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REVIEW ARTICLE

Pharmacokinetics and drug metabolism in the elderly

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Abstract

Aging involves progressive impairments in the functional reserve of multiple organs, which might also affect drug metabolism and pharmacokinetics. In addition, the elderly population will develop multiple diseases and, consequently, often has to take several drugs. As the hepatic first-pass effect of highly cleared drugs could be reduced (due to decreases in liver mass and perfusion), the bioavailability of some drugs can be increased in the elderly. Significant changes in body composition occur with advancing age. Lipophilic drugs may have an increased volume of distribution (Vd) with a prolonged half-life, and water-soluble drugs tend to have a smaller Vd. In the elderly, hepatic drug clearance of some drugs can be reduced by up to 30% and CYP-mediated phase I reactions are more likely to be impaired than phase II metabolism, which is relatively preserved in the elderly. Concerning the most important CYP3A4 studies with human liver microsomes and clinical studies with the validated probe, midazolam, it is indicated that there are no significant differences in CYP3A4 activity between young and old populations. Finally, renal excretion is decreased (up to 50%) in about two thirds of elderly subjects, but confounding factors such as hypertension and coronary heart disease account also for a decline in kidney function. In conclusion, age-related physiological and pharmacokinetic changes as well as the presence of comorbidity and polypharmacy will complicate drug therapy in the elderly.

Keywords: *Pharmacokinetics; drug metabolism; elderly; kidney function; liver function; cytochrome P450; clearance; frailty*

Introduction

Recently, about 100 major medical journals devoted considerable space to a topic regarded as the most important global issue—aging (Winkler, 1997). Conventionally, the "elderly" has been defined most frequently by a chronological age of 65 years and older because there are as yet no biological age markers. This population has been, and will be, steadily increasing and is expected to reach 22% in 2050. As elderly individuals are living longer, about 20% of our population will be older than 79 years at that time (United Nations, 2007).

The complex processes of aging involve progressive impairments in the functional reserve of multiple systems and organs, which will increase the susceptibility of elderly individuals to stress and drugs. The prevalence of diseases increases with advanced age. Because of this multimorbidity, the use of drugs in older patients is extensive. The elderly take, on average, two to five prescription medications on a regular basis and polypharmacy occurs in 20–50% of patients (Kennerfalk et al., 2002; Pizzuti et al., 2006). Consequently, adverse drug reactions are more frequent and more serious in the elderly (Doucet and Queneau, 2005; Cresswell et al., 2007) and drug interactions occur more often in this population of risk (Herrlinger and Klotz, 2001; Mallet et al., 2007). If the impact of aging is considered, one has to differentiate the group of fit elderly from that of frail elderly (Ahmed et al., 2007), which represents a subpopulation of patients in whom not age *per se*, but multiple disease states will primarily account for observed changes in pharmacokinetic and pharmacodynamic properties (Woodhouse & O'Mahony, 1997; Hubbard et al., 2008).

In the past, several comprehensive reviews have already focused on the pharmacokinetics, in particular drug metabolism, in the elderly (Benedetti et al., 2007; Hilmer et al., 2007; Hutchison and O'Brien, 2007; Kinirons and O'Mahony, 2004; McLean and Le Couteur,

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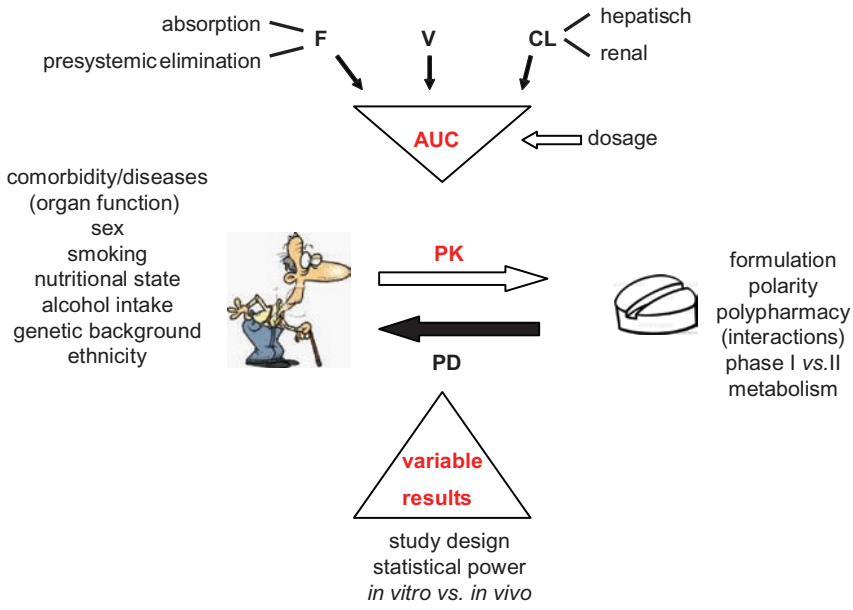

Figure 1. Complex relationships between a particular drug and an individual old subject, including various (i.e., confounding) factors modifying the pharmacokinetics (PKs) and causing variable clinical results.

2004; Schwartz, 2007; Wauthier et al., 2007). In addition, the clinical implications of aging for a rational drug therapy have been recently outlined (Shi et al., 2008) and pharmacokinetic dosage guidelines for elderly subjects have been suggested (Turnheim, 1998, 2005).

The present article will extract, from numerous published data, the actual evidence of whether there are age-related changes in drug disposition and metabolism, and if so, whether they are of clinical importance, which would necessitate dosage modifications for elderly individuals. According to Figure 1, one should be aware that several different (i.e., confounding) factors, both from the site of the drug and the patient, have to be taken into consideration, which often might also explain controversial results seen in the literature.

Age-related physiological changes and their pharmacokinetic consequences

In Table 1, such changes and their consequences have been summarized. In the following sections, drug examples will be provided on how aging can affect the absorption, distribution, metabolism, and elimination (ADME) system, with special emphasis on drug metabolism.

Table 1. Age-related physiological changes and their pharmacokinetic consequences.

Physiological changes in the elderly	Pharmacokinetic consequences
Increased gastric pH	Slightly decreased absorption (rarely clinically significant)
Delayed gastric emptying	
Reduced splanchnic blood flow	
Decreased absorption surface	
Decreased gastrointestinal motility	
Increased body fat	Increased V and $t_{1/2}$ of lipophilic drugs
Decreased lean body mass	
Decreased total body water	Increased plasma concentration of hydrophilic drugs
Decreased serum albumin	Increased free fraction in plasma of a few highly protein-bound acidic drugs
Increased α1-acid glycoprotein	Decreased free fraction of basic drugs
Decreased hepatic blood flow	First-pass metabolism can be less effective.
Decreased hepatic mass	Phase I metabolism of some drugs might be slightly impaired.
Decreased renal blood flow and glomerular filtration rate	Renal elimination of drugs can be impaired.

Absorption and bioavailability

In the aging gastrointestinal (GI) tract, some physiological changes (see Table 1) have been observed, but absorption, if accomplished by passive diffusion, remains unchanged for most drugs in the elderly (Saltzman et al., 1995). There is increasing evidence that uptake and extrusion processes via superfamilies of transporter proteins are effective in the epithelial cells of the GI tract, and apparently, such active transfer processes are rather the rule than the exception (Dobson

and Kell, 2008). However, so far, the impact of age on the expression and function of these GI transporters has not yet been investigated.

When considering oral bioavailability (F), presystemic elimination by the intestinal mucosa, and during the first pass through the liver, has to be taken into account (see Figure 2). As liver mass and hepatic perfusion are reduced in the eldery (Zeeh and Platt, 2002), F and, consequently, plasma concentrations (e.g., the area under the curve; AUC) of some highly cleared drugs, such as propranolol or labetalol, can be increased (Tateishi et al., 1995; Anantharaju et al., 2002). However, for other high clearance drugs, such as verapamil (Fromm et al., 1998) or propafenone (Dilger et al., 2000), no differences of F between healthy young and old subjects have been reported. Thus, no consistent effects of age on F have to be realized.

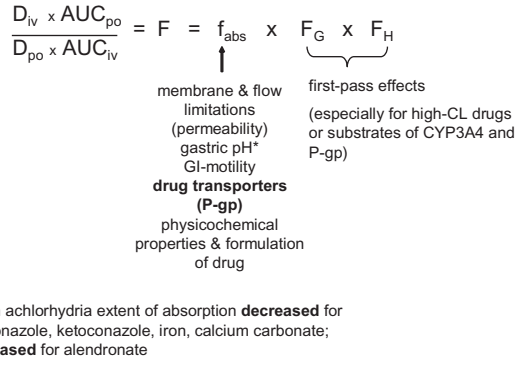

Figure 2. Putative factors that will affect drug absorption or oral bioavailability (F) and that might be altered, to some extent, in the elderly.

Distribution

As summarized in Figure 3, significant changes in body composition occur with advancing age (Ramsay et al., 2006). As body fat increases and total body water decreases, the apparent volume of distribution (Vd) of polar drugs (e.g., lithium, digoxin) will decrease (Hanratty et al., 2000) and that of lipophilic drugs (e.g., diazepam) will increase with advancing age (Klotz et al., 1975). Apparently, for many drugs, a relationship between the log of the octanol/water partition coefficient and the relative Vd values (old/young subjects) has been observed (McLean and Le Couteur, 2004), as illustrated in Figure 4.

Age-related changes in plasma protein binding are regarded to be of little clinical relevance (Benet and Hoener, 2002). Serum-albumin concentrations can be slightly decreased or remain unchanged, whereas α1-acid glycoprotein tends to be increased with age (Butler and Begg, 2008). Such possible alterations are generally not attributed to age *per se*, but rather to pathophysiological changes or disease states (Benet and Hoener, 2002).

The *MDR1* gene product, P-glycoprotein (P-gp), represents a barrier to drug absorption (Zang and Benet, 2001) and constitutes an essential part of the blood-brain barrier (Taylor, 2002). It is also expressed in organs with excretory function, such as the kidney and the hepatobiliary tract (Borst and Elfering, 2002). Therefore, the expression and activity of P-gp might affect drug disposition (Lin and Yamazaki, 2003). Concerning age effects, there is a gap between the stressed importance of P-gp for drug distribution and the lack of direct clinical data.

In one *ex vivo* approach, leukocytes were isolated from the blood of genotyped healthy (n=18) and frail (n=20) old subjects (age range, 68–80 years) and compared to those of young (mean age, 33 years) healthy individuals

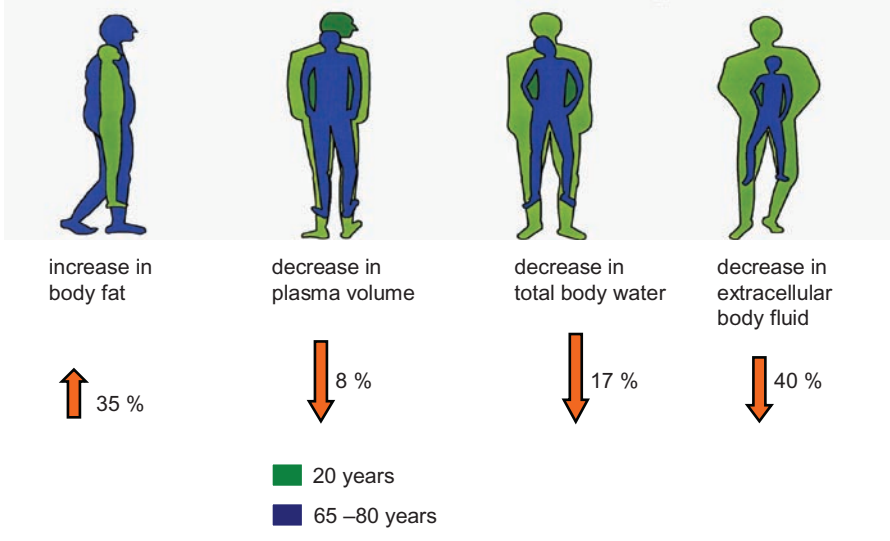

Figure 3. Age-dependent changes in body composition.

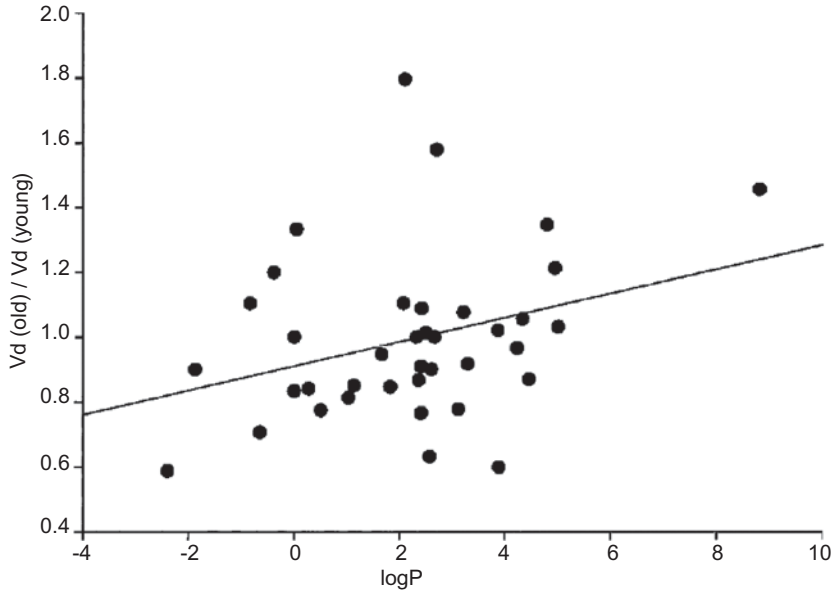

Figure 4. The relationship of lipophilicity (P) of drugs (determined by the octanol-water partition coefficient) and the relative volume of distribution of old/young people (data from Turnheim, 1998; McLean and Le Couteur, 2004).

($n = 21$), and it was tested whether the efflux of the P-gp probe, rhodamine 123, from $CD56^+$ natural killer (NK) cells was age dependent (Brenner & Klotz, 2004). This model provides a validated surrogate marker of cellular P-gp function (Robey et al., 1999). If the three groups were compared independently of the genotype (in regard to the two mutations, C3435T and G2677T), no age effects were observed. Moreover, for all assessed genotypes, there was no significant difference between fit and frail elderly subjects (Brenner and Klotz, 2004). Likewise, in NK cells isolated from blood samples from 90 normal volunteers (age range, 0–86 years), the function of P-gp, as assessed by the flow cytometric rhodamine 123 assay, did not vary with age (Machado et al., 2003).

In a clinical study, central nervous system (CNS) uptake of ^{11}C-R-verapamil was measured by positron emission tomography (PET) in 5 young (age range, 21–27 years) and 5 elderly (age range, 59–68 years) healthy volunteers. Based on a tracer kinetic model with the assumption of similar kinetics of verapamil and its multiple metabolites and no brain uptake of these metabolites (both assumptions have to be questioned), the PET time-activity data were used to estimate a hypothetical Vd of the labeled compound(s) in the brain. The mean values (± standard deviation; SD) differed slightly ($P = 0.03$) between the young (0.6 ± 0.1) and old (0.7 ± 0.1) group (no units given). It was concluded that P-gp activity might be decreased during aging (Toornvliet et al., 2006).

Renal elimination

Between the age of 30 and 80 years, kidney mass and the number of glomeruli is decreasing by about 20–30%, but in about one third of patients there is no decrease in renal function, and a small subpopulation has even an increase in creatinine clearance with aging (Lindeman et al., 1985; Froissart and Rossert, 2005). In a comprehensive study, aging *per se* had only a minor effect on kidney function. Confounding factors, such as hypertension and chronic heart diseases, account for a decline in kidney function in the elderly (Fliser et al., 1997). In Table 2, the total (CL) and renal clearance (CL_R) of some drugs are compared between young and elderly subjects. These data indicate that the values in the elderly are in the lower "normal" range observed in young controls. Therefore, it has to be concluded that in the absence of diseases, kidney function (e.g., glomerular filtration rate; GFR) is not decreased as greatly as previously thought (Fliser et al., 1999; McLean and Le Couteur, 2004).

GFR is routinely estimated by the empiral Cockcroft-Gault equation. Because this equation systematically underestimates GFR, the more sophisticated, better validated "modification of diet in renal disease (MDRD)" equation

$$\text{GFR} = 186 \bullet \text{Creat.}^{-1.154}\ [\text{mg/dL}]^{*} \bullet \text{Age}^{-0.203}\ [\text{years}] \bullet 0.742\ (\text{if female}) \bullet 1.212\ (\text{if African American})$$

(*divide by 88.4 if SI units [μmol/L] are used)

should be used (Froissart and Rossert, 2005; Laroche et al., 2006). In addition, the serum levels of the endogenous peptide, cystatin C, should be preferred instead of serum creatinine as a renal marker because it is less affected by extrarenal factors (Wasén et al., 2004; Grubb et al., 2005; Ognibene et al., 2006).

Table 2. Total (CL) and renal clearance of some drugs that are primarily eliminated by the kidney in young and elderly subjects.

	CL		
Drug	Elderly	Young	References
Lithium	0.83 (L/h)	0.6–2.4	Chapron et al., 1982
	0.94	(Sproule et al., 2000)	Hardy et al., 1987
Gentamicin	0.7–1.0 (mL/min/kg) (analysis of data from eight studies)	0.8–1.7	Triggs and Charles, 1999
Inulin	104 ± 12 (mL/min)	120 ± 14	11 elderly (68 ± 5 years) vs.10 young (25 ± 2 years) subjects
Atenolol[a]	151 ± 21	192 ± 18	
Piracetam[a]	62 ± 7	77 ± 6	Fliser et al., 1999
Hydrochlorothiazide[a]	266 ± 32 ($P < 0.05$)	413 ± 52	
Triamterene[a]	177 ± 18	223 ± 40	

[a]Renal CL (mean ± SD).

Hepatic elimination/drug metabolism

Before their final excretion, the vast majority of drugs have to be biotransformed to more polar metabolites by several cytochrome P450 (CYP)-dependent phase I reactions and/or phase II pathways, such as glucuronidation, acetylation, or sulfatation. This drug metabolism takes place mainly in the liver; however, the small bowel represents another site to be considered (Hämmerlein et al., 1998; Zang and Benet, 2001). Besides the enzymatic processing of drugs within the hepatocytes, various transporter proteins accomplishing the hepatic uptake of drugs and the biliary and hepatic extrusion of metabolites are indirectly involved in drug metabolism. Such transport processes and the oxygen supply (needed for phase I reactions) to the hepatocytes might demonstrate some age dependencies (caused by age-related changes of membrane structure). However, so far, such data are not yet available.

It is generally accepted that liver size/mass (–20–30%) and hepatic blood flow (–20–50%) decrease with age (see Table 1), and that these changes might affect especially the elimination of high-clearance drugs. However, hepatocyte volume remains unchanged between 20 and 95 years. Further, there are no specific age-related diseases of the liver and routine clinical tests of liver function do not change significantly with age (Le Couteur and McLean, 1998; Le Couter et al., 2005; James, 1997; Herrlinger and Klotz, 2001; Schmucker, 1998).

According to *in vitro* data, no age-related changes in hepatic microsomal protein content, the activities of NADPH cytochrome P450 reductase, aldrin epoxidation, 7-ethoxycoumarin-*O*-deethylation, epoxide hydrolase, and aspirin esterase have been noted (Schmucker, 2001; Woodhouse et al., 1984). Likewise, the content and activities of various CYP450 enzymes in hepatic biopsy samples did not decline with age in the range of 10–85 years (Schmucker et al., 1990; Hunt et al., 1992; Shimada et al., 1994; Hubbard et al., 2008).

In a comprehensive study with nearly 150 samples of human liver microsomes and 64 samples of cryopreserved human hepatocytes, the influence of the age of the donor has been investigated on various CYP activities (e.g., 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 4A11). If the age group 20–60 years ($n = 74$–86) was compared with the group above 60 years ($n = 29$–33), no differences were visible. Likewise, in hepatocytes, no age-related changes have been seen in the activities of CYP2D6, CYP2E1, CYP3A4, and UDP-glucuronosyltransferases (Parkinson et al., 2004). All these findings would suggest that drug metabolism appears to be quite well preserved in the elderly, at least up to 80 years.

To assess drug metabolism *in vivo*, different approaches have been applied, such as breath tests, calculations of metabolic ratios (MRs), or most often, clearance (CL) studies with probe drugs. Some examples should illustrate the present status.

The erythromycin breath test (ERBT) has been advocated as a tool to characterize CYP3A4 activity. However, as it reflects also other CYP activities and P-gp function (Frassetto et al., 2007; Kurnik et al., 2006), its use appears of limited value in quantifying CYP-mediated drug metabolism. In a comprehensive study by Schwarz (2006), the percentage $^{14}CO_2$ (derived from radiolabeled erythromycin) excreted per hour was similar in old men or women (age range, 65–101 years), either frail or non-frail, if compared to a large group ($n = 199$) of controls (age range, 20–60 years).

The paraxanthine/caffeine MR in plasma following a test dose of caffeine (or a cup of good coffee) reflects CYP1A2 activity, which is also induced by smoking (Faber and Fuhr, 2004). When young subjects (25 ± 0.3 years) were compared to elderly subjects (70 ± 1.7 years), there was some decrease ($P < 0.05$; 35%) in the MR. However, when MR was calculated from the vast majority of non-smokers, the difference between both age groups was not any longer significant (Simon et al., 2001), indicating a minor effect of aging on CYP1A2 activity.

Population pharmacokinetics (POP) can provide PK data from the "real clinical world" as, by its means, drug disposition can be described for populations (including the elderly) in which the drugs are actually used (Edholm et al., 2008). This approach has been recently successfully applied for olanzepine (probe of CYP1A2) and paroxetine (probe of CYP2D6). Based on 1,527 plasma levels from 117 patients with Alzheimer's disease

and 406 patients with schizophrenia, CL of olanzepine varied from 6.7 to 68.0 L/h in the age range from 18 to 103 years. Smoking status, sex, and race accounted for 26, 12, and 7% of the variability, respectively ($P < 0.0001$). However, height, weight, and age had no effect on the CL of olanzepine (Bigos et al., 2008).

In a similar POP study, 1,970 plasma levels of paroxetine from 171 patients with major depression (age range, 69–95 years) were used to calculate the maximal velocity (V_{max}) of paroxetine metabolism. As expected, there were significant differences in V_{max} between one poor metabolizer (PM; 125 μg/h), 28 intermediate metabolizers (IMs; 182 μg/h), 28 extensive metabolizers (EMs; 454 μg/h), and 5 ultrarapid metabolizers (Ums; 3670 μg/h) of CYP2D6, but age did not affect significantly the disposition of paroxetine (Feng et al., 2006).

In the past, the CL of the model drug, antipyrine (phenazone), has been extensively used in characterizing oxidative hepatic metabolic activity in man (Klotz et al., 1979). As it has been realized that several CYP isoforms (e.g., CYP3A4, CYP1A2, and CYP2C8/9) are involved in its metabolism (Engel et al., 1996), it can be used only as a kind of global liver function test. In three different studies (Vestal et al., 1975; Greenblatt et al., 1982; Sotaniemi et al., 1997), an approximately 20–25% decline in the CL of antipyrine has been observed in subjects (patients) between the age of 25 and 75 years. Thus, some minor impairment of hepatic drug metabolism with advanced age could be assumed.

Among the widely used proton pump inhibitors (PPIs), omeprazole represents the best probe for CYP2C19 (Klotz et al., 2004). Following a single intravenous (i.v.) dose, the effect of aging on the pharmacokinetics of this PPI in relation to the three CYP2C19 phenotypes (PM, IM, and EM) has been studied in Japanese volunteers (Ishizawa et al., 2005). As can be seen in Table 3, there were some genotype- and age-related differences in drug exposure, for example, the increase of AUC was more pronounced (about 2-fold) in elderly EMs and IMs but not in elderly PMs. Thus, when studying age effects for CYP2C19 substrates, all subjects have to be differentiated according to their defined genotype, which has much more impact than aging *per se*. In addition, the recently discovered new variant of CYP2C19*17 (coding for UMs) has to be included in the genotyping (Sim et al., 2006).

CYP2C9 is another polymorphically expressed enzyme that is involved in the metabolism of important drugs, such as warfarin (Scordo et al., 2002), some anticonvulants (Klotz, 2007), or NSAIDs (Shi and Klotz, 2008). Under steady-state conditions, AUC values of the standard nonsteroidal anti-inflammatory drug (NSAID), diclofenac (75 mg twice-daily [bid] for 15 days), and those of the cyclo-oxygenase-2 (COX-2) inhibitor, celecoxib (200 mg bid for 15 days), have been compared in *CYP2C9*-genotyped healthy young and old subjects (Brenner et al., 2003).

Table 3. AUC of omeprazole and its metabolites following a single intravenous dose.

		mean AUC (ng • h/mL)			
Group	*n*	Omepr.	5-OH-Omepr. (CYP2C19)	Omepr. Sulfone (CYP3A4)	AUC ratio (2C19/3A4)
Young: (21–36 y)	23				
homEM	8	1,441	316	97	10.3
hetEM	9	1,761	435	171	3.2
PM	6	6,892	232	971	0.24
Elderly: (66–85 y)	28				
homEM	8	3,292	217	70	5.5
hetEM	12	3,242	216	114	2.8
PM	8	5,650	72	255	0.3

Data from Ishizawa et al., 2005.

As can be seen from Figure 5, independent of the five genotypes, no age difference in the AUC values of both NSAIDs was visible. In addition, the CYP2C9 genotype had obviously no impact on the disposition of both NSAIDs, because apparently, CYP3A4 will be the major metabolic contributor under steady-state conditions (Brenner et al., 2003).

It is generally accepted that the short-acting benzodiazepine, midazolam, represents the best probe for assessing CYP3A4 activity (Link et al., 2008). Apart from an early study indicating that only elderly man had a significantly reduced (on average, 44%) CL of midazolam (Greenblatt et al., 1984), in four other studies, no significant reductions in CL, for example, only 19 (Harper et al., 1985) or 24% (Platten et al., 1998) and no impairments at all in the two remaining trials (Albrecht et al., 1999; Gorski et al., 2003) have been reported for various elderly populations. The higher sensitivity of older patients to the drug was due to alterations on the pharmacodynamic level because the EC_{50} values for the sedative-hypnotic action of midazolam were shifted to lower levels in the eldery (Platten et al, 1998; Albrecht et al., 1999). Since CYP3A4 is involved in the metabolism of more than 50% of all drugs (Shimada et al., 1994), it can be assumed that overall hepatic elimination by phase I reactions is relatively stable with increasing age.

Likewise, phase II pathways, such as glucuronidation, acetylation, or sulfatation, seem to be quite well preserved in the elderly (Advenier et al., 1980; Greenblatt et al., 1989; Klotz, 2003; Villesen et al., 2007) and, therefore, will not be considered in more detail.

Whether intestinal metabolism and inducibility of metabolism are affected by aging has not been extensively studied (Klotz, 1998). With the model drug, verapamil, metabolized by CYP3A, CYP1A, and CYP2C, both questions have been approached by the simultaneous i.v.

(10 mg deuteriumlabeled) and oral (120 mg bid) application of the drug. Both hepatic and intestinal extraction were inducible by rifampicin (600 mg/day for 10 days) to the same extent in 8 young controls and 8 healthy elderly subjects (see Figure 6). Further, the disposition of verapamil was not age dependent (Fromm et al., 1998).

In a similar study with propafenone, which is metabolized by CYP2D6, CYP3A4, CYP1A2, and by glucuronidation, the induction of all metabolic pathways by rifampicin was seen to the same extent in young and elderly subjects (see Table 4). Again, age did not affect drug elimination or CL to the metabolites; only V_{ss} was larger in the elderly (Dilger et al., 2000).

Frailty is not only an emerging geriatric syndrome (Ahmed et al., 2007), but an important issue and confounding factor when considering the impact of aging on drug disposition (Klotz, 2008). According to a recent publication, markers for inflammation (e.g., tumor

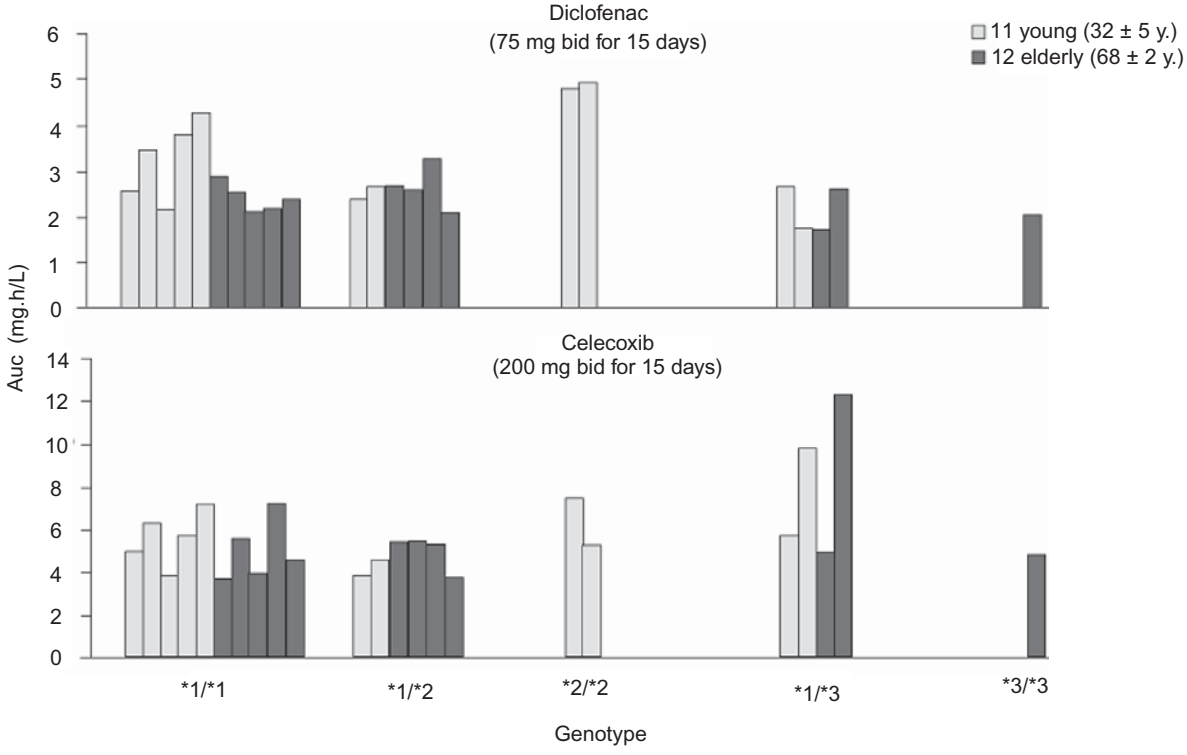

Figure 5. Individual AUC values of diclofenac (top) and celecoxib (bottom) in healthy, genotyped young (open columns) and elderly (solid columns) subjects (data from Brenner et al., 2003).

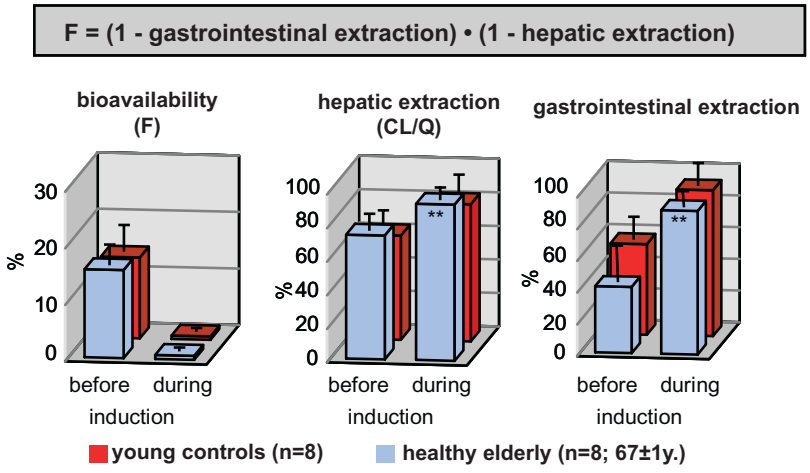

Figure 6. Disposition of verapamil in young and elderly subjects before and during induction by rifampicin (data from Fromm et al., 1998).

Table 4. Propafenone (PPF) elimination and induction by rifampicin in the elderly.

Mean	Young subjects		Elderly subjects	
($n=6$)	Control	+ Rifa	Control	+ Rifa
CL (mL/min)	616	706	905	762
$t_{1/2}$)h)	3.0	2.9	3.7	4.2
Vss (L/kg)	1.7*	1.7	2.5*	2.3
F (%)	30	10	30	4
CL to the metabolites (mL/min)				
5-OH-PPF **(2D6)**	39	97	35	61
N-desalkyl-PPF **(3A4/1A2)**	4	24	6	26
N-desalkyl-conj.	14	156	21	236
PPF-glucuronide	123	457	123	457

Data from Dilger et al., 2000. *$P<0.02$ (otherwise, no significant age effects).

necrosis factor alpha [TNF-α], interleukin-6 [IL_6], and C-reactive protein) might serve as biochemical indices for frailty, which are increasing with the degree of frailty. However, aspirin esterase, a phase I enzyme, was not affected by the severeness of frailty (Hubbard et al., 2008). Consequently, in future clinical trials, a more comprehensive genetic and biochemical characterization of the included elderly subjects/patients will be necessary to account for age and other (i.e., confounding) effects on pharmacokinetics, in particular drug metabolism.

Conclusions and future perspectives

When considering the effect of aging on drug disposition and metabolism for elderly populations, confounding factors such as comorbidities ("frailty") and multiple drug intake (interactions) as well as impairments in homeostasis and organ functions have to be accounted for. Presently, a few changes in some PK properties of certain drugs are likely to occur, to a variable extent, in the elderly and these can be summarized in the following way:

- An increase of bioavailability of some high-CL drugs
- An increase of Vd (and $t_{1/2}$) of lipophilic drugs
- Renal CL is less impaired than previously thought.
- Hepatic CL might be slightly decreased (*in vitro* data indicate no impairments in drug metabolism).
- Enzyme induction is still effective.
- The interindividual variability in drug disposition is increased with age.
- The genetic influence is much more striking than age effects.

To improve our knowledge on the impact of aging, future geriatric studies should provide a better, more detailed characterization of the included subjects/patients. It is mandatory to differentiate the fit (i.e., "normal" aging) from the frail (a frailty score should be developed) elderly. As there are no biological age markers available (work should be intensified in this area), we still have to rely on the chronological age. Dividing the elderly in three age groups (as done in pediatrics), such as 65–75, 76–85, and above 85 years, might help in a better understanding of the various aging processes. When performing PK studies in the elderly, PD assessments should be included because changes in drug action might not be caused by alterations in PK. During recent years, the importance of drug transporters for absorption, distribution, and elimination processes has been appreciated. However, concerning the effect of aging, there is an obvious gap in our present knowledge.

Finally, there should be a continous education/training of students, pharmacists, physicians, and health care authorities in geriatric clinical pharmacology. Based on the available PK data, no distinct and definite dosage guidelines can be given. In elderly populations, minor impairments in drug elimination are likely to occur, which would suggest some kind of dosage reduction to be on the "safe site." Careful dosing (i.e., titrating) and monitoring of drug action appears prudent, according to the general slogan "start low–go slow."

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