Clinical pharmacology and physiology of ageing: implications for drug therapy.

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Summary

The size of the oldest old section of the population is rising and as a consequence the prevalence of frailty is rising. The physiological changes with age have important implications for both the pharmacokinetics and pharmacodynamics of drugs. Changes in pharmacokinetics include the reduction in renal clearance of water soluble substances including drugs such as aminoglycosides, lithium and digoxin. These examples are of drugs not only cleared renally but also with a narrow therapeutic window making the risk of toxicity much higher. The physiological reduction in liver volume reduces the hepatic clearance of lipid soluble drugs. In addition, the increase in the proportion of lipid tissue per kg body weight (increasing the apparent volume of distribution) increases the elimination half life (t1/2z) of lipid soluble drugs independently of the prolongation due to reduced clearance. In addition to these changes caused by age related physiology, frailty is associated with further prolongation of t1/2z. Other age related physiological changes with important implications for clinical practice include changes associated with less efficient homeostasis such as reduced baroreflex efficiency and reduced efficiency of balance maintenance. These changes may be potentiated by prescribed medication. Cognitive ageing is associated with reduced attention and decline in some types of memory as well as slower processing. These effects however are very small in magnitude compared to the effects of pathology such as Alzheimer's disease. Dementia of any aetiology will adversely affect both compliance with medication regimens as well as the technique of administration where relevant.

Introduction

The size of the oldest old section of the population is rising and is set to continue to rise with the number of people aged 85+ in the UK predicted to more than double to 3.5 million by 2034 (1). This population has a higher prevalence of chronic illnesses including cardiovascular diseases, cancers, osteoporosis, diabetes, Parkinson's disease, dementia and many other conditions. An increasing body of research is adding further prescribing indications for diseases that occur in the elderly population. This, along with the increasing size of the population means that the numbers of prescriptions for elderly patients are increasing. Depending on the age group between 60% and 80% of elderly people are taking medication and 20% are taking at least five drugs (2). It is also estimated that although those over 75 years account for 14% of the population, they receive 33% of medication prescribed. In the period 2000-2010 the number of items prescribed to the 60+ age group in England has risen from 20.7 to 22.4 per person per year (3).

Individuals age at different rates and there is significant heterogeneity in physiological response. The hallmark of ageing is the progressive reliance on homeostatic reserves. Most organ systems show physiological reduction in function with age although the rate varies between systems within an individual as well as between individuals. There is reduced redundancy of function and ability to repair. The potential for harm from loss of functional reserve is further exacerbated by the increased prevalence of co-existing disease. An understanding of the relationship between physiological ageing and disease is often helpful in the interpretation of physical signs and investigation results.

A number of physiological changes are associated with ageing which have important implications for the pharmacokinetics of drugs.

Age-related changes in physiology, pharmacokinetics and pharmacodynamics

Pharmacokinetics is the description of how the body handles drugs after administration. It incorporates the liberation, absorption, distribution, metabolism and excretion of drugs and their metabolites. These processes are affected by the physiological changes associated with ageing resulting in changes in the pharmacokinetics of drugs.

Absorption
Most drugs are weak acids or bases and are present in solution as both ionised and non-ionised species. Non-ionised drugs are lipid soluble and diffuse easily across the cell membrane. Following liberation some absorption may take place in the stomach, however, for most drugs the large surface area of the small bowel makes it the main site of drug absorption.

With ageing, although many drugs show no change in absorption (4), there is slightly reduced small bowel absorption of some substances (including iron, calcium and glucose). There is slower colonic transit time with age, and an associated decrease in peristalsis, largely due to a loss of neurons involved in control of the GI tract. Passive intestinal permeability is probably unchanged in old age for most

substances. However, active transport of other agents, such as vitamin B12, is impaired. These age-related changes therefore primarily affect drugs with low permeability and low solubility such as cephalexin.

Distribution
The volume of distribution (Vd), also known as apparent volume of distribution, is a term used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing. It is defined as the volume in which an amount of drug would need to be uniformly distributed to produce a given plasma concentration. Put another way it refers to the fluid volume that would be required to contain the entire drug dose in the body at the same concentration as that in the blood or plasma. A drug with a high Vd (eg morphine – 300 litres) implies extensive distribution outside the blood or plasma to other tissues such as fat. The Vd is dependent on lipophilicity (increasing the Vd) and the ability of the drug to bind to plasma proteins such as albumin (acidic drugs) and α1-acid glycoprotein (basic drugs) thus holding drug in the blood compartment and reducing Vd. With ageing there is a decrease in lean body weight, muscle mass and body water and an increase in body fat per kg of body weight. As a result, lipid-soluble drugs such as benzodiazepines, morphine, neuroleptics and amitriptyline have an increased Vd due to the higher proportion of body fat. With ageing the higher Vd for such lipid soluble drugs, (along with reduced clearance) will result in a prolonged t1/2z (see below) and hence drug effects. For water-soluble drugs, Vd will fall.

Protein Binding
Many drugs are protein bound to a varying degree. Bound drugs are inactive. Unbound drug is free to mediate its effect. Most acidic drugs (eg ibuprofen, diazepam, phenytoin, warfarin) bind to albumin. Basic drugs such as lidocaine and tricyclic antidepressants bind to α_1-acid glycoprotein. With healthy ageing there is no substantial change in plasma proteins, however intercurrent illness can result in a drop in albumin and an increase in α_1-acid glycoprotein (as it is an acute phase protein). Chronic disease and frailty tend to accelerate the age-related decline in serum albumin. This can produce clinically significant increases in the free fraction of very heavily protein bound drugs such as ibuprofen (99.5% bound). Other highly protein bound drugs include benzodiazepines (>90%) and many anti-psychotics (>90%). In contrast some drugs are not protein bound at all (eg lithium).

Clearance – hepatic
Metabolism may occur in the gut wall or the liver prior to reaching the systemic circulation. Hepatic metabolism of drugs is dependent on the ability of drugs to penetrate hepatocytes. Lipophilic drugs enter hepatocytes and are metabolised into more hydrophilic compounds that are eliminated mainly through the urine. However, in some cases metabolites are biologically active or even toxic. Thus salbutamol (both enantiomers) is partially metabolised by sulphation with a short t1/2z of around 3 hours. Risperidone is metabolised to an active metabolite (9-OH risperidone), which has a t1/2z of 22 hours versus the parent drug t1/2z of 4 hours. Similarly, diazepam is metabolised to an active metabolite (desmethyl diazepam), amitriptyline is metabolised to nortriptyline and morphine is metabolised to the active metabolite morphine-6-glucuronide. Phase I metabolism introduces a functional group onto the parent compound, generally resulting in loss of pharmacological activity with notable exceptions already referred to. Several studies have shown an age-related decline in the clearance of drugs by phase I metabolism, probably reflecting a reduced hepatic mass as enzyme activity is preserved.

Clearance – renal
Excretion of drugs and metabolites in the urine involves three processes: glomerular filtration, active tubular secretion and passive tubular reabsorption. With ageing, renal mass decreases, as does the glomerular filtration rate (GFR). There is also a reduced ability to concentrate urine and a reduced thirst during water deprivation. Davies and Shock in a classic cross sectional inulin clearance study demonstrated that GFR decreases by about 8ml/min/1.73 m^2 per decade from the fourth decade onwards (5). There is wide individual variability in the age-related fall in GFR, further amplified by the presence of vascular and renal disease. Creatinine clearance is influenced by nutritional status, protein intake, muscle mass, body weight, gender and ethnicity. As people age, muscle mass is reduced and daily urinary creatinine excretion decreases, accompanied by an age-related reduction in creatinine clearance. The combined effect of these changes is that declining GFR in older patients is accompanied by lower rises in serum creatinine than would occur in younger patients.

Reduction in GFR with age affects the clearance of many drugs such as water-soluble antibiotics, diuretics, lithium and water-soluble non-steroidal anti-inflammatory drugs. GFR can be estimated using several equations. The Cockroft and Gault equation uses serum creatinine age, gender and weight (6) whereas the Modification of Diet in Renal Disease (MDRD) study equation uses serum creatinine, age, gender and ethnic group (7).

The adjustment of drug dosing in elderly patients becomes particularly relevant where drugs are substantially or entirely excreted by the kidney. The exception to this rule is where the therapeutic window is wide such as with penicillin. In this situation dosage modification is not needed as high

concentrations are not associated with an increase in adverse drug reactions. Routine pre-prescribing estimation of GFR is an essential adjunct to good prescribing in this vulnerable group. Given that the MDRD eGFR is now routinely provided this is the method of choice.

Where there is a narrow therapeutic index, significant toxicity can occur if doses are not adjusted downwards to account for renal impairment and subsequent reduced excretion. Examples include lithium, aminoglycosides and digoxin. The presence of risk factors for chronic kidney disease such as inadequately controlled hypertension and diabetes may potentiate the age-associated decline in renal function.

Elimination half life
The time taken for the plasma concentration of a drug to be reduced by 50% during the elimination phase is referred to as t1/2z. This is distinct from the absorption half life (t1/2abs) or distribution half life ($t1/2_1$). T1/2z is a function of both volume of distribution and clearance, where clearance is the nominal volume of blood that is cleared of drug per unit time:

$$t1/2z \ \alpha \ Vd/Cl$$

Where t1/2z = elimination half life; Vd = volume of distribution; Cl = clearance

The t1/2z provides a good indication of the time required to achieve steady state after a drug is started, and also an estimate of the time required to remove a drug from the body, and of appropriate dosing intervals. It takes approximately five half lives to reach steady state during chronic dosing and a similar time to remove the drug when dosing is stopped. Thus for amiodarone with a t1/2z in excess of 2 months during chronic dosing in elderly patients, it would take at least 10 months to reach steady state or to remove the drug from the body. For lipid soluble drugs, the elimination half-life increases with age, due to both reduced clearance and increased Vd. For water-soluble drugs such as lithium the reduced volume of distribution partially offsets the effect of reduced clearance on t1/2z.

Pharmacodynamics
Problems arise when older patients are assumed to respond to medications in the same way that a younger adult does. Although pharmacokinetic changes often result in increased drug concentrations for a given dose, changes in sensitivity can modify response to a given concentration – age related change in pharmacodynamics.

Age related physiological changes with important implications for clinical practice include changes associated with less efficient homeostasis such as reduced baroreflex efficiency and reduced efficiency of balance maintenance. These changes may be potentiated by prescribed medication such as antihypertensives and benzodiazepines respectively.

A related confounding factor is that an older patient's underlying pathology may present atypically. For example, painless peptic ulceration and myocardial infarction are both common as are non specific presentations of systemic infections and adverse drug reactions.

Polypharmacy and multiple pathology

One of the accompaniments of ageing is the accumulation of multiple pathology within an individual and is referred to as frailty, which is associated with a poor prognosis. This is in contrast to individuals who have isolated pathology. Associated with multiple pathology, polypharmacy is common in older people, with approximately 20% of people aged over 70 years taking five or more medications (2). In the last decade the average number of items prescribed to people aged 60 and over has almost doubled from 21.2 to 40.8 items per person per year (8). Polypharmacy is derived from the Greek meaning many medications but it has come to mean too many medications. This interpretation is incorrect, as all of the prescribed medications may have an appropriate indication. Polypharmacy is associated with increases in many adverse outcomes, including drug interactions, adverse drug reactions, falls, hospital admissions, length of stay, readmission rate soon after discharge and mortality rate (9). However, some of these effects are likely to be due to polypharmacy acting as a marker of multiple pathology or frailty, as opposed to being an independent risk factor.

Inappropriate prescribing

Inappropriate prescribing as a concept has the advantage over the term polypharmacy as it seeks to address both prescribing without evidence and the absence of prescribing when there is an indication. The latter is particularly important in the context of evidence-based prophylaxis such as heparin prophylaxis of venous thromboembolism, antithrombotic prophylaxis against stroke in atrial fibrillation and fracture prophylaxis in osteoporosis. Apart from being unnecessary, inappropriate medication contributes to the risk of an adverse drug reaction that is directly related to the number of medications

being taken. Adjustments in dose, formulation and delivery need to be made according to the age and frailty of the patient, and some drugs are best avoided altogether. These would include benzodiazepines, long acting hypoglycaemic agents drugs given specifically for their anticholinergic effects.

Implications for prescribing in old age

Medication for chronic disease should be regularly reviewed particularly in older patients where the background pathophysiology would be expected to change. The National Service Framework recommended annual review for patients on less than 4 medications and 6 monthly review for the remainder (10). When reviewing indications for treatment, patient involvement must be sought whenever possible as for adults of any age and new indications, contraindications and interactions sought.

Cognitive ageing is associated with reduced attention and decline in some types of memory as well as slower processing. These effects however are small in magnitude compared to the effects of pathology such as Alzheimer's disease and insufficient to require any change in clinical practice other than might be appropriate for any patient. Dementia of any aetiology may adversely affect both compliance with medication regimens as well as the technique of administration where relevant. Appropriate assessment should focus on both aspects.

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