Clinical Pharmacological Issues in the Elderly

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Evaluation for Possible Polypharmacy

- 85 yr. olds and older; average 5-8 drugs per patient
- Association exists between increased number and severity of illnesses and increased number of adverse drug reactions
Increased Medication Use and Perceived Health in the Oldest Old

- Increased medication use associated with poorer ratings on health self report
- Not associated with increased mortality except for use of digoxin

Factors Related to Adverse Drug Drug Reactions

- Chronicity and Multiplicity of Disease
- Increased Disease-Drug Interactions
- Increased Drug-Drug Interactions
  - Lanoxin and Quinidine
  - Theophylline and Erythromycin
- Visiting Multiple Prescribers
- Visiting Multiple Pharmacies
Factors Related to Increased Number of Adverse Drug Reactions, Cont’d

- Multiple Diseases
  - CHF
  - COPD
  - PVD
  - CRF
  - Chronic liver disease
  - Dementia
  - ASHD
  - Diabetes Mellitus
  - Osteoporosis
  - DJD
  - Others

Normal Changes of Aging

- Increased Fat
- Decreased Bone
- Decreased Muscle
- Decreased Water Content

Normal Physiological Changes of the Organ Systems

- Liver: decreased blood flow; Decreased Phase I Metabolism
- Kidney: decreased creatinine clearance with advanced age
- CNS: increased risk of confusional states primarily secondary to anti-cholinergic agents
- Intestinal tract: malabsorption – not clinically significant in absence of disease

Normal Changes of Aging-Hepatic

- Phase I Metabolism: rate of metabolism slows (oxidation, reduction, hydroxylation)
- Phase II Metabolism: rate stays the same (conjugation or deactivation process - sulfonuridation, methylation, acetylation)
  - Examples: benzodiazepines
    - Short acting: Phase II only - appropriate
    - Long acting: Phase I and II - inappropriate, long half-lives

Pharmaceutical Agents That Require Hepatic Metabolism

- NSAIDs; Aspirin
- Acetaminophen
- Erythromycin
- Ketoconazole
- Tetracyclines
- Lidocaine
- Metoprolol
- SSRIs
- Ca channel blockers
- Alpha blockers
- Statins
- Dilantin
- Valproic acid
- Carbamazepine
- Tricyclic Antidepressants
- Neuroleptics

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### Pharmaceutical Agents That Require Hepatic Metabolism

- Benzodiazepines
- Cimetidine
- Ranitidine
- Famotidine
- Terfenadine
- Proton pump inhibitors


### The Cytochrome System

- CYP1A2
- CYP2C
- CYP2D6
- CYP3A
  - Involves Model Compounds, Drug Substrates, Inducers, and Inhibitors

### Particular Agents of Concern in the Elderly—highly bound to protein

- Phenytoin
- Carbamazepine
- Barbiturates
- Warfarin

Malnutrition or hypoproteinemia is associated with increased free fraction of drug and increased toxicity

Normal Changes of Aging-Renal

- Age-related reduction in renal blood flow and creatinine clearance in the face of a normal BUN and serum creatinine:
- Implications:
  - Adjust dose of renally excreted drugs with age according to the following formula

Creatinine Clearance Calculation

- Cr Clearance = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine} \times 72}
  - (serum cr adjusted to 1, multiplied x .85 for female)

Pharmaceutical Agents Primarily Eliminated In the Kidneys Requiring Dosage Adjustment

- Penicillins
- Aminoglycosides
- Fluoroquinolones
- Lithium
- Digoxin
- Fluconazole
- Thiazides

Inappropriate Prescribing of Renally Excreted Agents in LTC

- One in three renally excreted drugs prescribed in Ontario nursing homes was inappropriately dosed based on the calculated creatinine clearance.
- Renal function is often overlooked when prescribing renally excreted drugs to older long-term care residents and emphasizes the need for consideration of creatinine clearance when prescribing such drugs in this population.

Aminoglycoside Dosing in the Elderly With Impaired Renal Function

- Once daily dosing of aminoglycosides associated with reduced risk of morbidity (ototoxicity and renal failure) in patients with reduced creatinine clearance (usually below 50 ml/minute). Also alleviates the need for expensive peak and trough testing.

“Good Rule of Thumb”

- Reduce by half the dose of the particular renally excreted agent with a creatinine clearance of 50 ml/minute or less.
Physiological changes of the GI Tract

• Stomach- little change in gastric acidity with aging. In presence of dysphagia and H2 blocker therapy, may increase risk of morbidity and mortality from pneumonia (bacteria more viable after aspiration due to reduced acidity).

• Decreased GI motility and blood flow-- increased frequency of constipation

CNS Changes with Aging

• Reduced numbers of receptors

• Subtle structural and physiological changes consistent with Alzheimer’s and Vascular Dementia

• Increased susceptibility to drugs with anticholinergic properties resulting in: urinary retention; constipation; dry mouth; blurred vision; sedation; cognitive dysfunction
Anticholinergic Agents

- Phenothiazine major tranquilizers (promethazine, thorazine, chlorpromazine, haloperidol)
- Tricyclic anti-depressants (imipramine, amitriptyline, nortriptyline, desipramine)
- Narcotics—demerol, codeine, morphine
- Anti-spasmodics—oxybutynin, dicloine, tolterodine, probanthine, atropine, hyoscyamine, probanthine, belladonna alkaloids

Anti-cholinergic Agents—continued

- Anti-histamines
  - Diphenhydramine
  - Cyproheptadine
  - OTC cold medications
  - OTC sleep agents
  - Trihexyphenidyl
  - Benztropine
Common Clinical Conditions Necessitate Adjustment of Dosage in the Elderly:

- Liver - cirrhosis, malnutrition, malignancy, hepatitis with resultant decreased albumin and total protein levels (ex: sodium warfarin and phenytoin)
- Kidney - chronic renal insufficiency, renal failure
- Brain - dementia, delirium
- Intestinal tract - malabsorption syndrome
- Stomach - gastritis, malignancy

Anorexia and Aging

- Reduced thirst and appetite with normal aging
- Reduced thirst and appetite is associated with depression and/or dementia

Anorexia-Drug Induced:

- Theophylline
- Macrodantin
- Pronestyl
- Digoxin
- Thyroxin
- SSRIs
Specific High Risk Drug Categories

Screening for potential toxicity of prescription drugs-H2 Blockers:

- Confusion at high doses- Creatinine clearance below 50/ml/min. = reduce dose, except famotidine (below 20 ml/min)
- Nonspecific use associated with inadequate healing of gastric and duodenal ulcerations and greater chance of recurrence
- Nonspecific use for prophylaxis when used with NSAIDs
- Only two specific indications for prophylaxis to prevent gastrointestinal bleeding in the ICU setting: respiratory failure or coagulopathy

H2 Blockers-continued

- Very common to use these agents in nursing home without specific indications
**High Risk Drugs-Beta Blockers**

- Beta-Blockers (propranolol) side effects of:
  - Precipitation or exacerbation of CHF
  - Masking of hypoglycemia
  - Development of hypotension
  - Masking of symptoms of endocrine disease (hypothyroidism)
  - Reduction in exercise capacity
  - Exacerbation of chronic lung disease or bronchospasm
  - Depression
  - Memory loss
  - Production of arthropathy


**Beta Blockers-continued**

- Use selective ones: atenolol and metoprolol
  - Less side-effect profile
  - Better compliance—once or twice daily
  - Use associated with reduced cardiovascular morbidity and mortality in high risk patients

Australia/New Zealand Heart Failure Research Collaborative Group, 1997

**Antihypertensives that cause Postural Hypotension or Sedation:**

- Alpha-methyl-dopa
- Clonidine
- Alpha-blocking agents: useful for combined hypertension and prostatic hyperplasia
- Reserpine
- Ismelin—same as reserpine
  - Physicians Desk Reference, 2003
Diuretics

- Once daily dosing increases compliance
- Inexpensive
- First line agents effective in reducing risk of stroke and CV disease
- Doses above 50 mg ineffective in achieving blood pressure control
- Thiazides generally not effective in the presence of renal insufficiency
- May cause hypercalcemia
- Contribute to or cause incontinence
- Use not associated with adverse effects on lipids

Diuretics-continued

- Use in older caucasian women associated with reduced risk of hip fracture
- Adverse reactions
  - Dehydration; postural hypotension; K loss (especially during the summer and sweating)
- Consider discontinuing in elderly when possible, especially advanced, demented, or depressed elderly (reduced thirst and appetite drive)
Diuretics-References

- Ref: SHEP (Systolic Hypertension in the Elderly) Cooperative Research Group, 1991
- Physicians Desk Reference, 2003
Major and Minor Tranquilizers* and Hypnotics:

- Worsen dementia and delirium
- Cause hip fractures and falls
- Cause postural hypotension
- Risk of tardive dyskinesia with phenothiazines

*Especially long acting minor and sedating, highly anti-cholinergic major ones


Newer Atypical Antipsychotics:

- Much less risk of tardive dyskinesia
- Much more expensive
- Olanzapine most anti cholinergic and sedating
- Risperidol-increased risk of CVA, works through dopaminergic mechanism

SSRIs

- May cause Falls
- Nuisance side effects-nausea, decreased appetite, insomnia, agitation
- Void of cardiac risks compared to tricyclic antidepressants
- Inappropriate-

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Oral Hypoglycemics:

- Cause Hypoglycemia -- chlorpropamide

- SIADH more frequent with aging (idiopathic 30%)

Lanoxin

(Few indications currently for use except for rate control or congestive heart failure to improve function). Side-effects:

- Confusion
- Anorexia
- Nausea
- Yellow Green Colors
- Agitation
- Depression


NSAIDs*:

- Can Worsen HBP - removal of NSAID can affect mean blood pressure control
- Fluid retention
- Worsen CHF
- Cause confusion
- GI bleeding
- Newer Cox-2 agents, gastric sparing
- Less risk of Alzheimer's and cognitive decline

*In big doses or used chronically

"Tips" for Safe Traditional NSAID Use

- Substitute acetaminophen when possible around the clock instead of NSAID
- Use PRN when possible
- Use lowest dose possible
- Use for acute flare for 7-10 days then d/c
- When necessary for chronic use, insist on routine q 3 month BUN and CBC

Narcotics:

- May cause cognitive dysfunction
- Have anti-cholinergic side effects
  - Urinary retention
  - Constipation
  - Dry mouth
  - Sedation

Theophylline Adverse Reactions:

- Anorexia
- Nausea
- Arrhythmias
- Hypotension
- Drug-drug interactions-erythromycin, cimetidine, diazepam, phenytoin
- Useful for acute wheezing or asthma, not for COPD
  - Ref: Physicians Desk Reference, 2003; Cefalu CA. Clinical Pharmacology. In: Burke MM & Laramie JA. Primary Care of the Older Adult. 2000, p. 112
Oxybutynin

- Anticholinergic-(XL form with less side effects)
  - Sedation
  - Cognitive dysfunction
  - Dry mouth
  - Blurred vision
  - Constipation
  - Urinary retention


Muscle Relaxers:

- Sedation
- Falls
- Anti-cholinergic side-effects
- Contraindicated in elderly
  - Ref: Physicians Desk Reference, 2003

Ophthalmologic Preparations

- Beta blocker preparations-can achieve significant systemic absorption leading to heart block, CHF, bronchospasm.
  - Physicians Desk Reference, 2003
List Of Inappropriate Drugs In Elderly:

- Diazepam
- Chlordiazepoxide- long acting
- Flurazepam- long acting
- Muscle relaxers- sedation, anticholinergic
- Vasodilators- ineffective, cause “Steal Syndrome” and postural hypotension-of historic interest only, no longer available
- Dipyridamole- ineffective
- Amitriptyline- sedation, anticholinergic
- Propranolol-???

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Inappropriate Drugs in Elderly - Cont'd

- Alpha-methyl dopa (Aldomet)
  - Depression
  - Hemolytic anemia
  - Drug-induced lupus

Inappropriate Drugs in Elderly - Cont'd

- Fluoxetine - long acting, may cause weight loss and anorexia
- Reserpine (cheap and once per day, ganglionic blocking agent)
  - Depression
  - Impotence
  - Sedation
  - Orthostatic hypotension

Inappropriate Drugs in Elderly - Cont'd

Short-acting Benzodiazepines in excess of the following doses:
- Lorazepam - 3mg
- Oxazepam - 6mg
- Alprazolam - 2mg
- Temazepam - 15mg
- Zolpidem - 5mg
- Triazolam - .25mg
Inappropriate Drugs in Elderly - Cont'd

- Anticholinergic
  - Diclomine
  - Hyoscyamine
  - Probanthine
  - Belladonna alkaloids

Inappropriate Drugs in Elderly - Cont'd

- Chlorpropamide-very old drug!!!-of historic interest only, not available
- Indomethacin (neurotoxic)- confusion, bleeding
- Proxpyphene- sedation and no more effective than acetaminophen
- Trimethobenzamide- extra-pyramidal side-effects and least effective anti-emetic

Pain Pill Use by Elders

Inappropriate Drugs in Elderly - Cont'd

• Pentazocine - sedation, confusion, and hallucinations
• Meprobamate - addictive and sedating - very very old drug - of historic interest only, not available
• Lanoxin (if higher than .125mg) - reduced renal clearance with normal aging
• Disopyramide - negative inotropic effect, may cause CHF, off the market - of historic interest only, not available

Inappropriate Drugs in Elderly - Cont'd

• Phenylbutazone - excess bleeding, not available, of historic interest only
• Doxepin - anticholinergic and sedating
• Ticlopidine - no more effective than aspirin, not available, of historic interest only
• Meperidine - addicting, short-acting associated with breakthrough, sedation, anticholinergic
• Barbiturates - sedation
• Clonidine - sedating

Inappropriate Drugs in Elderly - Cont'd

• Iron in doses greater than 325mg iron sulfate - constipation and no greater absorption at higher dose
Screening for Toxicity of OTC Drugs

- Laxatives - chronic use associated with development of chronic megacolon, terminal reservoir syndrome, subsequent fecal impaction, and cancer
- Vitamins A, C and E - added toxicity with little added benefit
- Acetaminophen or aspirin - several different doctors, different brand names

Screening for Toxicity - OTC Drugs - Cont.

- Especially diphenhydramine-containing OTC agents
  - Sleep aids
  - Cold Medications
Rules for Prescribing to the Elderly

• Start with one-third to one-half the normal starting dose
• Use one drug to treat two clinical conditions
  – PAT and HBP
  – HBP and angina

Rules, cont’d

• Maximize dose of one agent before adding second agent to treat same clinical condition (HBP)
  – Less confusing for elderly
  – Less expensive
  – Less risk of adverse drug reactions
• Maximize compliance to no more than once or twice daily

Rules, cont’d

• Use cheapest drug possible
• Review medications patient brings in at each visit
• Discontinue unnecessary drugs and taper psychotropic drugs when possible