PHARMACODYNAMICS OF AGING: NARROWING OF THE THERAPEUTIC INDEX IN THE FACE OF THERAPEUTIC OPPORTUNITY

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February 24, 2011

Pharmacodynamics of Aging

Systemic Cardiovascular

Local Cardiovascular

Other Effector Systems

Bar chart showing the incidence (%) of the number of drugs prescribed to older patients (from less than 5 to over 21).

(Adapted from Cluff LE et al: JAMA 188:976, 1964)

Two line charts, one showing the percent of patients over age (years) and the other showing percent courses of therapy over age (years)

Table 1. Types of the 189 Side-Effects of Drug-Drug Interactions

Type of Effect	%
Neuropsychological disorder and/or cognitive impairment	44.1
Global or orthostatic arterial hypotension	21.8
Acute renal failure secondary to dehydration	15.7
Hypo/hyperkalemia	5.6
Impairment of heart automatism, conduction, or rhythm	4.5
Increased anticholinergic effects	3.3
Other side effects	5.0

Distribution of Office Visits by Number of Drugs Administered or Prescribed for Patients ≥85 Years of Age

Number of Drugs	Office Visits: Number*	Per Cent
0	2,168,000	32.1
1	1,431,000	21.2
2	797,000	11.8
3	1,084,000	16.0
4	530, 000	7.8
5	363,000	5.4
6	160,000	2.4
7	117,000	1.7
8	14,000	0.2
9	73,000	1.1
≥10	27,000	0.4

* Total number of visits = 6, 763, 000, within rounding error.

Knapp, et al, J Amer Ger Soc. 1984:32:138-143.

Overall prescribing

Bar chart showing mean number of drugs/Resident in nursing homes.

Medication prescriptions per resident in the 12 nursing homes. 15 October 1992 - *Annals of Internal Medicine* - Volume 117 · Number 8 685

Age-related chronic medical conditions*

MEDICAL CONDITION FREQUENCY PER 1000 PERSONS IN USA

	Age <45 y	Age 46 - 64 y	Age > 65 y
Arthritis	30	241	481
Hypertension	129	244	372
Hearing impairment	37	141	321
Heart disease	31	134	295
Diabetes	9	57	99
Visual impairment	19	48	79
Cerebrovascular disease	1	16	63
Constipation	11	19	60

* From Zisook S, Downs NS. J Clin Psych 1998, 59 (suppl 4):80-91, data from Dorgan CA, editor. Statistical record of health and medicine. New York-International Thompson Publishing Co. 1995.

Bar chart showing the percent affected by age (years)

About 35% of patients over age 85 have cognitive impairment.

***Cognitive Impairment Defined by 6 or more Errors in the Mini-Mental Status Exam**

Data from: Robins LN, Regier DA, eds.: Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press, 1991

Alterations in the Cardiovascular System of the Elderly

Cardiovasular hemodynamics

- Tendency to contracted intravascular volume
- Increased peripheral vascular resistance
- Tendency to lowered cardiac output
- Decreased baroreceptor sensitivity
- Increased blood pressure variability
- Suppressed plasma renin activity
- Decreased vascular endothelium production of nitric oxide

Scatter chart showing isoproterenol resistance (I_{25}) μg in smokers and non-smokers by age, years. Resistance increases with age.

MAX AC stimulation by Isoproterenol (pmol cAM{/min/mg} over age. Another scatter chart showing MAX AC stimulation by Zinterol (pmol cAMP/min/mg)

Scatterplots: Net maximum adenylyl cyclase (AC) stimulation by isoproterenol (first chart) and zinterol (second chart) for left ventricular myocardial preparations in relation to donor age.

White, et al, Circulation, 1994; 90: 1225-1238

Two line charts. Chart A shows change in forearm blood flow (ml/100ml/min) in older and young patients on Tyramine (μg/100ml/min). Chart B shows changes in venous norepinephrine (pg/ml) in older and young patients on Tyramine (μg/100ml/min).

Changes in FBF (A) and deep venous norepinephrine concentrations (Chart B) to local tyramine administration. *P<0.001 vs young men.

Dinenno et al., *Circulation*. 2002;106:1349-54

Two line charts. Chart A shows changes in forearm blood flow (ml/100ml/min) for patients on Phenylephrine (µg/100ml/min). Chart B shows change in forearm blood flow (ml/100ml/min) for patients on Clonidine (µg/100ml/min)

Forearm vasoconstrictor responses to phenylephrine are blunted in older men (A), whereas responses to clonidine are not significantly different (B).

Dinenno et al., *Circulation*. 2002;106:1349-54

Two bar charts. Chart A shows forearm blood flow (ml/100ml/min) at baseline and after Phentolamine in young and older patients. Chart B shows forearm vascular conductance (U) in young and older patients.

Forearm hemodynamics at rest and after local α-adrenergic blockade with phentolamine. *P<0.001 vs young men.

Dinenno et al., *Circulation*. 2002;106:1349-54

Line chart showing labetalol concentration (ng/ml) at various times (hours) after dose in a 67 year old male and a 31 year old male.

Drug exposure is greater in the older subject.

Chart showing the change in heart rate from baseline (beats per minute) for a 25 year old female and a 69 year old female on intravenous labetalol (sitting rate) and labetalol plasma concentration (ng/ml). Heart rate changes occur at lower labetalol concentrations in the younger female subject.

Chart comparing systolic blood pressure (mm Hg) reductions for elderly patients and young patients on labetalol 200 mg p. o. at various times (hours) after dose when patients are standing and when sitting. Effects are more pronounced in the elderly.

Chart showing patients heart rates (beats per minute) on intravenous labetalol (sitting heart rate) in elderly and in young patients and time (hours) after dose.

Arterial Changes Related to Aging

Increased Calcium and Collagen

Reduces Elasticity and Compliance

Increased Pulse Pressure

Decreased Baroreceptor Sensitivity

Hyaline Thickening in Arterioles, Small Arteries

Increased Peripheral Resistance

Graphic illustration of the development of aortic pressure abnormalities due to age-related aortic stiffening

Schematic representation of the major mechanisms involved in the contraction and relaxation processes of vascular smooth muscle.

Scatter chart showing Amlodipine intravenous pharmacodynamics 0.5-96 hr following 1st dose in elderly and young patients.

Blood pressure changes are greater in elderly patients.

Scatter chart showing Amlodipine 14 week pharmacodynamics 0-144 hours following last dose in elderly and young patients receiving 10 mg qd

Blood pressure changes are similar in both groups.

Chart showing verapamil concentration (ng/ml)in a 25 year old patient, a 70 year old patient and an 82 year old patient at various times after dose (hours).

Drug exposure is greater in older patients.

Chart showing verapamil concentration (ng/ml) in a 30 year old male patient, a 70 year old male patient and an 87 year old male patient versus P-R prolongation (msec).

Changes are greater in younger subjects.

Two charts showing intravenous verapamil pharmacodynamics. In one chart the change in mean blood pressure (mmHg) in young, elderly and very elderly patients is shown. In the other chart the change in heart rate (bpm) is shown in young, elderly and very elderly patients. Blood pressure changes are greater in older patients with lesser changes in heart rate.

Chart showing P-R intervals (msec) hours after 25 mg x ± SEM of diltiazem and after 50 mg x ± SEM of diltiazem.

Chart showing the mean pressure (mm Hg) and heart rate (bpm) in 9 young patients and 11 old patients hours after administration of 50 mg of diltiazem.

HEART RATE RESPONSES

DECREASED RATE RESPONSES
- Parasympathetic
- Sympathetic

DIFFERING SENSITIVITY TO CALCIUM
- CHANNEL BLOCKADE OF THE SINUS NODE

Graphic illustration of receptor-mediated Ca^{2+} mobilization. The illustration shows Ca^{2+} influx through potential-dependent and receptor operated channels, mobilization of membrane-bound and intracellularly stored Ca^{2+}.

Bar chart illustrating ATPase activity measured at 10 μmol/L Ca^{2}+ in membrane preparations from adult uninfected rat hearts (n=4), preparations from senescent uninfected rat hearts (n=4), preparations of senescent hearts infected with Ad.β-Gal at day 2 (n=4), and preparations of senescent hearts infected with Ad.SERCA2a at day 2 (n=4). *P<0.05 compared with adult. ‡P<0.05 compared with senescent group plus Ad.β-Gal.

Schmidt et al., *Circulation*. 2002; 101:790-6

Bar chart illustrating measurements of systolic parameters **+dP/dt (B)** in adult uninfected rat hearts (n=6), senescent uninfected rat hearts (n=8), senescent hearts infected with Ad.β-Gal at day 2 (n=6), and senescent hearts infected with Ad.SERCA2a at day 2 (n=6). *P<0.05 compared with adult. ‡P<0.05 compared with senescent group plus Ad.β-Gal.

Schmidt et al., *Circulation*. 2002; 101:790-6

Graphic illustration of endothelial dysfunction: from physiology to therapy

JV Mombouli and PM Vanhoutte. J Mol Cell Cardiol 1999;31:61-74

Bar chart showing EC50 for acetylcholine (microgram/min) acetylcholine and acetycloline + L-NAME in young and old.

Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

Chauhan, et al, JACC, 1996; 28: 1796-1804

Graphic illustration of renal and hepatic clearance of drugs.

Grahic illustration

Phase I and Phase II metabolic enzymes.

DRUGS METABOLIZED BY KNOWN P450s

3A (4)	
Loratadine (in part)	Diazepam
Terfenadine	Midazolam
Astemizole	Triazolam
Verapamil	Cyclosporine
Nifedipine	Tacrolimus
Diltiazem	Lovastatin
Felodipine	Progesterone
Nimodipine	Testosterone
	Cisapride
	Lansoprazole

Modified from Flockart. *J Psychopharm*.

Chart showing the plasma triazolam concentration (ng/ml) in elderly female and young female hours after dose. Drug exposure is greater in the elderly subject.

Chart showing serum thiopental concentration (log scale) versus time for the young and the elderly patients.

Hoover and Stanski, Anesthesiology, 1985; 62: 714-724.

Two charts are shown. Specifically, the concentration of thiopental is shown versus 1) time and 2) spectral edge in an elderly patient (first chart) and in a young patient (second chart). The length of thiopental infusion is shown.

Homer and Stanski, Anesthesiology, 1985; 62:714-724.

Chart illustrating K_{10} and clearance over age (years).

Chart illustrating declining V_1 with advancing age.

Homer and Stanski, Anesthesiology, 1985; 62:714-724.

Chart showing midazolam clearance (ml/min) in young males, young females, elderly males, and elderly females.

Clearance is lowest in elderly males.

Scatter chart showing creatinine clearance (ml/min/kg) over age (years)

Clearance declines with advancing age.

PARTIAL LIST OF DRUGS THAT UNDERGO SIGNIFICANT RENAL EXCRETION IN HUMANS

Amantadine
Aminoglycoside antibiotics
Cimetidine
Digoxin
Furosemide
Lithium
Nitrofurantoin
Ouabain
Penicillin antibiotics
Phenobarbital
Quinidine
Sulfonamides
Tetracycline

COCKCROFT & GAULT EQUATION

$$CLCr = \frac{\textbf{(140 - age) (weight in kg)}}{72 \text{ (serum Cr in mg/dL)}}$$

[reduce estimate by 15% for women]

Bolded terms estimate creatinine synthesis rate.

Some drugs with decreased clearance in the elderly

REPRESENTATIVE DRUGS (Route of clearance – Renal)
All aminoglycosides
Sotalol
Vancomycin
Atenolol
Digoxin
Dofetilide
Procainamide
Cimetidme
Lithium

Single Phase I metabolic pathway	
CYP3A	Alprazolam
	Midazolam
	Triazolam
	Diltiazem
Dihydropyridine calcium channel blockers	
	Lidocaine
	Diazepam
	Phenytoin
CYP2C	Celecoxib
	Theophylline
CYP1A2	

Some drugs with decreased clearance in the elderly cont.

ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS
Multiple Phase I metabolic pathways	Imipramine Desipramine Trazodone Hexobarbital Flurazepam

PHARMACOKINETIC CHANGES IN THE ELDERLY

PROCESS	CHANGE WITH AGE
Gastrointestinal Absorption	**none**
Drug Distribution	
Central Compartment Volume	**none or ▼**
Peripheral Compartment Volume	
Lipophilic Drugs	**▲▲**
Hydrophilic Drugs	**▼▼**
Plasma Protein Binding	
Binding to Albumin	**▼**
Binding to α_1-acid Glycoprotein	**none or ▲**

PHARMACOKINETIC CHANGES IN THE ELDERLY

Process	Change with Age
Drug Elimination	
Renal Elimination	▼▼
Hepatic Elimination	
Phase I Reactions	
CYP3A	▼
CYP1A2,2D6,2C9,2C19,2E1	↔ or ▼
Phase II Reactions	
Glucuronidation	↔
Sulfation	↔
Acetylation	↔

Summary schematic of observed drug response as a function of age-related changes in PK and PD.

The Goals of Treating the Older Patient

↓ Morbidity & Mortality

Avoid or Minimize Drug-Related Problems

Improve the Quality of Life

By the time a man gets well into the seventies, his continued existence is a mere miracle

R.L. Stevenson:AES Triplex

“Come grow old along with me,
the best of things are yet to be.”

“Rabbi Ben Ezra,”
Robert Browning (1812 – 1889)