ADVERSE DRUG REACTIONS IN THE ELDERLY

Philip A Routledge
Department of Pharmacology, Therapeutics and Toxicology
Wales College of Medicine
Cardiff University

CAUSES OF DEATH IN THE USA 1994

1. Heart disease
2. Cancer
3. Stroke
4. Pulmonary disease
5. ADVERSE DRUG REACTIONS
6. Road traffic accidents

Lazarou J et al. JAMA 1998; 279: 1200-1205

THE AGEING POPULATION WORLDWIDE

PREDICTED PERCENTAGE GROWTH IN NUMBER of 60's AND OVER (2000-2020)

POPULATION OF HONG KONG

Life expectancy at birth:
- Total population: 79.54 years
- Male: 76.85 years
- Female: 82.41 years (2000 est.)

Age structure:
- 0-14 years: 18%
- Male 676,756; female 602,434
- 15-64 years: 71%
- Male 2,520,473; female 2,563,355
- 65 years and over: 11%
- Male 342,942; female 410,342 (2000 est.)

http://en.wikipedia.org/wiki/Demographics_of_Hong_Kong
AGE AND THE RATE OF DISEASE

Cancer

Heart Disease

Diabetes Mellitus

AGE AND THE PREVALENCE OF ADVERSE DRUG REACTIONS

RUDOLF BUCHHEIM 1820-1879

• “Fortunately a surgeon who uses the wrong side of a scalpel cuts his own fingers and not the patient.”

• “If the same applied to drugs, they would have been investigated very carefully a long time ago”

Association between NSAIDs and upper gastrointestinal tract bleeding/perforation

Table 5: Procedures or events to which AEs were related, by service most responsible for delivery of care at time of AE

<table>
<thead>
<tr>
<th>Type of procedure or event</th>
<th>Medicine</th>
<th>Surgery</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>4</td>
<td>115</td>
<td>2</td>
<td>123</td>
</tr>
<tr>
<td>Drug- or medication-related</td>
<td>69</td>
<td>11</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>Other clinical management</td>
<td>50</td>
<td>11</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>26</td>
<td>11</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Medical</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>System events</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Fracture</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Anaesthia-related event</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Obstetric</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>167</td>
<td>183</td>
<td>13</td>
<td>363</td>
</tr>
</tbody>
</table>

*Individual events in some of the categories may not add up to total due to rounding.

Copyright ©2004 CMA Media Inc. or its licensors
POLYPHARMACY AND ADRs

ADVERSE DRUG REACTIONS IN THE ELDERLY

- Extent of the problem
- Nature of the problem
- Recognition and reporting of ADRs
- Avoidance of ADRs

Type A versus Type B ADRs

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Accentuated&quot;</td>
<td>&quot;Bizarre&quot;</td>
</tr>
</tbody>
</table>

- Dose-related: Yes, No
- Predictable: Yes, No
- Frequency: Common, Less common
- Mortality: Low, Higher
- Morbidity: High, Lower

70% of ADRs predictable and therefore often avoidable

Adverse drug reactions as cause of admission to hospital

- 18,820 patients admitted over six months to a Liverpool Hospital and assessed for cause of admission
- Prevalence 6.5%, with ADR directly leading to the admission in 80% of cases
- Overall fatality was 0.15%
- Most reactions were either definitely or possibly avoidable (Type A ADRs)
- Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin, the most common reaction being gastrointestinal bleeding

FACTORS ASSOCIATED WITH AGEING

- PRIMARY
  - Slower metabolic processes, reduced autoregulation
- SECONDARY
  - Increased prevalence of disease
- TERTIARY
  - Psychological

PHARMACODYNAMICS
The response to a drug at any given concentration at its effector site
What the drug does to the body

PHARMACOKINETICS
The factors responsible for producing a given concentration at the effector site at any given time
What the body does to the drug
Pharmacokinetics and Pharmacodynamics

- Both often affected in the same situations
  - Extremes of age
  - Liver and renal disease
- Difficult to attribute responsibility
  - Pharmacodynamic mechanisms often inferred after exclusion of pharmacokinetic explanations

Pharmacokinetic factors in the elderly

- Reduced renal function
  - Obligatory or avoidable?
  - Glomerular filtration and age
- Reduced hepatic metabolism
  - Frail versus healthy elderly
  - Reduced hepatic mass and hepatic blood flow
- Changes in drug distribution
  - Increased proportion body fat
  - Decreased lean body mass & body water

AGE AND CREATININE CLEARANCE AND GENTAMICIN CLEARANCE


AGE AND THE ACTIVITY OF P450 ENZYMES IN HUMAN LIVER MICROSONIES

Shown as % of immunochemically determined enzyme concentrations (Shimada et al 1994)

Tanaka E. J Clin Pharm Ther. 1998; 23: 403-16

LIPOPHILICITY AND AGE-RELATED DIFFERENCES IN VOLUME OF DISTRIBUTION (Vd)


PHARMACODYNAMICS CHANGES IN THE ELDERLY

- Cardiovascular system
- Central nervous system
- Renal excretory system
- Hepatobiliary system
AGE AND THE CARDIAC CHRONOTROPIC RESPONSE TO ISOPRENALINE

Intravenous isoprenaline causes a smaller increase in heart rate in the elderly than in young healthy volunteers.


AGE AND ADRENOCEPTOR RESPONSES IN THE FOREARM HAND VEIN

Responses to the alpha, agonist, phenylephrine were not age-related beta, mediated venodilation was reduced in the elderly.

Pan HYM et al. J Pharmacol Exp Ther. 1986; 239: 802-7

AGE AND NITRIC OXIDE DEPENDENT VASORELAXATION

NG-monomethyl-L-arginine (L-NMMA) caused less reduction in forearm blood flow in healthy elderly volunteers (HEV) than in healthy young volunteers (HYV).


EFFECT OF AUTONOMIC BLOCKADE ON THE CARDIAC CHRONOTROPIC RESPONSE TO ISOPRENALINE

The elderly had significantly reduced CD25 to isoprenaline compared with young subjects.

This difference disappears after autonomic blockade with atropine and clonidine.


AGE AND BAROREFLEX SENSITIVITY

• Baroreflex sensitivity declines with increasing age

• It is also reduced in hypertensives at all ages


CARDIOVASCULAR EFFECTS OF INTRAVENOUS NIFEDIPINE

In 11 young normotensive volunteers, nifedipine (2.5 mg i.v.) produced tachycardia with no change in systolic blood pressure.

In 10 elderly normotensive volunteers, supine BP fell after IV (and oral) nifedipine while heart remained unchanged.

Robertson et al. Br J clin Pharmac 1988; 25:
BENZODIAZEPINES IN THE ELDERLY
• Elderly have pharmacokinetic and pharmacodynamic sensitivity to benzodiazepines
• No age-related changes in human benzodiazepine receptor binding in PET studies
• Mechanism of pharmacodynamic sensitivity remains unclear

AGE AND OPIOID SENSIVITY
FENTANYL sensitivity increased more than twofold between the ages of 20 and 90 in healthy volunteers.
ALFENTANIL showed similar changes. No age-related changes in pharmacokinetics of either drug.
Scott JC and Stanski DR. J Pharmacol Exp Ther 1987; 240: 159-66

Central Nervous System
Changes in the elderly
• Reduced brain weight
• Decline in grey matter
• Decreased number of synapses
• Reduced cerebral blood flow

Renal pharmacodynamics in the elderly
• Age and the excretion of water and sodium load

Free water clearance in young and elderly
Healthy elderly had lower hourly free water clearances (CH₂O) as compared with the young and a greater decline in serum osmolality in response to water loading.
HCTZ impaired minimum urine osmolality and CH₂O and delayed recovery of serum osmolality after the water load in both healthy young and old.

Free water clearance in young and elderly
The ability of younger individuals to excrete free water, when given ibuprofen, approaches that in elderly.
Defect in elderly may be due to lower renal prostaglandin production.
Hepatic pharmacodynamics in the elderly

• Oral anticoagulants

Warfarin concentration-response relationships

Concentration–response relationships for warfarin were calculated for 14 patients aged between 33 and 79 years by reducing the dose by 0.5-1 mg every two weeks.

The warfarin concentration required to produce a prothrombin time ratio of 1.8 was calculated.


THE FREE PLASMA WARFARIN CONCENTRATION PRODUCING A GIVEN INR FALLS WITH INCREASING AGE

\[ r = 0.682 \]
\[ p < 0.01 \]
\[ N = 14 \]

• The elderly respond differently to a variety of agents
• This may have pharmacokinetic and pharmacodynamic causes
• Reduced homeostasis and “reserve” play a major role
• These changes have importance consequences on safe drug use in the elderly


ADVERSE DRUG REACTIONS IN THE ELDERLY

• Extent of the problem
• Nature of the problem
• Recognition and reporting of ADRs
• Avoidance of ADRs

IATROGENIC DISEASE: THE GREAT MASQUERADER

• Increased prevalence of disease in elderly
• Stoicism in the elderly
• Increased Herbal and Over the Counter (OTC) use in elderly

PHOCOMELIA IN GERMANY 1959-61

ADVERSE DRUG REACTIONS IN THE ELDERLY

- Extent of the problem
- Nature of the problem
- Recognition and reporting of ADRs
- Avoidance of ADRs

PRESCRIBING IN THE ELDERLY

- Is drug therapy required?
- If yes, which drug is appropriate?
  - Careful with anticoagulants, anticholinergics, neuroleptics, NSAIDs, benzodiazepines
- What dose should I start with?
- Should I rationalise existing therapy?
- Will concordance (compliance) be an issue?
- How should I monitor therapy?
  BESPOKE PRESCRIBING

ANTICOAGULANTS and NSAIDs

- Adjusted incidence of hospitalisation for *haemorrhagic* peptic ulcer disease in patients aged 65 or more receiving oral anticoagulants = 10.2 per 1000 person years. Relative risk (rr) compared with non users = 3.3
- Relative risk of hospitalisation for *haemorrhagic* peptic ulcer disease in patients aged 65 or more on NSAIDs = 2.0
- Relative risk in patients aged 65 or more on oral anticoagulants and NSAIDs = 12.7

3.3 + 2.0 = 12.7

PREVALENCE OF NSAID AND ORAL ANTICOAGULANT USE IN THE ELDERLY

Shorr RI et al., Arch Intern Med 1993; 153: 1665-70
THE DAILY MAINTENANCE DOSE OF WARFARIN CAN BE PREDICTED BY THE RESPONSE TO A FLEXIBLE LOADING DOSE


**PROBLEMS WITH FIXED-DOSE ANTICOAGULANT REGIMENS**

"Over-anticoagulated"  "Under-anticoagulated"

**THE DAILY MAINTENANCE DOSE OF WARFARIN CAN BE PREDICTED BY THE RESPONSE TO A FLEXIBLE LOADING DOSE**

**BESPOKE PRESCRIBING OF WARFARIN**

- Methods developed in Cardiff
- Now part of British Society Of Haematology Guidelines
- On inpatient anticoagulant form

**Creatinine concentration and renal function**

- 40 year old male
  - weight 90 kg
  - Plasma creatinine 120 micromol/l
  - GFR 90 ml/min (normal renal function)

- 90 year old female
  - weight 45 kg
  - Plasma creatinine 120 micromol/l
  - GFR 19 ml/min (moderate renal impairment)

\[
\text{Creatinine Clearance} = \frac{140 - \text{age (years)}}{\text{body weight (kg)}} \times 0.82 \times \text{plasma creatinine (µmol/l)} \\
\text{Multiply result by 0.85 for female}
\]

**BESPOKE PRESCRIBING**

- Calculating Glomerular filtration rate

**DRUGS EXCRETED TO A LARGE EXTENT BY GLOMERULAR FILTRATION**

- Aminoglycoside antibiotics (e.g. gentamicin)
- Digoxin
- Atenolol
- Some ACE inhibitors (active metabolites)
- Allopurinol (active metabolite)
- Many diuretics
- Lithium

**THE IMPORTANCE OF A DRUG HISTORY**

- 545 discrepancies in 239 patients (76%) between what doctors prescribed and what patients were taking
- Correlation with patient age and number of recorded medications
- OTC or herbal therapies involved in one third of discrepancies


**BESPOKE PRESCRIBING**

**DRUGS EXCRETED TO A LARGE EXTENT BY GLOMERULAR FILTRATION**

- Aminoglycoside antibiotics (e.g. gentamicin)
- Digoxin
- Atenolol
- Some ACE inhibitors (active metabolites)
- Allopurinol (active metabolite)
- Many diuretics
- Lithium
Therapeutic drug monitoring

- Aminoglycosides
- Lithium
- Cyclosporin
- Digoxin
- Theophylline
- Phenytoin
- Carbamazepine

CONCLUSIONS

- The elderly are exposed to more medicines and have an increased risk of Type A (and of some Type B) adverse reactions
- Medicines should be reviewed regularly
- Doses should be titrated carefully if pharmacokinetic or pharmacodynamic sensitivity is likely to be a problem
- Age is not a reason for withholding effective therapies