel blockers and ACE inhibitors with respect to prevention of cardiovascular complications in hypertensive patients, irrespective of age ($<$ or $\geq$ than 65 years). But doubts remain regarding the benefits of antihypertensive therapy in the elderly. Hopefully the 'Hypertension in the Very Elderly Trial' (HYVET) and similar studies that are presently conducted (Zannad, 2000) will clarify the risk-benefit relation of this treatment.

The role of ACE-inhibitors in geriatric patients is debatable as renin secretion is decreased. On the other hand, ACE-inhibitors appear to be of benefit even in cases with perceived contraindications (Ahmed et al., 2002). Digoxin is recommended in patients with heart failure not adequately responsive to ACE-inhibitors and diuretics, and in cases with atrial fibrillation and ventricular tachycardia (Ahmed, 2003). The increased risk of digoxin toxicity in old patients can be primarily attributed to reduced renal excretion (Hanratty et al., 2000).

Many elderly patients are on long-term therapy with diuretics. Because of a decrease in total body water with advancing age, an equal volume of fluid loss in young and old patients represents more severe dehydration in the elderly. Combined with the decrease in thirst, fluid intake, and cardiovascular reflexes, hypovolemia may contribute to deficits in hemoperfusion of vital organs (Vestal, 1997; Turnheim, 1998). In addition, the risk of patients over 65 years of age, especially when they are female, to develop hypokalemia, hyponatremia, and prerenal azotemia under treatment with thiazides in combination with loop diuretics is markedly higher than in younger patients (Hörl, 2002; Howes, 2002).

Diuretic therapy in the elderly is also complicated by the fact that the site of action of both loop and thiazide diuretics is the luminal cell membrane of the renal tubule. The intensity of the diuretic effect of these agents is therefore not primarily related to their concentration in plasma but to that in the lumen of the tubule. The reduction of the renal clearance of loop and thiazide diuretics in the elderly results in higher plasma levels and systemic toxicity, whereas the diuretic and natriuretic effect is decreased (Oberbauer et al., 1995; Mühlberg et al., 2001).

The sensitivity of elderly patients to the anticoagulant effect of coumarines is higher than in younger individuals, the risk of bleeding is increased (Hylek, 2001; Russmann et al., 1997). The concentration-response relation of heparin, on the other hand, was shown not to change (Turnheim, 1998).

The age-related decrease in glucose tolerance appears to be a consequence of reduced insulin secretion and insulin sensitivity (insulin resistance), even when adjusted for

increased obesity and physical inactivity that are usually associated with old age (Muller et al., 1996; Ikegami et al., 1997). Because of an impairment of glucose counter-regulation in the elderly, advanced age is a risk factor for hypoglycemia caused by sulfonylureas (Turnheim, 1998).

The cell density of the bone marrow decreases and cell proliferation is curtailed in the elderly, hence these patients are particularly sensitive to the adverse effects of anticancer drugs. The hematological toxicity of these compounds is increased as are the adverse effects on the gastrointestinal tract, the heart, and the nervous system (Vestal, 1997; Turnheim, 1998). The properties of a number of individual cytostatic drugs in elderly individuals have been described elsewhere (Skirvin and Lichtman, 2002).

The frequency of adverse effects of non-steroidal anti-inflammatory drugs (NSAID) on the gastrointestinal tract and the kidney increases with age, 3–4% of elderly patients treated with NSAID experience bleeding from the intestine compared with about 1% in younger subjects (AGS Panel on Chronic Pain in Older Persons, 1998; Wolfe et al., 1999). The recently developed selective inhibitors of cyclooxygenase (COX)-2 have analgesic and anti-inflammatory properties comparable to the classical nonselective NSAID, but gastrointestinal complications are half as frequent (Bombardier, 2002). The prevalence and severity of renal side effects observed with the classical NSAID and the COX-2 inhibitors are equal (Harris, 2002). The American Geriatrics Society has endorsed the use of COX-2 inhibitors for management of persistent pain in older persons (Eitorial, 2002).

The central nervous system is a particularly vulnerable drug target in the elderly. Between the age of 20 and 80 years, brain weight is reduced by 20% and neuronal loss has been reported for several brain regions. The gray matter decreases continuously in volume with age, the white matter remains relatively unchanged. Most importantly, the number of synapses decreases (Katzman, 1995). Marked changes in brain phospholipid composition take place with increasing age that also involve the second messenger diacylglycerol (Giusto et al., 2002). The age-related reduction in dopamine content predisposes to an increased frequency and severity of extrapyramidal symptoms in response to dopaminergic blockade by neuroleptics and metoclopramide. A high incidence of tardive dyskinesia, akathisia, and Parkinson syndrome is observed in geriatric patients on long-term antipsychotic therapy. Similarly, the reduction in acetylcholine content renders old individuals more susceptible to the anticholinergic effects of neuroleptics and tricyclic antidepressants (Kompoliti and Goetz, 1998; Turnheim, 1998).

The prevalence for pain increases with advancing age. When poorly controlled, pain may lead to depression and reduce the activities of daily living. Pain management in the aged should follow the WHO three-step scheme using non-opioid analgesics, weak and strong opioids in sequential order with tricyclic antidepressants and antiepileptics as adjuvants (Davis and Srivastava, 2003). Care has to be exercised with opioids as the response to conventional doses may be increased in the elderly, frequently there is oversedation, respiratory depression, and a reduction of protective reflexes (Turnheim, 1998).

The potential for adverse reactions is also increased with antiepileptic drugs, more atypical effects such as cognitive deficits are observed in geriatric patients. The hematological toxicity of these agents is increased in old age as well. In addition, the cardiac symptoms caused for example by intravenous administration of carbamazepine and phenytoin may be life-threatening in the elderly, whereas they are usually irrelevant in young adults. The dosage of phenytoin is generally complicated because of its non-linear pharmacokinetic behavior (Bachmann and Belloto, 1999). It is advised to reduce the initial dose of antiepileptic drugs by 50% in geriatric patients. Plasma concentrations required for young adults may be toxic for the elderly, hence dosage should be primarily adjusted by clinical symptoms, not by target plasma levels established for therapeutic drug monitoring in young individuals (Willmore, 1995; Hetzel, 1997; Tallis et al., 2002).

Age-dependent changes in the $GABA_A$-benzodiazepine receptor complex were shown not only in number but also in subunit composition. Possibly these alterations are responsible for the high sensitivity of elderly patients to benzodiazepines, for instance midazolam (Klotz, 1998). Not only is sedation accentuated, but in addition there may be confusion, ataxia, and immobility. Benzodiazepines may cause impairment of short-term memory and contribute to subtle cognitive disturbances in the aged. Many elderly are dependent on benzodiazepines, withdrawal symptoms include tremor, agitation, insomnia, and seizures. Should treatment with these agents be absolutely necessary, short-acting benzodiazepines such as triazolam and oxazepam are to be preferred (Kompoliti and Goetz, 1998). Meprobamate is highly addictive, it should not be used in old individuals (Beers, 1997).

The prescription of psychotropic drugs is disproportionally high and frequently inappropriate in the elderly. This problem appears to be especially acute in nursing homes. Intellectual functions are not only diminished by benzodiazepines but also by antidepressants, neuroleptics, and anticonvulsants. Frequently neuroleptics are given for non-psychotic behavioral and psychological symptoms (Ruths et al., 2001).

As mentioned above, the antimuscarinic effects of tricyclic antidepressants are augmented in older individuals, they may react with symptoms such as agitation, confusion, impairment of attention and memory, and ultimately delirium. Selective serotonin reuptake inhibitors (SSRI) do not have significant anticholinergic effects, hence these drugs should be the first-choice antidepressants in the elderly (Kompoliti and Goetz, 1998; Turnheim, 1998).

Other drugs with antimuscarinic activity are phenothiazines and butyrophenones, histamine H_1-receptor antagonists, and conventional parasympatholytic agents such as atropine.

In addition, the antidepressants amitriptylin, imipramin, and maprotilin and the neuroleptics thioridazine, droperidol, and haloperidol may have adverse cardiac effects, causing prolongation of the QT-interval in the electrocardiogram and possibly life-threatening ventricular tachyarrhythmia ('torsade de points'). Old age, bradycardia, heart failure, and multiple drug use are risk factors for these effects (De Ponti et al., 2002). SSRI antidepressants and the newer atypical neuroleptics risperidone, quetiapine, olanzapine, and clozapine have no or only a negligible effect on the QT-interval.

In short, the uncritical use of sedative drugs appears to be an important cause for the increase in morbidity in old age. Some of these compounds may give rise to global cognitive deficits, motor incoordination and gait irregularities as well as cardiac arrhythmias. Consequently, the incidence of falls and injuries is increased both in community-dwelling older persons and those living in long-term care-facilities (Leipzig et al., 1999; Ensrud et al., 2002). Although there are some uncertainties concerning the association between drug use, illnesses, and falls (Agostini and Tinetti, 2002), clearly the use of CNS-active medication in the elderly should be curtailed as much as possible.

Individuals that sustain a hip fracture are at a greater risk of acquiring another. However, secondary prevention of hip fractures, including osteoporosis treatments with calcium, vitamin D, or bisphosphonates, is underutilized in geriatric patients (Kamel and Duthie, 2002; Wilkinson et al., 2002).

5. Antiaging or longevity medicine

Antiaging is a hot subject these days and there is brisk commerce in remedies that claim to slow, stop, or even reverse the aging process. But in spite of considerable hype to the contrary, there is no scientifically valid evidence that antiaging drugs presently on the market (ginseng, garlic, ginko biloba, chondroitin sulfate, DHEA, growth hormone, melatonin, fish oil, St Johns wort, procain) can increase longevity (Platt, 1990; Turnheim, 1995; Olshansky et al., 2002). In some cases these products may even be harmful (U.S. General Accounting Office, 2001) and those selling them often misrepresent the science upon which the antiaging claim is based. Nevertheless, experiments with laboratory animals indicate that it may be possible to alter the rate of aging or the maximal life expectancy, and legitimate research is under way to develop drugs that have this effect. Of interest is the observation that life is prolonged in mice and rats with caloric restriction, presumably in part by delaying the occurrence of age-related diseases (Masoro, 2000). Other strategies that may increase life expectancy include interventions that reduce oxidative stress, hormone and cell replacement therapies (including stem cells), telomerase activation, or other genetic manipulations (Butler et al., 2002). But the clinical studies concerning the effects of antioxidants on aging have been inconclusive, whereas the side effects of these agents are sizable (Dröge, 2002). Other interventions await testing in humans. An increases in life expectancy beyond that seen in the past century will require insights into the mechanism of the aging process which could provide the basis for its pharmacological manipulation. So far, no such progress is in sight (Holden, 2002).

6. Conclusions

Persons aged 65 or older are particularly susceptible to adverse drug reactions because of multimorbidity, the high number of medications used in this population, and age-associated changes in pharmacokinetic and pharmacodynamic properties. The rate of adverse drug effects is estimated to be 2-3 times higher in older individuals than in adult patients younger than 30 years (Turnheim, 1998). As much as one fifth of all hospital admissions of older subjects are attributed to adverse drug effects that are often not recognized by these patients (Mannesse et al., 2000). Changes in patient medical status over time can cause long-term drug therapy to become unsafe or ineffective. The quality of drug treatment in the elderly appears to be generally questionable (Pittrow et al., 2002; Sloane et al., 2002).

Certain drugs are rarely if ever indicated for the elderly because safer and/or more effective alternatives exist. Beers (1997) published a list of 'inappropriate medications' which should be avoided in old individuals, including amitriptylin, chlordiazepoxide, disopyramide, doxepin, meprobamate, α-methyldopa, pentazocine, propanthelin, belladonna alkaloids, and ticlopidine. Between 3 and 25% of prescriptions to elderly persons were classified as inappropriate (Spore et al., 1997; Sloane et al., 2002). Selection of medication is an important factor influencing the likelihood of adverse drug events.

Because of these uncertainties, advanced age is frequently considered an unpredictable risk factor for drug treatment, consequently the elderly may be denied adequate pharmacotherapy (Editorial, 1993; Hylek, 2001; Turnheim, 1998).

The drug doses that are usually prescribed for younger adults may be too high for old individuals. But it is important to recognize the heterogeneity of drug response in the elderly. Therefore there are no simple rules for prescribing that can apply to the entire elderly population, rather the dose has to be determined individually considering particularly the reduction in body weight

and renal elimination in a given patient. Pharmacokinetic guidelines may be used to calculate doses that result in drug serum levels in the aged equivalent to younger adults. But this procedure neglects changes in sensitivity to drugs. Hence, starting from a smaller initial dose than used in younger adults (for example 50%) the dose should be titrated to a clearly defined therapeutic response. It would be convenient to use therapeutic drug monitoring to adjust dosage in old patients, however, robust drug serum concentration—effect relations for the elderly are lacking, therapeutic target concentrations are not established for this age group. As a matter of fact, it may be difficult if not impossible to define such target concentrations for the elderly because of the marked interindividual variation in this segment of the population.

The number of drugs administered simultaneously should be reduced as much as possible in geriatric patients, the need for pharmacotherapy has to be evaluated very restrictively. The list of medications should be reviewed critically and periodically, drugs no longer needed are to be discontinued. Only basic diseases should to be treated, not epiphenomena. Hence, therapeutic priorities have to be identified. The age-dependent pharmacological properties of the drugs prescribed for the elderly should be clear to the physician. A once or twice daily drug administration is optimal. This goal may be reached using drug preparations with retarded release or fixed drug combinations.

It has to be realized that drugs may worsen the course of chronic diseases, for instance β-adrenergic blockers, calcium-channel blockers, and disopyramide may cause manifest cardiac failure, in patients with peripheral vascular disease β-adrenergic blockers can precipitate claudicatio, NSAID, aminoglycoside antibiotics, and intravascular X-ray contrast media may aggravate kidney damage, the use of antimuscarinic agents can result in glaucoma, constipation or urinary retention. Drugs that impair cognitive functions may cause social isolation and withdrawal. Adverse drug effects have to be considered when symptoms such as dehydration, postural hypotension, dementia or excitation, confusion, syncope and falls occur, especially when diuretic, antihypertensive, and psychotropic drugs are administered to elderly patients.

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