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The Aging Liver

Structural and Functional Changes and Their Consequences for Drug Treatment in Old Age

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Key Words
Liver · Aging · Elderly · Drug treatment · Old age

Abstract

Background/Objective: Numerous age-related changes in hepatic structure and function have been described, although liver function seems to be quite well maintained in old age. Few consistent and reproducible observations and a lack of correlation between structural and functional data characterize the present state of our knowledge. In contrast to renal clearance, no equally reliable method exists to estimate hepatic drug clearance. The contribution of age to altered drug clearance in the elderly is difficult to assess as drug interactions, numbers and types of drugs taken at a time, underlying disease and increased interindividual variability are superimposed to the aging process. ***Methods:*** A comprehensive computer-assisted search of the literature. ***Results:*** A decline in liver volume and blood flow and a reduction in in vitro and in vivo metabolic capacity have been shown in older subjects, and the physiologic basis of reduced hepatic drug clearance in this age group. ***Conclusions:*** After decades of research into the matter, the old and well-known aphorism 'start lower – go slower' is valid more than ever in the field of geriatric prescribing. Not only renally excreted drugs but also substances which are metabolized and excreted by the liver should be used at a starting dose which is 30–40% smaller than the average dose used in middle-aged adults.

Introduction

Due to age-associated changes and the sequelae of previous disease, the elderly – i.e. persons older than 75 years – represent a distinct population. They differ from younger adults in terms of pharmacokinetics and pharmacodynamics [1–3] and these differences can mainly be attributed to decreased liver and renal function, reduced cardiac output, impaired pulmonary function and to reductions in body weight, muscle mass and changes in body composition [4–6]. Furthermore, the possibility of drug interactions has to be taken into account as elderly patients frequently receive extensive drug treatment for coexistent illnesses.

The incidence of many diseases increases with age and multimorbidity occurs most often in the elderly and oldest old. Therefore, prescribing for those frail elderly

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Table 1. Age-related changes and the potential resulting problems in the pharmacotherapy of elderly persons and their estimated relative importance

Confounding factors	Remarks and examples	Relative importance
Compliance problems in old patients taking many drugs	Errors sharply increase when more than four drugs are being prescribed at a time	Very important
Altered drug absorption from the aging gastrointestinal tract		Less important
Altered protein binding due to altered plasma protein pattern	Increases glomerular excretion and tissue drug concentration	Possibly important
Altered volume of distribution due to changing body composition and body mass	Diazepam has a markedly prolonged half-life in the elderly due to a increased volume of distribution	Important
Impaired liver function		Important
Impaired renal excretion	Glomerular filtration decreases with age	Very important
Altered end organ susceptibility to drug effects	The risk of falls is increased in subjects taking sedative drugs	Very important
Failure of compensatory mechanisms	Arthritis and impaired postural control may aggravate the risk of falls after a variety of psychotropic drugs	Very important

subjects is a major challenge for the medical practitioner. On the one hand the frail elderly may require – and may potentially benefit from – several medications. On the other hand, such polypharmacotherapy may also be harmful, as untoward drug reactions are a recognized cause of morbidity in old age. Hurwitz [7], in a pioneering survey of more than 1,200 elderly patients admitted to an acute care hospital, found that the incidence of adverse drug reactions more than tripled beyond the age of 70 years. This tendency may even be more pronounced in frail nursing home patients. It has been shown that 11.6% of all patients beyond the age of 65 years admitted to community hospitals had been admitted because of drug-induced conditions [8]. In part, this is due to the fact that with declining renal and hepatic function and with a smaller body mass 'usual' adult doses may represent relative overdoses for many elderly. For renally excreted drugs this may be overcome by meticulous assessment of actual renal function, whereas at present no routine tests of hepatic drug-metabolizing capacity are available. Therefore, therapeutic drug monitoring may contribute to avoid dose-related drug toxicity. Whereas anaphylactic and allergic drug reactions seem to occur independent of age, the frequency of drug–drug interactions and adverse drug reactions due to unexpectedly high blood concentrations of the drug are increased in elderly patients. Therefore, the elderly not only have an increase in adverse drug reactions associated with abnormally high blood levels of many drugs but also have more adverse effects at therapeutic blood levels. Several mechanisms may account for this (table 1).

For most side effects encountered in the elderly remarkably little data are available to support the commonly held view that the incidence of adverse drug reactions increases with patient age as an independent risk factor [9]. After taking into account the doses administered and the duration of therapy, a positive correlation between increasing patient age and the occurrence of side effects may no longer be observed [10]. This underscores the importance of careful and sensible prescribing for the elderly. However, comorbidity and limited reserve capacity of many organ systems often make the elderly more vulnerable for untoward side effects of drugs (table 2).

Table 2. Characteristic side effects of drugs frequently used in the elderly

Target organ system, effect	Offending drugs	Reference
Metabolic system, hypokalemia	Diuretics	Levy and Lye [11], 1987
Genitourinary system, urinary retention	Anticholinergics, benzodiazepines	Iber et al. [12], 1994
Gastrointestinal system, ulcer bleed	Nonsteroidal anti-inflammatory drugs	Iber et al. [12], 1994
Cardiovascular system, postural hypotension	Diuretics, antihypertensive drugs	Sabanathan et al. [13], 1987
Nervous system, confusion	Anticholinergics, psychotropic drugs, H2-blockers	Iber et al. [12], 1994
Locomotor system, falls and fractures	Psychotropic drugs	Ray et al. [14], 1987

Table 3. Liver volume and age [6, 12, 15, 18]

Technique	n	Age range years	Decline relative, %	Decline absolute, ml	Year of publication
Autopsy	1,582	20–80	24 (male) 18 (female)	–	1933
Ultrasound	26	25–80	24	1,303 → 990	1978
Ultrasound	50	<50–<80	32	–	1988
Ultrasound	65	24–91	37	1,474 → 934	1989
Ultrasound	32	<55–>70	20	1,446 → 1,157	1994

Morphological Changes of the Aging Liver

Macroscopically the liver is described as undergoing brown atrophy with old age. In autopsy studies, aging was found to be associated with a 24% reduction in liver weight in males and a 18% reduction in females. This trend has been confirmed with different techniques (table 3), and in general the reduction in liver size is noted to be in the order of 25–35% [15]. Apart from this decline in liver volume there are few if any age-associated changes in liver structure that correlate with perturbations in hepatic function. Physiological and morphological studies suggest that, compared to other organs, the liver seems to age fairly well. Routine liver function tests do not show age-associated changes and even the synthesis rate and concentration of albumin seems to be stable into old age [16]. Perhaps the most compelling evidence for the maintenance of hepatic function into advanced age comes from clinical practice, wherein livers from elderly subjects, including one donor aged 86 years, have been transplanted successfully [17].

Hepatic Blood Flow

Old age is unambiguously associated with a reduction in hepatic blood flow of about 35–40% (fig. 1). This has been documented using a variety of technical methods including dye dilution and indicator clearance, indicator distribution and Doppler ultrasound [6, 19, 20]. This decrease is probably due to diminished splanchnic blood flow with reduced input of blood into the portal vein. Bile flow and bile salt formation are reduced by about 50% reflecting, at least in part, impairment of energy-dependent and microtubule-dependent transport processes [15].

Principles of Hepatic Drug Clearance

By examining the characteristics and behavior of some drugs and their metabolites it is possible to infer certain characteristics about the aging liver. Phase I of hepatic drug metabolism leads to structural alteration of the

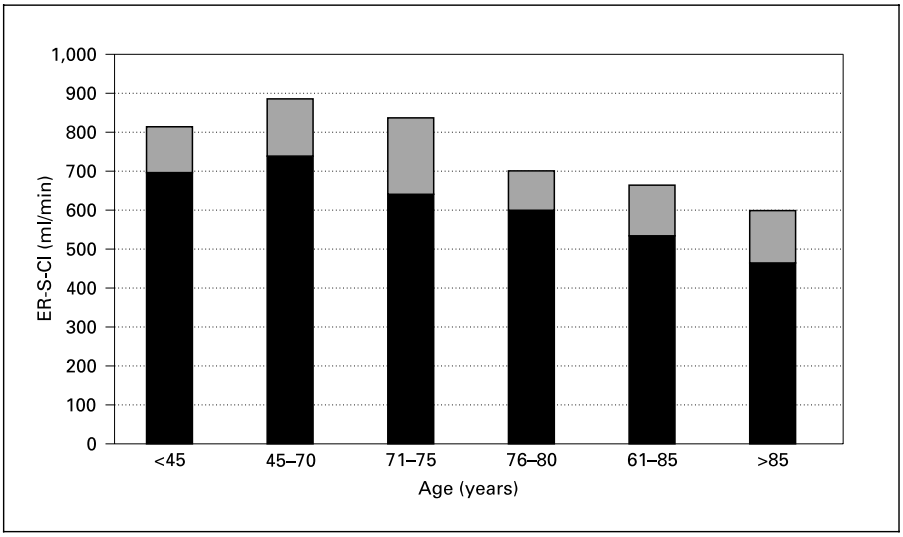

Fig. 1. Liver perfusion as determined by extrarenal sorbitol clearance (ER-S-Cl) in 86 subjects aged 40–95 years without liver disease [21]. Black columns denote mean values, topped grey columns indicate SD.

Table 4. Examples of high- and low-extraction drugs [4, 22]

High-extraction drugs	Low-extraction drugs
Amitriptyline	Antipyrine
Bromocriptine	Carbamazepine
Clomethiazole	Chlordiazepoxide
Diltiazem	Caffeine
Dothiepin	Diazepam
Ergotamine	Flunitrazepam
Isosorbitdinitrate	Indomethazine
Labetalol	Oxazepam
Metoprolol	Phenprocoumone
Nifedipine	Phenytoin
Propranolol	Prednisolone
Triamterene	Theophylline
Verapamil	

metabolized drug by oxidation, reduction and hydrolysis, and depends on the amount and activity of the specific microsomal enzymes. Thereafter, phase II of metabolism leads to conjugation with chemical ligands such as glucuronide, sulfate, acetate or glutathione, again dependent upon the activity of specific cytosolic enzymes.

Hepatic clearance (Cl_{hep}) is defined by the equation

$$Cl_{hep} = Q \times E,$$

where Q is the hepatic blood flow and E is the hepatic extraction fraction, the fractional removal of a certain drug by the liver. Some substances eliminated by the liver have an extraction rate that approximates unity. This type of metabolism is called flow limited, because hepatic clearance will be almost equal to hepatic blood flow. Using this principle, the clearance of highly extracted like indocyanine green and sorbitol have been used to estimate hepatic blood flow [21]. On the other hand, the clearance of drugs with a low extraction fraction is not influenced by blood flow. The metabolism of these drugs is influenced by intrinsic clearance (a term that describes total enzyme activity and liver mass) and/or protein binding and is termed capacity-limited (table 4). The clearances of these compounds, such as antipyrine and galactose, have been used to describe liver size. The relationship between hepatic clearance (Cl_{hep}) and parameters such as hepatic flow (Q), intrinsic clearance (Cl_{int}) and the unbound fraction (f_u) has been described by various models. The simplest model is the venous equilibrium model, which assumes complete mixing of substrates within the liver and can be summarized thus:

$$Cl_{hep} = \frac{Q \times f_u \times Cl_{int}}{Q + (f_u \times Cl_{int})}$$

Phase I and phase II are terms used to describe the major enzymatic pathways in the liver that metabolize drugs and other xenobiotics. Both pathways tend to increase the water solubility of compounds and facilitate renal excretion. Phase-I reactions alter the structure of a compound by oxidation, reduction, hydrolysis and demethylation and are performed mostly by the CYP system of enzymes within the endoplasmic reticulum. Phase-II reactions involve the addition of polar chemical groups such as glucuronide, sulfate, glycine, glutathione and ace-

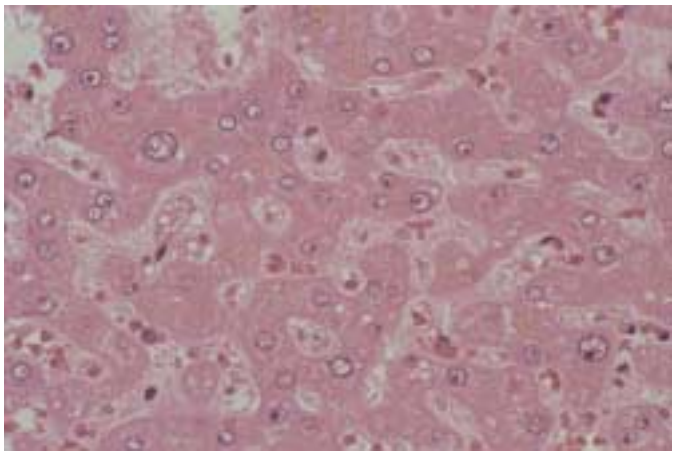

Fig. 2. Liver of a 100-year-old man.

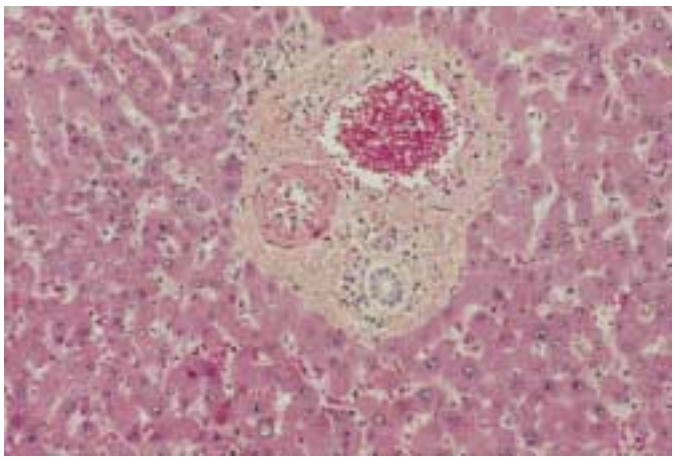

Fig. 3. Anisomorphology of hepatocytes.

tate. These reactions occur mainly in the cytosol. Recent studies indicate that the activity of phase-I enzymes is more dependent on the delivery of oxygen than phase-II enzymes. Many drugs, including some tricyclic antidepressants and benzodiazepines, are metabolized extensively by both pathways prior to excretion by urine or bile. Drug elimination can also be influenced by many other factors such as drug absorption, extrahepatic metabolism, tissue distribution, protein binding and renal excretion. Therefore, in order to assess the effects of age on the liver, it is preferable to examine drugs that are not influenced by renal excretion or other routes of elimination and where absorption is not affected by age. It should be noted that these traditional approaches to the understanding of hepatic drug metabolism make the assumptions that there are no limitations on the supply of oxygen and/or other cofactors and that other substrates including drugs have unimpeded access to enzymes. It also assumes that any changes in physicochemical parameters such as intracellular pH and osmolality will not impact on enzyme function.

Potential Limitations of Drug Studies on Aging

The aging process is quite different from person to person, such that among a group of 70-year-old persons there are a few who appear much younger, those who appear that age and some who appear older. This heterogeneity of an aging cohort of normal individuals is also evident in physiological terms, which affects the metabolism, excretion and toxicity of drugs [12]. Furthermore, subclinical

Fig. 4. Periportal fibrosis.

disease in apparently normal persons, the parallel intake of drugs both over-the-counter and prescribed ones, smoking habits, nutritional differences and other factors may be superimposed to the aging process. In patients, the effects of disease and of comedications need to be considered, making things even more complex. At all ages there is a wide genetic variability or polymorphism in the rates of drug clearance, which is commonly 2- to 5-fold and occasionally up to 30-fold and clearly persists into old age (fig. 2). Examples are the acetylator status and differences within the family of cytochrome P450 isoenzymes. Furthermore, differences in the clearance or hepatic metabolism of one stereoisomer compared with another have been found for metoprolol, verapamil, salbutamol and felodipine. All these factors provide 'noise' and contribute to the wide variability in drug-clearance studies performed to detect the effects of aging.

Findings, Considerations and Hypotheses

In an attempt to reduce the incidence of adverse drug reactions much research into the effect of age on drug metabolism has been done. Despite significant efforts, the effect of age on hepatic drug metabolism continues to be a controversial issue. Well-known changes in the clearance of drugs that undergo hepatic metabolism may be attributed to age-associated alterations in hepatic enzyme activity and – more importantly – to reduced liver size and hepatic blood flow.

The ability of the aging liver to metabolize drugs does not decline in a similar way and extent for all pharmacological agents. Several changes in hepatic function and structure have been noted in the elderly, and many of them seem to be of limited relevance (fig. 3, 4). Two, however, are of major importance. These are an absolute and relative to body-weight decrease in liver size and mass and a reduced regional blood flow to the organ [23]. The most frequent changes involve the mixed-function oxidative system of phase-I oxidation and reduction, with little or no change in the processes of phase-II conjugation. However, there have also been reports where the activities and amounts of liver microsomal monooxygenases remained unaltered with increasing age [24]. More recently, in a study among 226 subjects, the cytochrome P450 content of liver specimens declined from the age of 40 to 69 years by 16% and further declined by 32% after age 70. The antipyrine clearance remained unaltered during the fourth decade and declined thereafter by 29% with a rate of 0.34 ml/min per year [25]. The reasons for these discrepancies between different studies and between clinically observed decline in drug elimination and – in some studies – unchanged metabolic activity in vitro are probably attributable to interindividual variability and the difficulty of getting representative liver samples from healthy elderly subjects. A review of age-related changes in drug clearance established that patterns of change are not simply explained in terms of hepatic blood flow, hepatic mass and protein-binding changes. In particular, further explanations are required for the following situation: the maintained clearance of drugs subject to conjugation processes during oxygen-dependent metabolism declines, although all in vitro tests of enzyme function are normal. By analogy with our understanding of drug metabolism in liver disease it may be assumed that a hepatocyte diffusion barrier to oxygen develops with increasing age. This provides a plausible explanation for the paradox and has some experimental support [15].

Consequences for Clinical Practice

Ten years after our previous review of the topic [18] and after an other decade of research into the consequences of aging upon drug treatment of the elderly patient, the old and well-known aphorism 'start lower – go slower' is valid more than ever. Compared to the potentially important impact of altered drug disposition in elderly people, who consume the majority of drugs, remarkably little research is devoted to the field of age-associated functional hepatic changes. In a recent paper, Sotaniemi et al. [25] cited 42 references. Only eight of these were published during the last 5 years, seven were 6–10 years, 16 were 11–20 years and 11 were more than 20 years old. As a rule of thumb not only renally excreted drugs by also substances metabolized and excreted by the liver should be used at a starting dose which is 30–40% smaller than the average dose used in middle-aged adults. The steps by which this dose is increased as clinically indicated should also be smaller and the patient should be closely monitored for the occurrence of drug toxicity. As compliance problems may be regarded as a major problem in the elderly and intake errors rise sharply with the number of drugs prescribed, the most hazardous drug in the elderly may be 'the fourth', which is added to a treatment regimen of three other drugs [26].

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