Prescribing medicines for older patients

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Abstract

Prescribing medicines for older patients is more challenging than prescribing for younger adults. The physiological changes and co-morbidities associated with ageing alter both the pharmacokinetic handling of and pharmacodynamic response to drugs. Water-soluble drugs are cleared more slowly with increasing age by virtue of a reduced number of functioning nephrons. Lipid-soluble drugs are cleared more slowly via hepatic metabolism and are distributed into a larger volume as a result of the physiological reduction in the proportion of body water. There can also be changes in the response to drugs because of altered sensitivity of target organs such as the heart, kidney and brain. These changes affect the likely therapeutic response and risk of adverse effects and require careful consideration by prescribers when selecting drugs and dosage regimens. The prevalence of frailty rises dramatically with increasing age and is associated with changes over and above those seen as a result of age alone. Reductions in protein binding and consequent increases in volume of distribution and elimination half-life, as well as reduced hepatic enzyme activity, are seen in frail elderly patients. Awareness of appropriate prescribing guidelines is key to successful management of such patients.

Keywords Adverse drug reactions; ageing; frailty; pharmacodynamics; pharmacokinetics; prescribing

Key points

- The population is progressively ageing so the number of elderly patients with multiple co-morbidities encountered by prescribers is increasing
- Ageing leads to changes in the pharmacokinetic handling of drugs and the pharmacodynamic responsiveness of target tissues, and these changes are made worse in the additional presence of frailty
- Important changes in drug handling with age include water-soluble drugs being cleared more slowly by the kidney, and lipid-soluble drugs being cleared more slowly by the liver and distributed into a larger volume because of the physiological reduction in the proportion of body water
- The ratio of the beneficial therapeutic effects and risk of adverse effects of drugs can be significantly altered in elderly patients, especially because of the vulnerability of organs such as the heart, kidney and brain to toxic effects
- Prescribers can improve outcomes for elderly patients by undertaking effective medication reviews, taking advantage of recently developed tools to identify inappropriate prescribing (e.g. STOPP)

Introduction

The global population is ageing; 841 million people were older than 60 years in 2013 and this figure is set to increase to 2 billion by 2050. The group aged >80 years will expand at the fastest rate. Therefore, doctors increasingly have to possess the necessary skills to prescribe and supervise the use of medicines in this vulnerable group of patients.

Prescribing well for older adults is often challenging. Whereas the benefits of medicines are clear, the risks of adverse effects are increased. These risks can be minimized by a good understanding of the physiological changes that occur with ageing and how these impact on drug pharmacokinetics and pharmacodynamics.

Forty-five per cent of the medications prescribed in the UK are for people aged ≥65 years, and 36% of people aged ≥75 years take four or more prescribed drugs on a daily basis. These figures are likely to rise with growth in the evidence base to support prescribing for this progressively increasing proportion of the population.

Ageing versus frailty

At a physiological level, ageing can be described as the time-related loss of functional units. A functional unit is the smallest structure still capable of performing the specific physiological activity characteristic to the organ involved (e.g. nephrons in the kidney, alveoli in the lung, neurons in the brain). A feature of cellular ageing is disruption of regulatory processes between cells and organs, causing a failure to maintain homeostasis when the body is under stress. Chronic illness in older age can further compound the resulting organ dysfunction.

Ageing is distinct from the clinical state referred to as frailty. Frailty is defined by the progressive physiological decline in multiple body systems resulting in loss of function, loss of physiological reserve and increased vulnerability to disease and death. The recognition and characterization of frailty now features in multiple disciplines and helps to identify patients who are vulnerable to the adverse effects of treatment. Frail older people are the prime users of healthcare resources. Frailty is associated with an exaggeration of the changes in

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pharmacokinetics associated with ageing. Aminoglycosides are excreted 12% more slowly in frail older people than in non-frail older people, independent of age.

The impact of frailty on therapeutic decision-making is illustrated by considering the impact of antihypertensive therapy. The HYVET (HYpertension in the Very Elderly Trial) demonstrated that lowering blood pressure prevents cardiovascular disease in those >80 years of age who are not frail (i.e. have relatively little co-morbidity). In contrast, other studies have shown that frail patients >65 years can have worse outcomes, possibly because of the requirement for higher cerebral perfusion pressures than in their non-frail counterparts.

A variety of frailty scores have been developed and validated against comprehensive geriatric assessment.[1] The key features of frailty include evidence of multisystem dysfunction such as cognitive impairment, impaired mobility and impaired functional capacity.

Pharmacokinetics

Absorption

Pharmacokinetics comprises the processes of liberation, absorption, distribution, metabolism and excretion. Absorption occurs predominantly in the small bowel where the surface area is extensive and, although there is some reduction in this area with ageing, there is no reduction in the rate or extent of absorption of a drugs absorbed by passive diffusion. This is traditionally measured by identifying the appearance of a drug in the blood after oral dosing. It is also a measure of gastric emptying — usually the rate-limiting step in drug absorption. The process of gastric emptying can be increased by drugs such as the prokinetics (e.g. erythromycin, metoclopramide) and reduced by drugs with anticholinergic effects (e.g. tricyclic antidepressants). A few drugs, such as vitamin B_{12}, are absorbed by active mechanisms, for which there is evidence of an age-related decline.

Distribution and metabolism

Before an orally administered drug is presented to the systemic circulation after small bowel absorption, it must pass through the hepatic portal vein. For a lipid-soluble drug, some degree of metabolism would be expected — sometimes in the gut wall but more usually in the liver. This is referred to as first-pass metabolism and it reduces the bioavailability of the drug.

There is a reduction in first-pass metabolism with advancing age. This is probably because of a reduction in liver mass and, for high-clearance drugs, the consequential reduction in blood flow. The bioavailability of drugs undergoing extensive first-pass metabolism can be significantly increased via the reduction in first-pass metabolism. By contrast, the first-pass activation of several pro-drugs, such as the angiotensin-converting enzyme (ACE) inhibitors enalapril and perindopril, can be reduced, resulting in delayed appearance of the active metabolite in the plasma.

Significant changes in body composition occur with advancing age, including a progressive reduction in the proportion of total body water and in lean body mass. This results in a relative increase in body fat. Polar drugs that are mainly water-soluble (e.g. gentamicin, digoxin, lithium, theophylline) tend to have a smaller volume of distribution (V_d), resulting in higher serum concentrations in older people. By contrast, non-polar compounds (e.g. benzodiazepines, morphine, amiodarone) tend to be lipid-soluble, so their V_d increases with age. Increased V_d and elimination half-life ($t_{1/2}$) have been observed for drugs such as diazepam, thiopental, lidocaine and clomethiazole. The reduction in V_d is more than offset by a larger reduction in renal clearance (CL), with a smaller effect on $t_{1/2}$, as shown in the following equation:

$$t_{1/2} = \frac{\ln(2) \cdot V_d}{CL}$$

where ln(2) is the natural log of 2 (0.693).

Protein binding

Acidic compounds (e.g. diazepam, phenytoin, warfarin) bind mainly to albumin, whereas basic drugs (e.g. lidocaine, propranolol) bind to α_1-acid glycoprotein. Although no substantial age-related changes have been observed in the concentrations of either of these proteins, albumin is commonly reduced in malnutrition, chronic illness and frailty, whereas α_1-acid glycoprotein is increased during acute illness. The main factor determining drug effect is the free concentration of the drug. Although plasma protein binding changes might theoretically contribute to drug interactions or physiological effects for drugs that are highly protein-bound, their clinical relevance for ageing itself is limited. Acutely ill frail patients may be an exception, although drug kinetics has been little studied in this group.

Clearance

Renal: ageing is associated with a reduction in the number of functioning nephrons of about 1% per annum.[2] This inevitably reduces the renal clearance of water-soluble drugs, such as digoxin, lithium, gentamicin, risperidone, gabapentin, apixaban, and metabolites such as the active metabolites of ACE inhibitors (e.g. ramiprilat). In the case of renally cleared drugs with wide therapeutic windows (e.g. penicillin), the resulting accumulation is of no clinical relevance.

Glomerular filtration rate (GFR) is routinely estimated by clinical chemistry departments using the Modification of Diet in Renal Disease (MDRD) formula, taking into account serum creatinine, age, gender and ethnic group. The clinical interpretation of the estimated GFR (eGFR) must involve an assessment of muscle bulk. The MDRD formula uses average decline in muscle bulk with age and falsely estimates eGFR for those at the extremes of muscle bulk, such as frail elderly patients.

Hepatic: liver volume can fall by 20–40% across the adult age range, resulting in a similar magnitude of reduction in the hepatic clearance of lipid-soluble drugs (e.g. benzodiazepines, selective serotonin reuptake inhibitors, morphine), resulting in an increase in $t_{1/2}$.[3]

Pharmacodynamics

While the age-related changes in pharmacokinetics described above result in higher plasma concentrations of drugs from a given dose, there may also be changes in sensitivity to the effects of drugs (pharmacodynamics) (Table 1). These changes can be