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

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Table 1. Age-related chronic medical conditions*

<table>
<thead>
<tr>
<th>MEDICAL CONDITION</th>
<th>FREQUENCY PER 1000 PERSONS IN USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;45 y</td>
</tr>
<tr>
<td>Arthritis</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>129</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>37</td>
</tr>
<tr>
<td>Heart disease</td>
<td>31</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>19</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
</tr>
</tbody>
</table>

Figure 1. Medication prescriptions per resident in the 12 nursing homes. 15 October 1992 · Annals of Internal Medicine · Volume 117 · Number 8 · 685
(Adapted from Cluff LE et al: JAMA 188:976, 1964)
Cardiovascular Pharmacodynamics of Aging

Pharmacokinetics of Aging

Multimorbidity and Polypharmacy

Assessment of Functional Effects of Polypharmacy
Alterations in the Cardiovascular System of the Elderly

Cardiovascular 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
Fig. 1. Relationship between isoproterenol resistance and age in smokers (●) and non-smokers (○).
SYSTOLIC BLOOD PRESSURE
LABETALOL 200 mg p. o.

ELDERLY

YOUNG

SYSTOLIC BLOOD PRESSURE (mm Hg)

TIME AFTER DOSE (hours)
FIGURE 1. Schematic representation of the major mechanisms involved in the contraction and relaxation processes of vascular smooth muscle. See text for complete discussion. Ca = calcium ion; Ca, = trigger calcium; CLMD = calmodulin molecule; M = mitochondria; MLC = myosin light chains; MLC-P = phosphorylated myosin light chain kinase; MLCK = myosin light chain kinase; NE = norepinephrine; PDC = potential-dependent calcium channel; ROC = receptor-operated calcium channel; SL = sarcolemmal membrane; SR = sarcoplasmic reticulum vesicle. The reaction of adenosine triphosphate (ATP) going to adenosine diphosphate (ADP) plus inorganic phosphate (P) is shown as either ATP → ADP + P or ATP → P.
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
<table>
<thead>
<tr>
<th>1. Aortic BP (mm Hg)</th>
<th>Normal Aorta (Young Adults)</th>
<th>Stiff Aorta (Older Adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>130 Systolic 80 Diastolic</td>
<td>140</td>
</tr>
<tr>
<td>2. PWV (m/s)</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>3. Reflected Wave</td>
<td>Early Diastole</td>
<td>Late Systole</td>
</tr>
<tr>
<td>4. Pulse Wave Shape</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Aortic BP (mm Hg)</th>
<th>Normal Aorta (Young Adults)</th>
<th>Stiff Aorta (Older Adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>130 Systolic 80 Diastolic</td>
<td>160</td>
</tr>
</tbody>
</table>

**Figure.** Development of aortic pressure abnormalities due to age-related aortic stiffening. 1. Increased systolic blood pressure (BP) and decreased diastolic blood pressure due to decreased aortic distensibility. 2. Increased pulse wave velocity (PWV) as a result of decreased aortic distensibility. 3. Return of the reflected primary pulse to the central aorta in systole rather than diastole because of faster wave travel. 4. Change in the shape of the pulse wave because of early wave reflection. Note the reduction in diastolic pressure-time despite the increase in systolic pressure. Horizontal lines indicate systole, vertical lines indicate diastole. 5. The aortic blood pressure resulting from decreased aortic distensibility and early reflected waves. * Primary reflected wave. Adapted from reference 18; pulse calibrations added by the authors.
HEART RATE RESPONSES

- DECREASED RATE RESPONSES
  Parasympathetic
  Sympathetic

- DIFFERING SENSITIVITY TO CALCIUM CHANNEL BLOCKADE OF THE SINUS NODE
Endothelial Dysfunction: from Physiology to Therapy

Agonists

Endothelial cell

Ca^{2+} → Ca → Ca^{2+} → Calmodulin → AA → P-450 ?

Cyclooxygenase → AA → PGI_2 → NO → EDHF

Smooth muscle cell

PGI_2 → NO → EDHF → Relaxation

soluble guanylate cyclase → cGMP → ATP → cAMP → Ca^{2+} → K^+ → hyperpolarization

Figure 2. Scatterplot of correlation of age and peak (percent of control values) coronary blood flow response to acetylcholine.

Pharmacokinetics of Aging
PARENT DRUG ➔ KIDNEY ➔ RENAL CLEARANCE

PARENT DRUG ➔ LIVER ➔ HEPATIC CLEARANCE ➔ METABOLITES
Drug → Phase I enzymes → Oxidation Reducing Hydrolysis Metabolites → Phase II enzymes → Conjugated metabolites
Some Phase I Drugs

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>• duloxetine</td>
<td>• phenytoin</td>
</tr>
<tr>
<td>• olanzapine</td>
<td>• warfarin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>CYP2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>• carvedilol</td>
<td>• diazepam</td>
</tr>
<tr>
<td>• duloxetine</td>
<td>• phenytoin</td>
</tr>
<tr>
<td></td>
<td>• clopidogrel</td>
</tr>
</tbody>
</table>
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

\[
CL_{Cr} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum Cr in mg/dL}}
\]

[reduce estimate by 15% for women]
# PHARMACOKINETIC CHANGES IN THE ELDERLY

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>CHANGE WITH AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Absorption</td>
<td>none</td>
</tr>
<tr>
<td>Drug Distribution</td>
<td></td>
</tr>
<tr>
<td>Central Compartment Volume</td>
<td>none or ▼</td>
</tr>
<tr>
<td>Peripheral Compartment Volume</td>
<td></td>
</tr>
<tr>
<td>Lipophilic Drugs</td>
<td>▲▲</td>
</tr>
<tr>
<td>Hydrophilic Drugs</td>
<td>▼▼</td>
</tr>
<tr>
<td>Plasma Protein Binding</td>
<td></td>
</tr>
<tr>
<td>Binding to Albumin</td>
<td>▼</td>
</tr>
<tr>
<td>Binding to α₁-acid Glycoprotein</td>
<td>none or ▲</td>
</tr>
</tbody>
</table>
### PHARMACOKINETIC CHANGES IN THE ELDERLY

<table>
<thead>
<tr>
<th>Process</th>
<th>Change with Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Renal Elimination</td>
<td>▼▼</td>
</tr>
<tr>
<td><strong>Hepatic Elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Phase I Reactions</td>
<td></td>
</tr>
<tr>
<td>CYP3A</td>
<td>▼</td>
</tr>
<tr>
<td>CYP1A2,2D6,2C9,2C19,2E1</td>
<td>↔ or ▼</td>
</tr>
<tr>
<td>Phase II Reactions</td>
<td></td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>↔</td>
</tr>
<tr>
<td>Sulfation</td>
<td>↔</td>
</tr>
<tr>
<td>Acetylation</td>
<td>↔</td>
</tr>
</tbody>
</table>
Multimorbidity and Polypharmacy
Assessment of Functional Effects of Polypharmacy: Anticholinergic and Sedative Drugs
Older people carry

High burden of illness: medications indicated

Increased risk adverse drug events

Limited evidence base to guide prescribing

Need evidence based model to assess functional risk/benefit
Equation Derived for Drug Burden Index (DBI)

\[
DBI = \sum \frac{D_{AC}}{\delta_{AC} + D_{AC}} + \sum \frac{D_{S}}{\delta_{S} + D_{S}}
\]

DBI  Drug Burden Index  
AC  Medications with anticholinergic properties  
S  Medications with sedative properties  
D  Daily dose  
\(\delta\)  Minimum recommended daily dose approved by US Food and Drug Administration; estimate of DR\(_{50}\)
Functional Measures

• Physical function – Health ABC Score (HABC)
  – Objective measures:
    • Chair stands
    • 6 m walk
    • Narrow 6 m walk
    • Standing balance
  – Higher score, better physical function
  – Validated (Established Populations for Epidemiologic Studies of the Elderly)

• Digit Symbol Substitution Test (DSST)
  – Psychomotor performance, attention, concentration, STM
  – Higher score, better cognitive function
  – Validated (Wechsler Adult Intelligence Scale)
Association of Anticholinergic Burden with Function and Sedation
Association of Sedative Burden with Function and Sedation

![Graph showing the association between sedative burden and HABC Score/DSST. The graph plots sedative burden on the x-axis and HABC Score/DSST on the y-axis. As sedative burden increases, HABC Score decreases and DSST increases. The graph includes data points for different sample sizes (n=2704, n=102, n=163, n=54, n=24).]
Relative Impact of Drug Burden Index on Function

- Multiple regression analysis
- Degree of variance in HABC score captured by a one point increase in drug burden index is:
  - ~ 3 additional physical co-morbidities
  - > cog impairment, depression or anxiety
Longitudinal Association Between DBI and Function in Health ABC Study Participants

Association of
– Drug Burden Index at each time point
– Cumulative drug burden exposure

with function over 5 years
Conclusions

• In Health ABC participants, Drug Burden Index at years 1, 3 and 5 and total drug burden exposure (AUCDB) are associated with reduced functional performance at year 6.
Other Populations

• Womens Health and Aging Study (WHAS)
  – Community dwelling frail older women (USA)
• Concord Health in Ageing Men Project (CHAMP)
  – Community dwelling older men (Australia)
• FREEDOM
  – Older people living in low level residential aged care (Australia)
• Department of Veterans Affairs
  – DVA linked data bases (Australia) - pending
Why Include Patients with Multiple Chronic Conditions (mostly older) in Clinical Trials?

• Efficacy
  – Is the same therapeutic benefit seen on the background of multiple illnesses and medications used to treat them?
  – Should the trial be powered to independently assess efficacy for the MCC patients?

• Safety
  – Is the safety profile adequately characterized without direct study of the MCC patient population?
  – What are the “off-target” drug effects that may have particular impact in MCC patients?

Are Older Patients Being Included?
Older Patients with MCC?
Goals for 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)