Special Considerations in Geriatric Prescribing: Issues of Safety and Efficacy

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Objectives

- Upon completion of the learning activities, the participant will be able to:

1. Identify the effects of aging and disease state on pharmacokinetics and pharmacodynamics.
2. Recognize safety issues with the use of select medications in the elder.
3. Describe the impact of impaired renal function and age-related changes on prescribing select medications in the older adult.

We do not start off old….

What changes in older adult?

- Pharmacokinetics?
- Pharmacodynamics?
- Neither?
- Both?

Pharmacodynamics

- Study of biochemical and physiological effects of drugs
  - What the drug does to the body
    - Unchanged in elder
- *Mechanism of action knows no age*.
  - However, age-related changes can influence efficacy of a given medication.

Pharmacokinetics

- What the body does to the drug
  - Absorption
  - Distribution
  - Biotransformation (metabolism)
  - Excretion

Summary of Age-related Changes

	Adults age **20-30 y**	Adults age **60-80 y**
% body weight as water	60%	53%
Lean muscle mass	Baseline	=>20% reduction
% body weight as fat	26- 33% (women) 18-20% (men)	38-45% (women) 36-38% (men)
Serum albumin (average)	4.7 g	3.8 g
Relative kidney weight	100%	80%
Relative hepatic blood flow	100%	55-60%

Katzung, BG. (2007) *Basic and Clinical Pharmacology (10th ed.).* New York: Lange Medical Books/ McGraw-Hill.

Pharmacokinetic changes with aging

- GI absorption
  - Gastric pH increases due to reduction in acid secretion
  - Decrease in gastric emptying, overall gastrointestinal motility
- Likely altered rate of absorption but total absorption is not changed to any clinically significant effect.

Pharmacokinetic changes with aging

- Distribution
  - Total body water, proteins, and lean body mass decrease
    - Yields reduce volume of distribution for certain drugs such as aminoglycosides, digoxin
  - Total body fat increases
    - Yields a larger volume of distribution for lipid soluble drugs such as phenytoin (Dilantin), diazepam (Valium)

Pharmacokinetic changes with aging

- Metabolism (AKA biotransformation)
  - Hepatic mass reduced as is hepatic blood flow
  - Yields reduced rate of drug metabolism

Pharmacokinetic changes with aging

- Excretion
  - Glomerular filtration rate (GFR) reduced, and tubular function changes
  - Yields slower excretion of drugs and drug metabolites, less renal reserve and increases susceptibility to effects of nephrotoxic drugs
    - Source- Prescribing for older people, available at http://archive.student.bmj.com/issues/07/10/education/372.php, accessed 6.20.10.

Two Patients
Kidney size? Liver size? Body fat?

- 70 yo man who weighs 75 kg, at ideal body weight
- Cr= 1.4 mg/dL
- GFR= 53 mL/min/1.73 m2

- 70 yo woman who weighs 75 kg, at ideal body weight
- Cr= 1.4 mg/dL
- GFR= 40 mL/min/1.73 m2

General pharm rule in prescribing for the elder: When you have multiple choices in a drug class, choose a product with shorter half-life.

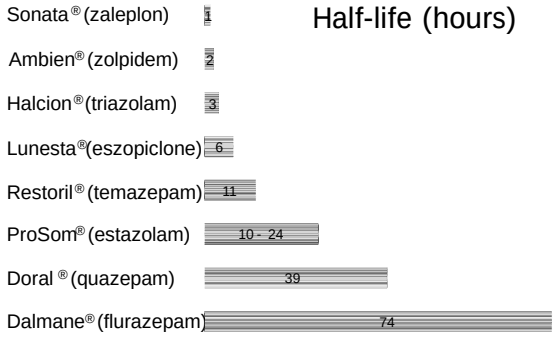
T ½

- Time required for amount of drug to be reduced by ½
  - Also known as elimination T ½
- Pharm principle
  - 3-5 T ½ needed to reach steady state
  - 3-5 drug-free T ½ needed to eliminate drug from body

What is left of original drug dose?

- 1 T ½
  - 50% left
- 2 T ½
  - 50% of 50%= 25% left
- 3 T ½
  - 50% of 50% of 50%=12.5% left
- 4 T ½
  - 50% of 50% of 50% of 50%= 6.25% left
- 5 T ½
  - 50% of 50% of 50% of 50% of 50%=3.125% left

Half-life (hours)



BZD pharmacokinetics

	Dose equivalent	Half-life in hours
Alprazolam (Xanax)	0.5	6-20
Chlordiazepoxide (Librium)	10	30-100
Clonazepam (Klonopin)	0.25	18-50
Clorazepate (Tranxene)	7.5	30-100
Diazepam (Valium)	5	30-100
Lorazepam (Ativan)	1	10-20
Oxazepam (Serax)	15	8-12

Source- Arana & Rosenbaum (2000) Handbook of Psychiatric Drug Therapy.

Clinical Examples of T ½

- Levothyroxine
  - T ½ = 7d in person who is euthyroid, longer in hypothyroidism, shorter in hyperthyroidism
  - 5 T ½= 35 d
- Penicillin
  - T ½= 1-2 h
  - 5 T ½=5-10 h

Your patient is a 75 year-old man…

- …who is in general good health with well-controlled HTN and dyslipidemia. He presents today with a chief complaint of difficulty initiating and maintaining sleep for about the past year.

Your patient is a 75 year-old man…

- He drinks about 5 cups of coffee a day but states, "I really do not think this had anything to it. I have done this for years."

What age-related changes might be contributing to his problem?

- Pharmacokinetic?
  - Kidney
  - Drug-metabolizing hepatic enzymes
- Pharmacodynamic?
- Others?

Caffeine's PK

- T ½ range= 1.5- 9 h
- Cmax= ~15- 100 mins
- Minimum first-pass effect
- CYP 450 substrate 1A2

Source- http://books.nap.edu/openbook.php?isbn=0309082587, accessed 6.20.10.

True or false?

- When compared with a healthy 40 yo adult, CYP 450 isoenzyme levels can drop by up to 30% in elders after age 70.
- CYP 450 1A2's activity is influenced by the presence or absence of estrogen in women.

What do we know about the pharmacokinetics in the older adult of select medications?

Sitagliptin (Januvia)

- Per PI, geriatric use
  - "Of the total number of subjects (n= 3384) in clinical efficacy and safety studies, 725 were 65 years and older and 61 patients were 75 years and older…age alone does not have a clinically meaningful impact on the pharmacokinetics of sitagliptin…

Sitagliptin (Januvia)

- Per PI, geriatric use
  - "Elderly subjects (65-85 years) had approximately 19% higher plasma concentration of sitagliptin compared to younger patients."
- Mechanism of metabolism
  - Excreted largely unchanged in urine

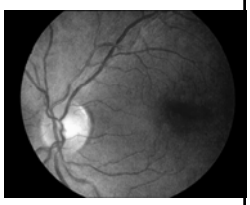
General pharm rule in prescribing for the elder: While PD does not change with aging, some age related changes will result in less drug effect.

Case example 75 yo man

- Former smoker X 10 years w/ 60 pk-yr hx and 20 yr hx HTN
- Prior provider retired recently
  - Lisinopril 20 mg qd w/ BP= 155/94
  - Albuterol 2 puff 3-6 X d to manage recurrent cough, "doesn't work as well as it once did."

Case example 75 yo man

- Cr= 1.2 mg/dl
  - GFR= 63 mL/min/1.73 m2
- UA= 30 mg/dl protein
- Gr 1 HTN retinopathy
- FEV1, FVC ratio <70%



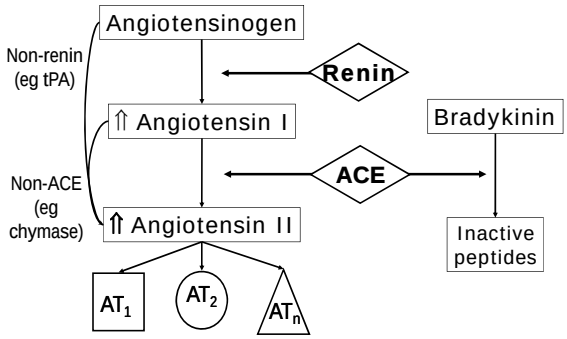
Age-related changes

- Maximum breath capacity
  - Peak achieved in 3d decade of life
  - Reduced every subsequent decade
  - Likely as low as 40% of greatest level by age 90
    - Add COPD, impaired mobility, diminished cough reflex, heart failure

In the elder

- Loss of B-2 receptor sites
  - Less bronchodilator effect with the beta2-agonits (–terol medications, such as albuterol, salmeterol, formoterol)
    - Add an anticholinergic (bronchodilatation via minimizing cholinergic tone in the airways) such as ipratropium bromide (Atrovent), tiotropium bromide (Spiriva)

Renin-angiotensin cascade: What works where?



In the elder

- Less renin-angiotensin production
  - Less antiHTN effect by ACEI, ARB
    - Add CCB, low dose diuretic
- At the same time, ACEI/ ARB use is recommended in a number of clinical conditions found in the older adult including heart failure, DM, renal impairment

General pharm rule in prescribing for the elder: Avoid medications with systemic anticholinergic effect due to risk of confusion, urinary retention, constipation, visual disturbance, and hypotension.

If anticholinergic effect unavoidable, choose the product in the class with the least amount of this effect.

See Beers List for additional information.

Medications with Significant Anticholinergic Effects

- 1st generation antihistamines
  - Chlorpheniramine (Chlor-Trimeton)
  - Diphenhydramine (Benadryl)
  - Hydroxyzine (Atarax)
  - Cyproheptadine (Periactin)
  - Promethazine (Phenergan)
- Doxepin (Sinequan)

Higher vs. Lower Anticholinergic Effect

- Examples
  - Oxybutynin (Ditropan)
  - Tolterodine (Detrol)
- Examples
  - Amitriptyline
  - Nortriptyline

Comparing Psychotropic Medications
(Katzung, 2007, Goldberg, 2007)

Drug	Sedation or activation?	Anti-cholinergic	Serotonin	NE	Dopamine
Citalopram, escitalopram	+ Sedation +/ ++ Activation	0	+++	0	0
Fluoxetine	+ Sedation +/ ++ Activation	+	+++	0/+	0/+
Paroxetine	+ + Sedation + Activation	++	+++	0	0
Sertraline	0 Sedation +/ ++ Activation	0	+++	0	0

Comparing Psychotropic Medications
(Katzung, 2007, Goldberg, 2007)

Drug	Sedation or activation	Anti-cholinergic	Serotonin	NE	Dopamine
Bupropion	Sedation 0 Activation +++	+	0	+	+++
Venlafaxine	Sedation + Activation +/ ++	0	+++	+/++	0
Duloxetine	Sedation + Activation +/ ++	0	+++	++ +	0
Mirtazapine	Sedation ++++ Activation 0	+	0	0	0

General pharm rule in prescribing for the elder: Given number of medications many elders take, avoid choosing medications with known, significant drug interaction potential.

You see a older woman…

- … With valvular heart disease who is taking warfarin. She also is seeking treatment for a longstanding depression.
- What should you consider in prescribing an SSRI?

CYP450 Isozyme Inhibition by the SSRIs *(in vitro*)*

	CYP Isoenzymes				
	1A2	2C9	2C19	2D6	3A4
Escitalopram	0	0	0	0	0
Citalopram	+	0	0	+	0
Fluoxetine	+	++	+ to ++	+++	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition

* Clinical significance of *in vitro* data is unknown

There are limited *in vivo* data suggesting a modest CYP 2D6 inhibitory effect for escitalopram 20 mg/day.

von Moltke et al., 2001; Greenblatt et al., 2002; Greenblatt et al., 1998

You see a patient in urgent care who states,

- "I am on a big list of medications, but I am not sure of the names."
- He needs an antibiotic for a RTI.

Assuming all of the following would be effective,

You prescribe:

- Clarithromycin
- Erythromycin
- Azithromycin

Caution: DI of select statins and clarithromycin

- "Clarithromycin significantly ($p < 0.001$) increased the AUC and Cmax of all 3 statins (atorvastatin, lovastatin, simvastatin {CYP 3A4 substrates}), most markedly simvastatin (approximately 10-fold increase in AUC)…"
  - Am J Cardiol (2004) 94: 1140-6.

Simvastatin PI

- "If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment."

General pharm rule in prescribing for the elder: Keep in mind normative age-related changes in the kidneys as well as the high rate of impaired renal function.

Age-related Renal Effects

- Reduce renal mass
- Loss of functional nephrons
  - Ethnic/genetic differences with fewer at birth
- Diminished renal blood flow
- Less ability
  - Conserve Na+
    - Increased urine sodium
  - Off-load K+

Age-related Changes

- Glomerular filtration rate (GFR)
  - Cr Cl approximates GFR
  - Function stable through age 60
  - Reduced to about 55% of this level by age 90 in the absence of renal impairment
    - Add heart failure, dehydration

Creatinine clearance calculator available at http://www.globalrph.com/crcl.htm, accessed 6.20.10.
GFR calculator available at http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm, accessed 6.20.10.

Cockcroft-Gault Equation
Use IBW

- To calculate Cr cl in men
  - (140-age) x wgt in kg/(72 X serum cr)
  - 70 yo man, weighs 75 kg, serum cr = 1.4 mg/dL
  - (140-70 = 70) X 75/(72 x 1.4 = 100.8)= 70 X .744 = Cr Cl= 52.08 ml/min
- Cr Cl= 52.08 ml/min
- Calculated GFR= 53 mL/min/1.73 m2

Cockcroft-Gault Equation
Use IBW

- To calculate Cr cl in women
  - 70 yo woman, weighs 75 kg, serum cr = 1.4 mg/dl
  - (140-age) x wgt in kg/(72 X serum cr) X 0.85
  - (140-70 = 70) X 75/(72 x 1.4=100.8) = 70 X .744=52.08 x .85 = Cr Cl= 44.268 ml/min
- Cr cl= 44.268 ml/min
- Calculated GFR = 40 mL/min/1.73 m2

What is the significance in clinical practice?

- 70 yo woman with Cr Cl= 44 ml/min
  - Levofloxacin 500 mg day 1 then 250 mg qd if 500 mg was typical dose
  - Lisinopril= 50-75% of typical dose
- 70 yo man with Cr Cl= 52 ml/min
  - Example - No dose adjustment for levofloxacin at current Cr Cl

Glomerular filtration rate formula

- Needed patient information
  - Age
  - Gender
  - Serum creatinine
  - Ethnicity
    - Black vs. non black

Source- www.kidney.org/professionals/kdoqi/gfr_calculator.cfm, accessed 6.20.10.

Example

- 70 yo non-black woman
- Cr= 1.4 mg/dL
- GFR results= 40 ml/min/1.73 m2

True or false?

- If the prescribing information about a given medication includes a warning about the need for dose adjustment in the presence of renal impairment, then that product is likely nephrotoxic.

As renal dysfunction progresses…

- Reduced functional reserve
  - GFR=50-65 mL/min (~50% of younger adult normal), remaining nephrons able to compensate, lab chemistries remain NL
- Most drug doses unchanged

As renal dysfunction progresses…

- Renal insufficiency
  - GFR=25-49 mL/min, functional reserve exhausted, fluid, electrolyte balance an issue, particularly when stressed with infection, dehydration, nephrotoxins, mild HTN and anemia common
- Many drug doses need adjustment.

As renal dysfunction progresses…

- Renal failure
  - GFR<25 mL/min, 80% of nephrons destroyed, kidneys unable to maintain normal fluid and electrolyte balance, signs, sx renal failure (hypertension, heart failure, edema, hyperkalemia, hypocalcemia, anemia) present
- Many medications contraindicated or used in small, infrequent doses.

As renal dysfunction progresses…

- End-stage
  - GFR <10 mL/min, virtually all renal function lost, dialysis or transplant needed or terminal illness
- How is the medication affected by dialysis?

Source-Anaizi, N, The Drug Monitor- Review Renal Pharmacology, available at http://www.thedrugmonitor.com/RIT97.html, accessed 6.20.10.

You see an older adult with a UTI.

- This person is being seen at a walk-in center and you do not have ready access to her record. She mentions that she has a “bit of kidney trouble” but is not sure of what nature. She has no allergies and is being treated for HTN, DM and dyslipidemia. Random glucose= 110 mg/dl, BP= 140/88, HR= 80, RR= 18. UA= Trace protein, + nitrites. + WBC.

As a result of this information, you consider prescribing:

A. Nitrofurantoin.
B. Ciprofloxacin.
C. TMP-SMX.
D. None of the above.

Antimicrobial dose adjustment in renal impairment: Nitrofurantoin

- If Cr Cl => 50 ml/ min
  - Standard dosing according to indication
- If Cr Cl <50 ml/ min
  - Avoid use as medication will likely have inadequate concentration in the urinary tract with subsequent risk of treatment failure.

65 kg, 80 yo old with HTN, on ACEI, thiazide diuretic

Her daughter calls today for a SV for her mother, stating, “She does not seem herself today.”

65 kg, 80 yo old with HTN, on ACEI, thiazide diuretic

- With a 3-day history increasing confusion, new onset urinary incontinence
  - H / H= 11g / 38%
    - H:H ratio > 1:3
  - WBC= 2, 600 mm33
  - Neuts= 35% (AMNC= 910)
  - Bands= 48% (ABC= 1248)
  - Metas= 2%

65 kg, 80 yo old with HTN, on ACEI, thiazide diuretic

- BUN= 55 mg/ dl
- Cr= 2.1 mg/ dl
  - BUN: Cr ratio=>20, C/W volume depletion
- GFR per NKF calculator= 24 ml/min/1.73 m2
- Previous Cr 2 months ago
  - Cr= 1.1 mg/ dl
  - GFR per NKF calculator= 51 ml/min/1.73 m2

What type of renal failure?

- Prerenal?
- Intrarenal?
- Post renal?

Antimicrobial Dose Adjustment in Renal Impairment

- No dose adjustment required
  - Ceftriaxone
  - Linezolid
  - Minocycline
  - Doxycycline
  - Clindamycin
  - Moxifloxacin
  - Nafcillin

Source- 2009 Sanford Guide, pp 185.

General pharm rule in prescribing for the elder: Once a medication is no longer needed, make sure it is discontinued.

72 yo Man

- Hx HTN, dyslipidemia, stroke
- Resides in long term care facility
- Develops heart failure with CAP
- Hospitalized, meds adjusted
- Now back in your care for follow-up

72 yo man

- Current medications
  - Atorvastatin 20 mg qd
  - Lisinopril 40 mg qd
  - Furosemide 40 mg qd
  - Spironolactone 50 mg qd
  - KCl 40 mEq bid

72 yo man

- Prior to illness
  - Cr= 1.1 mg/dL
  - BUN=18 mg/dL
    - BUN:Cr<20:1
  - K+=4.5 mEq/L
- 1 mo p illness
  - Cr= 1.5 mg/dL
  - BUN= 44 mg/dL
    - BUN:Cr>20:1
  - K+=6.3 mEq/L

General pharm rule in prescribing for the elder: Be aware of specific geriatric related drug warnings.

Arch Intern Med. 2009;169:867-873.

- "Use of cholinesterase inhibitors is associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia. The risk of these previously underrecognized serious adverse events must be weighed carefully against the drugs' generally modest benefits."

Risperdal (risperidone): Boxed warning

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Risperdal (risperidone): Boxed warning

- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
  - Source- http://www.risperdal.com/risperdal/shared/pi/risperdal.pdf, accessed 10.2.09.

General pharm rule in prescribing for the elder: Start low, go slow, but get to goal.

Do not put patient in situation of perhaps having some of the adverse effects but none of the benefit of a give medication.

End of Presentation!

Thank you for your time and attention.

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Resources

- The Beers List
  - Updated periodically, provides information about particularly problematic medications for the older adult
  - Available at http://www.tahsa.org/files/DDF/medbeer1.pdf, accessed 7.25.10.

Resources

- National Council on Aging, Medication Management section
  - Available at http://www.healthyagingprograms.org/content.asp?sectionid=109, accessed 6.2.10.
- Center for Medication and Healthy Aging
  - Available at http://www.medsandaging.org/, accessed 6.2.10.

References

- Katzung, BG. (2007) *Basic and Clinical Pharmacology* (10th ed.) New York: Lange Medical Books/ McGraw-Hill.
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For more information...

- Fitzgerald, M., Miller, S. Comprehensive Clinical Pharmacology Course, Available at http://155.212.249.34/pharmlive.aspx?BC=home, accessed .