Review on Pharmacokinetics and Pharmacodynamics and the Aging Kidney

Christian Aymanns,* Frieder Keller,† Sebastian Maus,† Bertram Hartmann,† and David Czock‡

*Division of Nephrology, Department of Internal Medicine A, University of Greifswald, Greifswald, Germany; †Division of Nephrology, Medical Faculty, Ulm University, Ulm, Germany; and ‡Department of Clinical Pharmacology and Pharmacoepidemiology, University Hospital Heidelberg, Heidelberg, Germany

In people who are aged >65 years, pharmacokinetics are influenced more by the loss of kidney function than by the aging process of any other organ. A GFR of 30 to 60 ml/min, suggestive of stage 3 kidney disease, is observed in 15 to 30% of elderly people. Drug dosing must be adjusted to both changing pharmacokinetics and pharmacodynamics; the pharmacodynamics might be influenced by the aging of other organs, too. Using our NEPharm database, we extracted abstracts with pharmacokinetic parameters since 1999 from a weekly PubMed search. The recorded data were analyzed and compared with published recommendations on drug dosage and use in the elderly. Purely age-related changes in pharmacokinetic parameters were recorded from publications on 127 drugs. The analysis of our NEPharm records revealed an average (mean ± SD) age-related prolongation of half-life of 1.39-fold (corresponding to +39 ± 61%). Contrasting to common opinion, mean changes in clearance (−1 ± 54%) and volume of distribution (+24 ± 56%) were even less. The modest changes in pharmacokinetics do not suggest general dosage modifications in the elderly for most drugs. Changes in pharmacodynamics justify the common medication rule in the elderly—"start low + go slow"—especially for drugs that act on the central nervous system; however, in the case of anti-infective and anticancer therapy, the rule should be "hit hard = start high + go fast" to produce the target effect also in the elderly.

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The population in modern societies is becoming older; those who are older than 65 years will represent 20% of the population according to predictions for the year 2025 (1). For practical reasons, an age >65 years is used to describe elderly people (2). In general, purely age-related effects should be distinguished from those of coexisting diseases (3). Frailty and disease-related alterations are more obvious and less prone to underestimation in the clinical routine (4,5).

This article addresses the less obvious, purely age-related effects on pharmacokinetics and pharmacodynamics. The aim of our review is to discuss whether classifications and guidelines such as the Beers criteria must be used (6) or an approach that is based on pharmacokinetic and pharmacodynamic principles should be adopted also in gerontopharmacology.

Age-Related Changes in Organ Function

Age-related processes that occur in the absence of apparent diseases affect muscles, liver, and kidneys (7,8). Muscle mass and total body water are reduced (9), which can affect pharmacokinetics, especially of hydrophilic drugs, resulting in a smaller volume of distribution (V_d; Table 1). Conversely, body fat increases from 20 to 40% with age (10,11), resulting in a larger V_d, especially of lipophilic drugs (Table 1).

An age-related decrease in the apparent liver blood flow from 1445 to 1717 ml/min to 807 to 1020 ml/min has been reported (12,13). This change is expected to affect phase I catalysis by cytochrome P450 enzymes more than phase II conjugation (2,10,11). As a consequence, both total drug clearance (Cl) and free drug Cl can decrease (Table 1).

The most significant organ changes in the elderly occur in the aging kidneys. The age-related loss of renal parenchyma approximates 10% per decade of increasing age (14). This loss is accompanied by a decrease in renal plasma flow from 618 to 689 ml/min to 349 to 485 ml/min (15–18). Tubular functions are compromised by life-long oxidative stress (19). Telomere shortening and decreased expression of the klotho antiaging gene lead to tubular atrophy and impaired organic acid, proton, and potassium Cl (20). The age-related decline in GFR is due to a reduced number of functioning and an increased number of sclerotic glomeruli (21). The average age-related loss in GFR is reported as 0.40 to 1.02 ml/min per year (7,22,23). The general decline in cross-sectional studies is often near linear (22), but serial determinations in individual patients demonstrate that GFR temporarily can change, and one longitudinal study demonstrated that GFR did not decline with time in 33% of elderly individuals (24).

The variable effects of both acute kidney injury and chronic

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Correspondence: Dr. Frieder Keller, Division of Nephrology, Center of Internal Medicine, Internal Medicine I, University Hospital, Albert Einstein Allee 23, D-89070 Ulm, Germany. Phone: +49-731-500-44561; Fax: +49-731-500-44567; E-mail: frieder.keller@uni-ulm.de

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Table 1. Age-related changes in pharmacokinetics

Drugs	Age-Related Effects on Pharmacokinetics	References
Chlormethiazole, labetalol, levodopa, lidocaine, propranolol, verapamil	Increase in bioavailability → F ↑	(2,10)
Calcium, vitamin B_{12}	Decreased bioavailability → F ↓	(2)
Digoxin, edrophonium, ethanol, famotidine, lithium, salicylates	Decrease in volume of distribution → V_d ↓	(2)
Amiodarone, diazepam, fluoroquinolones, daptomycin, linezolid, quinupristin-dalfopristin, teicoplanin, vancomycin, verapamil	Increase in volume of distribution → V_d ↑	(2,43)
Antipyrine = phenazone	Indicator of cytochrome P450 enzyme activity → Cl ↓ to 70% by age 70	(11,74)
Acetaminophen = paracetamol, amitriptyline, amlodipine, argatroban, chlormethiazole, citalopram, diltiazem, imipramine, lidocaine, morphine, pethidine, propranolol, rabeprazole, ropinirole, theophylline, verapamil	Decreased hepatic metabolism and reduced drug Cl → Cl ↓	(2,10)
Antiepileptic drugs	Cl ↓ by 20 to 40%	(42)
Lamotrigine	Cl ↓ → neuropathy, fatigue and fluid retention	(75)
Diazepam, ibuprofen, lorazepam, naproxen, oxaprozin, phenytoin, temazepam, valproate, warfarin	Decreased Cl_{free} → Cl_{free} ↓	(45)
Docetaxel (oral)	Cl/F ↓ 1.9 → 1.3 L/min	(72)
Lithium, digoxin, hydrochlorothiazide	Renal Cl ↓ → Cl ↓ −36%	(10,47)
Vildagliptin	32% reduced renal Cl → Cl ↓	(76)
Enoxaparin	Elevated anti-Xa levels if GFR <30 ml/min → C_{peak} ↑	(50)
Eptifibatide, tirofiban	Renal Cl ↓ → higher bleeding risk	(77)
Levofloxacin	$T_{1/2}$ ↑ +27%	(78)
Oxycodone	$T_{1/2}$ ↑ 3.7 hours → 5.7 hours	(79)
Cefotaxim	Decreased GFR → $T_{1/2}$ ↑ 1.1 hours → 2.7 hours	(80)

F, bioavailability.

kidney disease on drug kinetics can best be derived from GFR estimates, because serum creatinine (S-crea) may stay unchanged in the so-called "creatinine-blind" range (Figure 1). In the elderly, the logistical difficulties with the 24-hour urine collection increase, and a poor correlation between endogenous creatinine Cl and GFR has been reported (25). Estimation of the GFR using the Modification of Diet in Renal Disease 2 (MDRD-2) equation might be more accurate (26,27). Some cystatin C–based GFR formulas are independent from age, weight, gender, or race as determinants of renal function (28,29).

For calculating dosage adjustments, the individual GFR (assuming GFR = creatinine Cl) according to Cockcroft and Gault (in ml/min) can be used to predict the drug Cl from S-crea (in mg/dl), weight (in kg), and age (in years) better than the normalized MDRD GFR (30). For females, 15% should be subtracted from Cockcroft and Gault GFR, and for overweight individuals, the lean body weight should be considered (31).

$$C\ \&\ G\_GFR = \frac{140 - Age}{72 \cdot Screa} \cdot Weight$$

As a convention, stage 3 or higher chronic kidney disease has been set at a GFR of <60 ml/min with a prevalence of 22% in people who are older than 68 years (32).

Pharmacokinetics in the Elderly

Impaired function of aging kidneys affects renal drug excretion but also cytochrome P450 activity (11), metabolic Cl (33), plasma binding (PB%) (34,35), tissue binding (36), and thereby absorption, distribution, and elimination processes of many drugs; therefore, measured pharmacokinetic parameters are needed for the elderly.

NEPharm Database

In our NEPharm database, we have recorded pharmacokinetic and pharmacodynamic parameter values from the published scientific literature using the indexes "pharmacokinetics," "pharmacodynamics," "clearance," and "half-life" to retrieve new citations from PubMed on a weekly basis (37). Only articles and abstracts cited in PubMed were included;

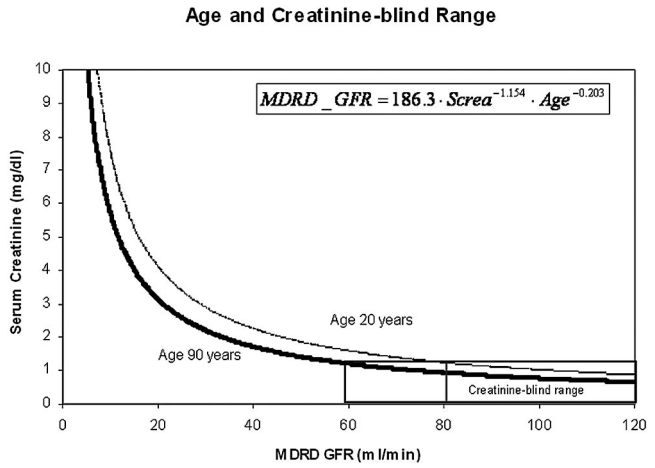

Figure 1. S-crea depends on GFR according to a hyperbolic function. For graphic representation, the S-crea value (norm <1.2 mg/dl) was calculated from the MDRD GFR (27) by using the reverse formula for men: S-crea = $(186.3 \times GFR^{-1.0} \times age^{-0.203})(1/1.154)$. For a 20-year-old man, the "creatinine-blind" range (thin line) ends with a GFR value of <80 ml/min but for a 90-year-old ends with a GFR of <60 ml/min (modified according to a proposal by Danilo Fliser).

preclinical data from animals or purely web-based data were excluded. At present, approximately 90,000 values on 30 parameters of 3000 drugs and metabolites are recorded from 10,000 publications. The recorded values are statistically synthesized by the calculated median or arithmetic mean with SD. Data are recorded for 12 clinical categories (*e.g.*, normal kidney function, kidney failure, liver failure, hemodialysis, pregnancy, neonatal) and among them age >65 years.

The three fundamental pharmacokinetic parameters are drug Cl, V_d, and elimination half-life ($T_{1/2}$), where (ln2 = 0.693). When two parameters are given, the third can be calculated; and when three parameters are given, this relationship can be used for plausibility and consistency testing within the NEPharm database. With multiexponential kinetics, whereby more than one $T_{1/2}$ applies, the dominant $T_{1/2}$ that corresponds for some drugs to the mean residence time is selected (MRT = V_d/Cl = 1.44 × $T_{1/2}$) as specified in the pharmacokinetic literature (38).

$$T1/2 = 0.693 \cdot \frac{Vd}{Cl}$$

In our NEPharm database, studies with purely age-related changes in pharmacokinetic parameters have been recorded for 127 drugs (references on file). Differences between young and elderly people were found for $T_{1/2}$, Cl, and volume parameters (Table 2). After elimination of inconclusive data, paired values for $T_{1/2}$ were available for 104 drugs. The difference between these $T_{1/2}$ values was statistically significant ($P = 0.01$, Dixon and Mood sign test), indicating a generally longer $T_{1/2}$ in the elderly (Table 2). A greater than two-fold increase in the $T_{1/2}$, however, was found only for cefotaxime, dicloxacillin, mecillinam, sulbactam, droperidol, olanzapine, oxcarbazepine, phenytoin, methotrexate, and the active metabolite of toremifen (Table 2).

The ratio of relative differences [(elderly − young)/young] was calculated. The median of relative changes in $T_{1/2}$ was variable (Table 2), and the overall mean relative difference (± SD) is only +39 ± 61% in the elderly ($T_{1/2elderly}$ = 1.39 × $T_{1/2young}$). Others have reported a +50% $T_{1/2}$ change from a geriatric pharmacokinetic database on 46 drugs (11).

The age-related prolongation in $T_{1/2}$ can be predicted by an age-dependent decline in GFR, affecting such drugs for which disease-related complete kidney failure (GFR <5 ml/min) also affects $T_{1/2}$ values ($T_{1/2fail}$).

$$T1/2 = \frac{T1/2\text{norm} \cdot T1/2\text{fail}}{T1/2\text{norm} - (T1/2\text{norm} - T1/2\text{fail}) \cdot \frac{GFR}{GFR_{\text{norm}}}}$$

When no data are available on Cl or $T_{1/2}$ in kidney failure, the elimination fraction (f_e) of the drug by the normal kidney can be used for predicting the effect of impaired kidney function (39). As exemplified for carisbamate, age does not influence the pharmacokinetics of many CNS or antiepileptic medications because of their small renal f_e (40,41). This f_e is estimated from values for normal renal Cl and normal total Cl of the drug (f_e = Cl_{ren}/Cl_{norm}).

$$Cl = Cl_{\text{norm}} \cdot \left[1 - fe \cdot \left(1 - \frac{GFR}{GFR_{\text{norm}}}\right)\right]$$

$$T1/2 = \frac{T1/2\text{norm}}{1 - fe \cdot \left(1 - \frac{GFR}{GFT_{\text{norm}}}\right)}$$

The Cl depends on GFR in a linear manner (39), but the $T_{1/2}$ depends in a hyperbolic manner (Figure 2). With a 90% renal elimination (f_e = 0.90), the normal cefazolin $T_{1/2}$ is 2 hours but 34 hours in kidney failure (GFR <5 ml/min). The $T_{1/2}$ will increase on average to only 3.2 hours for a GFR of 60 ml/min and to 5.9 hours for a GFR of 30 ml/min. Thus, a relevant increase in $T_{1/2}$ in many cases is to be expected for a GFR <30 ml/min.

In our NEPharm database, however, only a small mean decrease of −1 ± 54% was observed for the drug Cl. The relative difference [(elderly − young)/young] was calculated for 71 drugs for which values for young and aged individuals were recorded (Table 2). A decrease in Cl would be consistent with the age-related increase in the $T_{1/2}$; however, the average decrease in drug Cl is considerably less than the increase in the $T_{1/2}$ values. This discrepancy could be due to the paradox (Table 2) that a +24 ± 56% increase in the apparent V_d was found for 51 drugs in the elderly (expressed as the mean relative difference).

Plasma Binding

An increase in volume (V_d) with age partly can be explained by the 10% decrease in PB% with both increasing age (10,42) and kidney impairment (34,35). Free plasma fraction (f_p) will increase with decreasing PB%, where plasma (V_p) and tissue volume (V_t) stay constant.

$$fp \uparrow = 1 - \frac{PB\% \downarrow}{100}$$

Table 2. Pharmacokinetic parameters in young and elderly individuals

Drug	$T_{1/2}$ (hours)		Cl (ml/min)		V_d (L)	
	Young	Elderly	Young	Elderly	Young	Elderly
Analgesics						
antipyrine	12.0	15.7	2.7	1.8	37.7	22.8
butorphanol			121.0	168.0		
flurbiprofen	4.0	5.5	6.0	1.5	8.5	10.5
methadone	32.0	53.0				
morphine			87.2	100.8		
nabumetone	23.0	23.0	1.0	1.6	32.9	55.3
nalbuphine	2.3	2.0	92.4	124.7	266.0	378.0
naproxen					9.4	11.2
oxycodone	3.7	5.7				
paracetamol					66.5	66.5
pethidine			50.4	71.4		
median change (%)	+31		+35		+22	
Antiarrhythmics						
amiodarone			7.9	8.0		
diltiazem	4.6	4.7				
mexiletine	10.0	9.2	27.0	26.5		
verapamil					255.0	350.0
median change (%)	−3		+1		+37	
Antibiotics, antifungal agents, virostatics						
amoxicillin					28.0	15.0
ampicillin	1.2	1.9	18.9	10.1	19.6	26.7
balofloxacin	7.8	13.7				
cefdinir	1.5	2.2				
cefixime	3.2	4.2	4.4	4.1		
cefodizime	3.9	6.2	2.5	2.5	14.3	20.0
cefotaxime	1.1	2.7				
cefotaxime-metabolite	2.0	4.6				
ceftazidime	1.8	2.0				
ceftriaxone	7.4	12.2	1.0	0.5		
cefuroxime					16.1	14.0
cilastatin	0.9	0.8	13.8	12.6	15.6	14.0
ciprofloxacin			34.0	31.9	175.0	154.0
clarithromycin	4.5	7.7				
clinafloxacin	5.7	7.2				
daptomycin	7.9	11.9	0.7	0.7	8.4	11.9
dicloxacillin	0.8	1.9	6.7	5.2	10.6	13.3
ertapenem	4.0	5.2				
gentamicin	2.5	5.8	5.0	2.2	18.0	19.3
grepafloxacin	12.0	15.9				
imipenem			13.3	12.2	19.9	16.1
isoniazid			20.0	15.5		
levofloxacin	7.4	9.8				
meropenem	1.0	1.2	15.2	8.3		
meropenem-metabolite	2.0	3.1				
metronidazole			4.5	5.5		
ofloxacin	5.45	5.7	14.0	14.7	93.0	126.0
oseltamivir	6.0	8.0				
mecillinam	1.0	4.0				
posaconazole	24.0	41.8				
propicillin	0.6	0.8			29.0	19.9

Table 2. (Continued)

Drug	$T_{1/2}$ (hours)		Cl (ml/min)		V_d (L)	
	Young	Elderly	Young	Elderly	Young	Elderly
rifabutin	25.2	41.5	15.4	14.3	574.0	612.5
rifampicin = rifampin	3.4	3.5	14.7	14.7	66.5	67.9
rimantadine	30.0	30.0				
roxithromycin	10.8	15.0				
sulbactam	1.0	2.2	14.4	10.0	20.0	37.1
sulfisoxazole	5.9	6.6	1.4	1.4	10.2	10.5
tobramycin	2.2	2.4	5.7	5.3	17.5	20.3
vancomycin			5.5	3.6	42.4	60.0
median change (%)	+45		+8		+7	
Antihypertensive agents						
amlodipine	42.2	39.0	27.1	24.8	470.0	1120.0
benazeprilat	20.4	10.5				
betaxolol	20.0	18.0	20.0	19.7		
candesartan	9.0	10.5				
felodipine	9.34	14.0	50.2	52.5	689.5	700.0
irbesartan	14.5	18.0			50.4	46.9
lisinopril					124.0	168.0
metoprolol	4.0	3.2	60.0	63.0		
prazosin	2.9	2.3				
propranolol	4.0	3.9				
temocapril	4.15	1.5				
median change (%)	+9		+2		+19	
CNS agents						
alfentanil	1.5	1.6	20.7	28.1	29.4	56.0
alprazolam	13.1	12.0	4.1	3.1	77.0	50.4
amantadine	14.3	23.0	20.2	20.2	336.0	462.0
amitriptyline	21.0	21.0				
carbamazepine	31.0	21.0				
diazepam	40.4	71.5	1.6	1.1		
donepezil	65.4	104.0	11.4	9.1		
droperidol	2.8	10.1				
duloxetine	11.5	14.0				
felbamate	19.6	21.0			54.6	45.0
fluoxetine-metabolite	264.0	264.0				
levetiracetam	7.4	10.6	3.3	3.2		
lorazepam	14.0	14.0	4.9	4.6	91.0	91.0
midazolam	2.5	3.9	27.7	22.4		
olanzapine	30.4	66.0	23.7	18.5		
oxcarbazepine	8.0	22.5				
phenytoin = diphenylhydantoin	18.9	45.0				
ramelteon	1.9	1.9	708.6	1612.8		
rizatriptan	2.0	2.4				
selegiline		10.6				
selegiline-metabolite	11.0	17.0				
thiopental			9.9	16.4		
tiagabine	7.0	9.6				
triazolam	3.2	2.9	31.0	16.0	75.0	77.0
valproate			0.6	0.5		
venlafaxine	4.0	7.6	59.5	92.4	455.0	525.0
zolpidem	2.4	2.5	18.9	14.5		
median change (%)	+29		+11		+3	

Table 2. (Continued)

Drug	$T_{1/2}$ (hours)		Cl (ml/min)		V_d (L)	
	Young	Elderly	Young	Elderly	Young	Elderly
Cyctostatics						
docetaxel			41.5	30.0	123.3	273.0
epirubicin			86.5	64.0		
etoposide	5.3	7.0	2.12	1.7	14.7	14.9
ifosfamide	7.0	6.0	4.4	5.7	41.1	42.0
melphalan			23.4	27.7		
methotrexate	4.5	14.5	7.4	5.7	39.8	133.0
paclitaxel			24.0	14.2		
vinorelbine	30.0	37.0	50.4	47.5		
median change (%)	+23		+14		+121	
Others						
atorvastatin	14.0	19.5	27.5	121.8		
atropine			33.6	33.6		
cetirizine	7.8	12.0	3.2	2.0	34.1	31.5
desloratadine	23.9	35.0				
eniporide			31.8	20.8		
finasteride	6.6	7.0				
fluvastatin		36.0	68.0			
fondaparinux	17.0	21.0				
glipizide	4.0	3.4	2.0	2.2	10.6	11.9
isosorbide-5-mononitrate	5.1	4.9			48.7	51.1
metoclopramide	5.0	5.0	24.9	26.0	236.5	238.0
omeprazol			31.8	2.1	23.8	23.8
ondansetron					154.0	133.0
pancuronium					17.54	18.2
PEG-IFN-α 2b	37.9	44.4				
PEG-IFN-α-2a (40 kD)	77.0	110.0				
pranlukast	3.6	2.7				
pravastatin	2.0	1.8	56.7	56.7		
quinidine					189.0	189.0
ranitidine					115.0	150.5
tadalafil	17.5	21.6				
tamsulosin	6.8	13.0				
theophylline	7.9	8.9	3.0	2.7	35.0	35.0
tolbutamide	7.1	5.9				
toremifene	120.0	172.8				
toremifene-metabolite	171.6	458.4				
vapiprost	1.12	1.1				
vardenafil	3.9	6.0				
warfarin	40.9	37.0	0.26	0.2		
ximelagatran-metabolite (melagatran)	2.3	3.3	6.3	6.8		
yohimbine	0.7	2.0				
median change (%)	+23		±0		±0	
Overall arithmetic mean ± SD of changes (%)	+39 ± 61		−1 ± 54		+24 ± 56	

The data for $T_{1/2}$, total drug Cl (free and bound), and V_d were extracted from our NEPharm database and the analysis of the published literature. Median values are stated for young and elderly (>65 years) when more than one parameter value for a given drug and parameter was recorded.

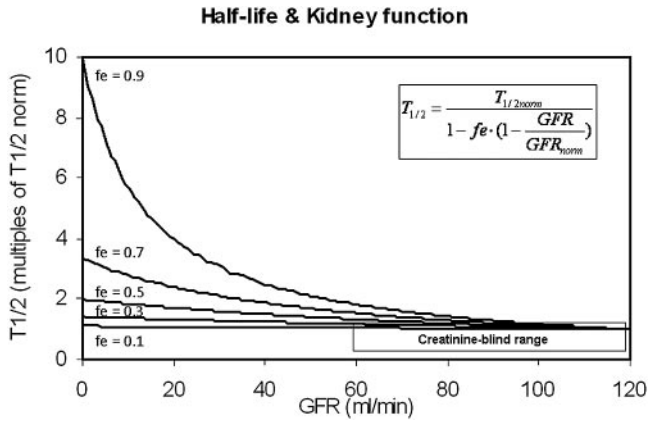

Figure 2. Increase in T½ as predicted from the f_e by renal route in healthy volunteers (GFR = 120 ml/min). Because of the hyperbolic dependence and in analogy to the creatinine-blind range, a noncritical range (GFR >60 ml/min) of drug kinetics can be proposed when the influence of GFR alterations on T½ is still limited.

$$Vd_{aged} \uparrow = Vp + Vt \cdot \frac{fp \uparrow}{ft}$$

Generally, an increase in the volume parameter should not call for an increase in dosage if decreased PB% and increased f_p are the reason. Also, for lipophilic drugs such as diazepam and amiodarone (Table 1), for which the volume is expected to increase as a result of an increase in the proportion of body fat, a dosage increase is not advisable because the total Cl will simultaneously decrease in the elderly; however, for antimicrobial drugs (Table 1), a larger volume as a result of a higher fat tissue fraction must be compensated for by a larger dosage, especially with the initial loading dose (43). In addition, an increase in volume as a result of disease-related overhydration must be followed by an increased loading dose of, for example, carbapenems or aminoglycosides (44).

The age-related decrease in PB% and increase in the f_p can even mitigate the age-related decrease in free Cl (Cl_{free}), resulting in a minimal net effect on total drug Cl. This becomes apparent with an otherwise unexplained increase in volume (V_d aged).

$$Cl \uparrow = fp \uparrow \cdot Cl_{free}$$

$$Cl_{aged} = fp \uparrow \cdot Cl_{free} \downarrow$$

Cefodizime T½ increases from 3.9 to 6.2 hours in the elderly (Table 2). The Cl decreases only from 2.52 to 2.50 ml/min. This can be explained by decreased PB% as indicated by the volume increase from 14.3 to 20 L (Table 2). The considerable changes in pharmacokinetic parameters with alterations in PB% do not lead to proportional changes in the pharmacodynamic effects of protein-bound drugs (*e.g.*, methylprednisolone). Alterations that affect PB% only have little clinical relevance for drug dosing (35), because the drug effect is assumed to be exerted by the free drug concentration (C_{free}) that stays constant on average.

$$C_{free} = fp \uparrow \cdot C \downarrow = fp \uparrow \cdot (C_{free} + C_{bound} \downarrow) = const.$$

In cases in which the drug Cl_{free} decreases as a result of age-related changes in organ function, the need for a dosage reduction possibly arises. The 30% reduction in total Cl of some antiepileptic drugs could be explained by reduced Cl_{free} in the elderly (42,45). If Cl_{free} decreases (Table 1), then the paradox that a dosage reduction is needed might come true (*e.g.*, diazepam, ibuprofen, lorazepam, naproxen, oxaprozin, phenytoin, temazepam, valproate, warfarin), although the total Cl could stay unchanged (Table 1). In addition, bioavailability (F) can increase with decreasing Cl_{free} mainly in drugs that are subjected to first-pass elimination (Table 1).

Accumulation Kinetics

The pharmacokinetic basis for drug dosage adjustment to age-related kidney impairment can be derived from accumulation kinetics in analogy to disease-related kidney impairment. In the steady state after repetitive dosing with a constant administration interval (Tau), the drug concentrations will fluctuate between peak (C_{peak}) and trough levels (C_{trough}). The equations derived for one-compartment pharmacokinetics also enable reasonable predictions for drugs with a dominant T½ after two-compartment pharmacokinetics.

$$C_0 = \frac{D}{Vd}$$

$$C_{peak} = \frac{C_0}{1 - exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}}\right)}$$

$$C_{trough} = C_{peak} \cdot exp\left(-0.693 \cdot \frac{Tau}{T_{1/2}}\right)$$

Digoxin has the values C_0 = 0.7 mg/L, C_{peak} = 1.9 mg/L, and C_{trough} = 1.2 mg/L for Tau = 24 hours, and T½ = 36 hours under normal conditions. A toxic C_{peak} = 3.4 mg/L and C_{trough} = 2.7 mg/L will result for T½ = 72 hours, as with renal failure; however, if the elimination T½ is shorter than the administration interval (T½ < Tau), the drug will usually undergo a less than two-fold accumulation considering C_{peak} ($< 2 \times C_0$). For many drugs, a dosage adjustment must be recommended only when the T½ is longer than the administration interval. One example is flucloxacillin, for which the T½ increases from 1.3 to 3.0 hours in kidney failure and the area under the curve (AUC) will increase 2.3-fold, but a dosage adjustment is not required, because the standard administration interval is 8 hours and accumulation of peaks is only 1.2-fold and negligible. Exceptions are drugs for which toxicity closely correlates with the AUC (*e.g.*, carboplatin), drugs with deep or slow compartment kinetics (*e.g.*, gentamicin, methotrexate, enoxaparin), and drugs with a narrow therapeutic range (*e.g.*, digoxin, lithium, carboplatin).

Drug Dosage Adjustment to Age-related Kidney Impairment

When drug dosage adjustment must be performed (*e.g.*, for antimicrobial and repetitively administered anticancer drugs),

a loading dose (D_{start}) should be considered to obtain the target effect immediately. The subsequent doses should be reduced after the loading dose has been given (*i.e.*, the second day of such drug treatment), even in elderly patients because accumulation needs time (44).

$$D_{start} = C_{peak} \cdot Vd$$

Anticancer drugs are often given in intermittent cycles with bolus doses. The single bolus dose must be adjusted to the drug Cl because the toxicity of carboplatin or methotrexate, for example, depends on the AUC (D/Cl). If the T½ increases, then a lower peak must be targeted.

$$AUC = T½ \uparrow \cdot 1.44 \cdot C_{peak} \downarrow$$

For repetitive dosing, two different dosage adjustment rules exist to derive the individual maintenance dose (D) and administration interval (Tau) depending on whether the AUC or the C_{peak} represents the clinically relevant pharmacokinetic marker most closely associated with desired and/or adverse effects.

1. Dettli's proportional dosage reduction rule can be based on the drug Cl (39). The Dettli rule produces the same area (AUC = constant) as with normal dosage and applies also to single bolus dosing (Tau = 1). For repetitively administered drugs, the dose (D), the interval (Tau), or both can be changed.

$$\frac{D}{Tau} = \frac{D_{norm}}{Tau_{norm}} \cdot \frac{Cl}{Cl_{norm}}$$

2. Kunin's half-dosage rule is based on the standard dosage for patients with normal kidney function ($D_{start} = D_{norm}$) and estimated T½ (Tau = T½), where one half of the normal dosage is administered after one T½ (46). The Kunin rule leads to a generally higher dosage and larger AUC than the Dettli rule, but peak levels are more similar to that with normal dosing (C_{peak} = constant), which may be desirable (*e.g.*, for concentration-dependent antibiotics).

$$\frac{D}{Tau} = \frac{1/2 \cdot D_{start}}{T½}$$

The ceftriaxone T½ increases from 7.4 to 12.2 hours, and the Cl decreases from 1.01 to 0.52 ml/min in the elderly (Table 2). A dosage reduction from the normal 2000 to 1000 mg/d results from use of the Dettli rule, whereas the dosage can stay unchanged at 2000 mg/d with the Kunin rule (because 1000 mg/12 h = 2000 mg/24 h).

When using Dettli's dosing rules, a proportional adjustment could yield unfavorable underdosage if the age-related T½ is increased but to less than the normal interval (T½ < Tau norm). Besides flucloxacillin, cefotaxime (active metabolite) provides another example, where the T½ increases from 1.1 to 2.7 hours (metabolite 2.0 to 4.6 hours) in the elderly (Table 2), but a dosage adjustment to the age is not required, because the standard administration interval is 8 hours. In line with these considerations, it has been stated that no dosage adjustment is needed for most drugs that are given to an elderly person without overt disease (47). Exceptions may be seen for drugs with a narrow therapeutic range (48) and a potential for severe toxicity (*e.g.*, carboplatin, cefepime [49], digoxin, enoxaparin [50], gentamicin, lithium [51], metformin [52,53], methotrexate [54,55]).

The different adjustment rules result in different sizes of maintenance dose (D) and adjustment interval (Tau). Pharmacokinetics are the required basis but become the sufficient basis for drug dosage adjustment decisions only in conjunction with pharmacodynamics. Whenever pharmacodynamic knowledge is lacking, we propose using Kunin's rule, leading to higher dosages for intensive care and anti-infective therapy, but to use Dettli's rule, leading to lower dosages in outpatient care and for the CNS drugs.

Pharmacodynamics in the Elderly

The dosage adjustment dilemma and age-related adverse drug reactions have brought pharmacodynamics wide attention. One single pharmacokinetic concentration can produce multiple pharmacodynamic effects—beneficial and harmful. Thus, pharmacodynamics affect not only therapeutic effects but also toxic and adverse events.

Effect-Concentration Correlation

The most general pharmacodynamic concept for both beneficial and adverse effects is derived from the sigmoid E_{max} model. The effect (E) is a nonlinear function of drug concentration (C) and depends on the maximum effect (E_{max}), on the concentration producing the half-maximum effect (CE_{50}), and on the Hill coefficient (H) describing the sigmoidicity of the effect-concentration relationship.

$$E = \frac{E_{max}}{1 + \left(\frac{CE_{50}}{C}\right)^{H}}$$

Drug potency is reciprocal to the CE_{50} value (56). What potency means for the drug, that means sensitivity for the patient. Patient-related changes in sensitivity reflect on changing CE_{50} values that also indicate the respective potency of the drug (potency = $1/CE_{50}$ = sensitivity). Increased drug sensitivity (as to CNS drugs) might correspond to a lower CE_{50} value already producing the CE_{50} in the elderly (Table 3). Conversely, the widely known need for higher furosemide or torasemide dosages can be explained by a higher CE_{50} required to produce a diuretic effect in renal impairment. The emergence of bacterial or viral resistance to anti-infective drugs corresponds to a higher minimal inhibitory concentration that is closely related to a higher CE_{50} (56). Thus, a higher concentration is needed to stop bacterial or viral growth, as shown with fluoroquinolones or with threshold trough concentrations of antiviral drugs (44).

Generally, the concentration decreases with time. Thus the concentration-dependent effect also decreases with time (57). The integration of the effect-time curve yields the pharmacodynamic area under the effect curve (AUEC), analogous to the pharmacokinetic area under the concentration-time curve (AUC) where (1/ln2 = 1.44). After a single dose (58), the AUEC depends on T½, C_0, CE_{50}, and H.

Table 3. Age-related changes in pharmacodynamics and adverse drug effects

Drug	Age-Related Effects and Predicted Pharmacodynamics	References
NSAIDs (*e.g.*, diclofenac, celecoxib)	Volume overload, hypertension, decline in GFR	(10,81)
NSAIDs, antibiotics, diuretics, H2-blockers (*e.g.*, cimetidine)	Idiosyncratic acute interstitial nephritis and acute kidney injury	(8,10)
Bisphosphonates	Nephrotoxicity in 17% of elderly → vulnerability ↑	(82)
Gatifloxacin	Increased sensitivity to adverse reactions → hypoglycemia	(44)
Levofloxacin, moxifloxacin	Confusion, seizures, psychoses	(44)
Moxifloxacin	QTc interval prolongation	(44)
Anticholinergic drugs (*e.g.*, donepezil)	Cognitive impairment, psychosis	(83,84)
Nondihydropyridine calcium channel blockers (*e.g.*, diltiazem, verapamil)	Decrease in PR interval prolongation without consequences	(85)
Dihydropyridine calcium channel blockers (*e.g.*, nifedipine, amlodipine)	Increased effect → CE_{50} ↓	(85)
Opioids (*e.g.*, morphine)	Impaired neurotransmitter production, increased receptor affinity → CE50 ↓	(86)
CNS drugs (*e.g.*, benzodiazepines), psychotropic drugs, anesthetics, antiepileptic drugs (*e.g.*, phenytoin)	Increased sensitivity, tremor, ataxia, cognitive difficulties → CE_{50} ↓	(10,41,62–64,85)
Warfarin	Increased sensitivity → CE_{50} ↓	(10)
Lecozotan	Increased 5-HT1A receptor occupancy → CE_{50} ↓	(87)
Midazolam	Increased sensitivity (CE_{50} ↓ from 522 → 223 ng/ml)	(10,88)
Benzodiazepines, β-adrenergic agents (*e.g.*, norepinephrine), β blockers (*e.g.*, albuterol, dopamine D2), muscarinic agents, verapamil	Decreased sensitivity and downregulated receptors → CE_{50} ↑	(2,64)
Metoprolol	Decreased Gs protein interaction → CE_{50} ↑	(85)
Atracurium, rocuronium, vecuronium	Prolonged action	(89)
ACEIs	Impaired metabolic and renal clearance → $T_{1/2}$ ↑ → effect duration ↑	(90)

The changes in CE_{50} values are inferred from the basic assumption on potency and sensitivity (sensitivity = $1/CE_{50}$). ACEI, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

$$AUEC = T½ \cdot 1.44 \cdot \frac{E_{max}}{H} \cdot \ln\left(1 + \left(\frac{C_0}{CE_{50}}\right)^H\right)$$

The AUEC can be derived for the direct response model as for the examples of heparin and gentamicin (57). The AUEC approach has also been derived for the indirect response models only considering the production but not the disposition of the effect (58). A potential time delay between the concentration and the effect furthermore needs to be modeled by an effect compartment or by indirect response models for the effect disposition.

For gentamicin, the apparent parameter values have been estimated with $T_{½}$ = 2.5 hours, H = 3.1, and CE_{50} = 18.2 mg/L (56), yielding an AUEC = 0.169 × E_{max} for a standard C_0 = 10 mg/L (59). A two-fold longer $T_{½}$ ($T_{½}$ = 5.0 hours) produces a proportional two-fold higher effect area (AUEC = 0.338 × E_{max}); however, a two-fold increase in concentration to C_0 = 20 mg/L—as with once-daily bolus dosing—produces a 5.8-fold increase in the effect area (AUEC = 0.987 × E_{max}), giving reason to the presumably more efficient bolus dosing.

The target concentration (C_{target}) can be derived from the AUEC, because the effect integral should stay constant with

dosage adjustment (AUEC = constant). The C_{target} is a complex function of the normal initial concentration ($C_{0\ norm}$) and of the CE_{50} (60).

$$C_{target} - CE_{50} \cdot \left\{ \left[1 + \left(\frac{C_{0norm}}{CE_{50}} \right)^{H} \right]^{T_{1/2norm}/T_{1/2}} - 1 \right\}^{1/H}$$

For the simple condition ($T_{½elderly} = T_{½norm}$), the C_{target} is the normal initial concentration ($C_{target} = C_{0\ norm}$). The effect AUEC is unchanged for drugs that are administered by a continuous infusion rate when the average concentration is the target and the drug infusion is adjusted in close proportion the Cl. Intermittently administered drugs have a schedule dependence of the effect, and for the condition ($T_{½aged} > T_{½norm}$), the C_{target} is not constant ($C_{target} < C_{0\ norm}$). If the $T_{½}$ is prolonged, then the C_{target} must decrease, because the effect area should stay constant (AUEC = constant). This might allow for a lower dosage—but less than proportionally lower. This can be illustrated for the example of gentamicin, for which a GFR of 20 ml/min leads to a 10-fold longer $T_{½}$ ($T_{½}$ = 25 hours), allowing for only a reduction to one half (½ not 1/10) of the normal dosage ($C_{target} = 0.5 \times C_{0\ norm}$). The once-daily bolus dose of gentamicin should be given also to elderly patients (44). We propose reducing the once-daily gentamicin dosage of 240 to 120 mg only for patients with a GFR <30 ml/min.

Dosing Dilemma

A dosage reduction in proportion to the drug Cl (as with Dettli's rule) could produce an overproportional reduction in the effect area AUEC ($AUEC_{aged} \ll AUEC_{norm}$), as illustrated with an exemplary drug (Figure 3). Disproportionate to the $T_{½}$ increase from 6 to 12 hours, the initial concentration should be reduced only from 150 to 113 U, not to 75 U, to keep the effect area AUEC constant; however, the pharmacokinetic area AUC will increase 1.5-fold in this example, illustrating the dosing dilemma: Keeping the intended effect (AUEC) constant could end up with unfavorable toxic effects.

The increased CNS toxicity of fluoroquinolones as a result of age-related impaired kidney function exemplifies the therapeutic dilemma between efficacy and toxicity. Mild pharmacokinetic alterations of fluoroquinolones can induce more adverse drug reactions when they are enhanced by additional pharmacodynamic alterations with higher sensitivity. This could suggest not a dosage reduction but preferably the use of another class of antimicrobial drug.

In the elderly, drug–drug interactions pose a special risk (*e.g.*, ciprofloxacin + olanzapine), but drug–disease interactions (*e.g.*, metoclopramide and Parkinson's disease) are two to three times more frequent (48,61). With CNS and antiepileptic drugs, age affects pharmacodynamic parameters such as drug sensitivity and thus can induce more adverse events (62). Monotherapy is recommended for antiepileptic drugs (63).

With the former rule to reduce the dosage to 50% in the elderly (2), however, the therapeutic effect could be completely missed (Figure 3), especially when the Hill coefficient is high (H >1). Because the pharmacodynamic parameters (CE_{50} and H)

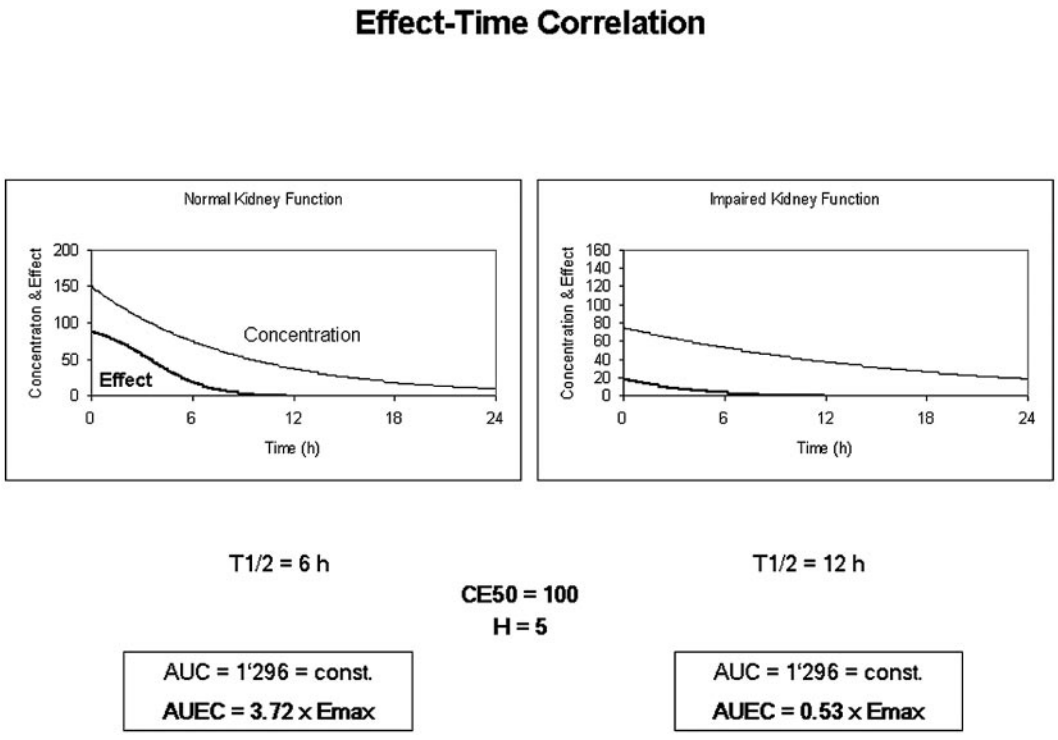

Figure 3. Mathematical simulations to illustrate the potential problem of indiscriminate use of proportional dosage reduction. For a hypothetical drug and normal kidney function, the $T_{½}$ is set to 6 hours and for impaired kidney function to 12 hours, indicating a decrease in Cl by one half. If the dosage is reduced in proportion to the Cl, then the initial C_0 decreases from 150 to 75 U. The AUC remains constant when linear pharmacokinetics apply. The concentration producing the CE_{50} and the H are assumed to stay constant; however, the AUEC ($0.53 \times E_{max}$) is only 14% of the normal ($3.72 \times E_{max}$), and the therapeutic effect could be missed.

are still unknown for many drugs, it is advisable to avoid the possible overproportional decrease of the effect area AUEC when reducing the dosage in proportion to the Cl, thereby missing the required C_{target}. This might be critical with some anticancer drugs, for which a seemingly adequate dosage reduction (in view of the AUC) could miss the therapeutic action (*e.g.*, cyclophosphamide, melphalan).

When concentration-dependent effects apply, as is likely with some anti-infective or anticancer drugs (*e.g.*, fluoroquinolones, cyclophosphamide), the C_{target} should be selected close to the peak concentration (C_{target} = constant), and it will be more prudent to prolong the administration interval (Tau) than to reduce the dosage (D). Conversely, prolongation of the interval (Tau) in proportion to the T½ might be critical for anti-infectives with a time-dependent action (antivirals, betalactams) because concentrations should not fall below a threshold value that is required for a specific time to maintain the minimum effect (56).

There is wide agreement in gerontopharmacology to "start low + go slow" in the elderly (64–67). This rule has primarily been proposed for antipsychotic drugs (3); however, for anti-infective and anticancer therapy, this rule could be counterproductive. A meropenem dosage that was twice the standard was associated with an increased response (71 *versus* 58%) without increased adverse effects in a group of elderly patients who had *pseudomonas* infection (68). Following Paul Ehrlich "hit hard and hit fast" (91) and according to the Tarragona strategy (69), for anti-infective treatment, the rule should be "hit hard = start high + go fast." This contrasting rule applies mainly to the first day of anti-infective or repetitively administered anticancer therapy because size and timing of the first dose are critical also in the elderly (44). Drug tapering can be performed subsequently, because drug toxicity usually appears later in the course.

Consequently, age is not a contraindication to high-dosage daunorubicin (70) or to normal-dosage chemotherapy with paclitaxel or docetaxel on low-dosage weekly regimens except on high-dosage three-weekly regimens (71,72). Within the therapeutic range, full-dosage chemotherapy has also been considered for the examples of temozolomide, topotecan, doxifluridine, capecitabine, etoposide, hydroxyurea, tamoxifen, and oral alkylating agents (73).

Conclusions

In general, drug dosage should be adjusted not to old age *per se* but to the individual organ function (44). Such organ function can be quantified (*e.g.*, by the GFR). Adjustment to pharmacokinetic changes alone, however, could expose elderly patients to the risk of underdosage, of mainly anti-infective and anticancer drugs, for which the target drug effect is at stake. Age-related changes of pharmacodynamics result in an increased sensitivity. Dosage adjustment to such pharmacodynamic changes might be advisable mainly for drugs with intended CNS effects (*e.g.*, antipsychotics) or adverse CNS effects (*e.g.*, fluoroquinolones). To individualize drug therapy, computer-assisted information systems might help in the future (6). Not only every patient but also every drug is different.

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None.

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