DRUG THERAPY IN ELDERLY PEOPLE

Dr. R. Jamuna Rani MD,
Professor & HOD,
Department of Pharmacology
INTRODUCTION

Old people get ill and often have multiple diseases and symptoms requiring treatment; our task is to learn how best to use drugs to treat them in order to MAXIMIZE EFFICACY AND MINIMIZE ADVERSE REACTIONS
INTRODUCTION

The term ‘old people’ implies a homogeneous group, but this is not so. People are very variable in their handling of and responses to drugs, and the degree of biological variability becomes greater as people age, because ageing occurs at different rates in different people.
There are several factors in old people that signal potential trouble, and difficulties in drug therapy. The important factors are: frailty, severe illness, poor appetite and nutrition, poor fluid intake, immobility, multiple diseases, confusion and forgetfulness, and inability for self-care, and lack of supervision.
VARIOUS FACTORS MODIFY DRUG THERAPY IN ELDERLY.

- Pharmaceutical factors – mode of administration;
- Pharmacokinetic factors – absorption, distribution, metabolism, and excretion;
- Pharmacodynamic factors – different pharmacological sensitivity to drug effects;
- Therapeutic and toxic effects peculiar to old people – differences in the disease process and its interaction with drugs;
- Practical matters – appropriate prescribing, compliance, understanding, dosage schedules, and physical problems.
PHARMACEUTICAL FACTORS

Many old people find it difficult to swallow tablets, and more frail, the more ill, the more dehydrated, and the more confused they are the more difficult it becomes. For example, many potassium tablets are quite large and can cause difficulty, particularly as diuretic therapy may have caused dehydration. Some tablets or capsules can adhere to the oesophageal mucosa; to avoid hold-up in the oesophagus, tablets should be swilled down with at least 60 ml of water.

The use of elixirs may help, but not all drugs are available as elixirs, and they have their own problems.
Absorption

ABSORPTION IS AFFECTED IN CHF patients due to mucosal edema and splanchnic vasoconstriction.
(b) Distribution

It is important to adjust dosages for body weight in old people, particularly for drugs with a low therapeutic index.

There are reductions in plasma protein binding of some drugs in old people (for example phenytoin), the fall being accounted for by the fall in plasma albumin concentration with age.
The distribution of body water and fat is altered in old people (see Table 11.1), and lipid-soluble drugs accumulate to a greater extent than in younger patients because of an increased proportion of fat in elderly people. Because of different sources of variability, it is exceedingly difficult to predict what might happen to the apparent volume of distribution of a drug in old people. For instance, the apparent volume of distribution of diazepam is increased while that of nitrazepam is not.
Examination of the literature on the subject of drug metabolism in old people heightens the confusion. For example, the rates of clearance of Warfarin, indomethacin, phenylbutazone, and ethanol are reportedly and unexpectedly unaffected by age.

However, there are some clear-cut examples of reduced drug metabolism in old people, and these include propranolol, lidocaine, theophylline, phenobarbital, and paracetamol.
The example of nifedipine is shown in Fig. 11.2. Plasma nifedipine concentration after an intravenous dose of nifedipine are higher in old people than in the young, and this difference is entirely attributable to reduced metabolism of nifedipine to its metabolite nitropryridine, the apparent volume of distribution of nifedipine being unaltered in old people. As a result, the half-life of nifedipine is prolonged.
The GFR falls with age, and by the age of 80 years will have fallen to 60-70 ml/min. Tubular function also falls with age. So, drugs that are excreted mainly in the urine, or that have active metabolites which are so excreted, require reductions in dosage. Examples include digoxin, gentamicin and other aminoglycosides, lithium, and procainamide. The reduction in the renal excretion of furosemide that occurs in old people is shown in Fig.11.3.
Some drugs are best avoided in old people. For example, tetracyclines accumulate when renal function is poor, causing nausea and vomiting, which in turn causes dehydration, which may cause further deterioration in renal function. In addition, tetracyclines have an antianabolic action, which worsens uraemia and promotes muscle wasting. All of these adverse effects are particularly hazardous in old people.
For various reasons, drug sensitivity (independent of pharmacokinetics) can be altered in old age; in many cases, this results in increased sensitivity to drugs.

In some cases, altered sensitivity to drugs in old people is due to an alteration in the response of their pharmacological receptors. For example, old people are more sensitive to the effects of digoxin, probably because of increased sensitivity of their Na/K-ATPase. This, combined with their increased susceptibility to potassium loss due to diuretics and their reduced renal function, makes them more liable to digitalis toxicity.
PHARMACODYNAMIC FACTORS

On the other hand, the sensitivity of β-adrenoceptors is reduced in old people, and this may reduce some of the pharmacological effects of β-adrenoceptor agonists and antagonists. An example of this is shown in Fig. 11.4. The increase in heart rate that occurs in response to the β2-adrenoceptor agonist terbutaline is less in old people than in the young.
In other cases, altered sensitivity to drugs in old people can be due to altered physiological responses. For example, there is evidence of reduced baroreceptor function in old people, and this can lead to increased hypotension after the administration of antihypertensive drugs.
Other examples of altered pharmacodynamic sensitivity in old people include increased sensitivity to the anticoagulant effects of warfarin and increased responsiveness of the brain to centrally active drugs, for example hypnotics, sedatives, tranquillizers, antidepressants, and neuroleptic drugs.
THERAPEUTIC AND TOXIC FACTORS PECULIAR TO OLD PEOPLE

Take the treatment of hypertension:

- The cerebral circulation in old people does not autoregulate efficiently;
- Old patients easily become hypovolaemic with diuretics (or even without, if not eating and drinking normally);
- Peripheral autonomic responses are sluggish in response to hypotension.
All these factors make the treatment of hypertension in old people a matter to be careful about, as it is often very easy to produce hypotension inadvertently, causing syncope, which results in a fall, injury (for example fractured femur or subdural haematoma), immobilization, and all the consequent complications, such as hypostatic pneumonia and pulmonary emboli, which can be fatal. It currently is believed that treatment of hypertension in old people is associated with a reduced risk of stroke. Nevertheless, hypotensive therapy should be undertaken with great care in old people, because of these other problems.
Or take diuretic therapy:

- Old people are particularly prone to diuretic-induced hypokalaemia, which may increase the effects of digoxin and cause digitalis toxicity;

- A brisk diuresis in an old man with prostatic enlargement can cause acute urinary retention, and diuretics can also cause urinary incontinence in women;

- In old people, who are at an increased risk of gout anyway, gout is precipitated more easily by diuretics.
Confusion and hyperactivity in an old person are often treated with a neuroleptic drug, such as chlorpromazine or haloperidol, and this can result in severe Parkinsonism, to which old people are more prone.
Inappropriate prescribing is a particular hazard in elderly people. It usually involves a misjudgement of the benefit:risk ratio in the individual patient and is often born of an unrealistic expectation of the likely efficacy of treatment. For instance:
The unreviewed, repeated, and recurrent prescription of non-steroidal anti-inflammatory drugs for osteoarthritis, originally prescribed for a painful joint and continued by the patient for minor joint pain for which paracetamol might be just as effective without the risks of gastrointestinal bleeding;
PRACTICAL MATTERS

- The prescribing of a tricyclic antidepressant to an elderly person with heart failure who is miserable because of feeling ill, being lonely and unable to get out and about, with its dangers of cardiac arrhythmias and worsening of heart failure.
Old people can be slow of comprehension, forgetful, and hard of hearing. They can have difficulty in understanding what to you seem simple instructions. It is worth taking the time to write things down, so that the patient can consult the written instructions when necessary. Writing the names of drugs on bottles may not be enough: In some cases, it is worth writing ‘water tablets’ on a bottle of diuretic tablets, or ‘heart tablets’ on a bottle of digoxin tablets. Remember to write large, since old patients may have poor eyesight.
In general, when prescribing drugs for old people, try to use as few drugs as possible, Avoid polypharmacy, start with low dosages, and increase the dosages carefully only if required. Choose easily swallowed formulations, and keep therapy as simple as possible (for example with once-a-day drugs and formulations).
Liver disease (specially cirrhosis) can influence drug disposition in several ways:

(i) Bioavailability of drugs having high first pass metabolism is increased

(ii) Serum albumin is reduced – protein binding of acidic drugs (Sulfonamides is reduced and more drug is present in the free form)
(iii) Metabolism and elimination of some drugs (morphine, pentobarbitone, lidocaine, propranolol) is decreased and their dose should be reduced.

(iv) Prodrugs needing hepatic metabolism for activation. (eg) Enalapril
Drug action can also be altered in liver disease, (e.g.)

- The sensitivity of brain to depressant action of morphine and barbiturates is markedly increased in cirrhotics – normal doses can produce coma.

- Brisk diuresis can precipitate mental changes in patients with impending hepatic encephalopathy because diuretics cause hypokalemic alkalosis which favours conversion of Ammonium to Ammonia which enters the brain more easily.
- Oral anticoagulants can markedly increase prothrombin time because clotting factors are already low.

- Fluid retaining action of NSAIDs and lactic acidosis due to metformin are accentuated.

- Hepatotoxic drugs should be avoided in liver disease. paracetamol, INH, chlorpromazine
KIDNEY DISEASE

- It markedly affects pharmacokinetics of many drugs as well as alters the effects of some drugs.

- Clearance of drugs that are primarily excreted unchanged (aminoglycosides, digoxin, pheobarbitone) is reduced parallel to decrease in creatinine clearance ($\text{CL}_{\text{cr}}$).
Loading dose of such a drug is not altered (unless edema is present) but maintenance doses should be reduced or dose interval prolonged proportionately. A rough guideline is given in the box:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose rate to be reduced</th>
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<tbody>
<tr>
<td>50-70 ml/min</td>
<td>1.5. times</td>
</tr>
<tr>
<td>30-50 ml/min</td>
<td>2times</td>
</tr>
<tr>
<td>10-30 ml/min</td>
<td>3times</td>
</tr>
<tr>
<td>5 -10 ml/min</td>
<td>6 times</td>
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</tbody>
</table>
The permeability of BBBs is increased in renal failure opiates, phenothiazines, benzodiazepines etc. produced more CNS depression. Pethidine should be avoided because its metabolite nor-pethidine can accumulate on repeated dosing and cause seizures. The target organ sensitivity may also be increased. Antihypertensive drugs produce more postural hypotension in patients with renal insufficiency.
Certain drugs worsen the existing clinical condition in renal failure, (e.g.)
tetracyclines have an anti-anabolic effect and accentuate uraemia; nonsteroidal
antiinflammatory drugs and carbenoxolone cause more fluid retention; potentially
nephrotoxic drugs, Cephaloridine, cephalothin, aminoglycosides,
tetracyclines (except doxycycline), sulfonamides (crystalluria), cyclosporine,
penicillamine, gold, vancomycin should be avoided.
Thiazide diuretics tend to reduce g.f.r.: are ineffective in renal failure and can worsen uraemia. Potassium sparing diuretics are contraindicated; can cause hyperkalemia → cardiac depression. Phenformin is more prone to induce lactic acidosis in patients with kidney disease.
Urinary antiseptics like nalidixic acid, nitrofurantoin and methylamine mandelate do not achieve high concentration in urine and are likely to produce systemic toxicity.