Pharmacokinetics of drugs in the elderly

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Introduction

Despite the fact that older people comprise only 12-20% of the population in most westernized countries, they receive between 30-40% of prescribed drugs[1]. In addition, they are particularly at risk of developing adverse drug reactions, especially those which are pharmacologically predictable and dose-dependent (type A reactions)[2].

There are many possible reasons for this, some of which are dealt with in this supplement, but one factor is an alteration in pharmacokinetics.

General principles

The term pharmacokinetics describes the fate of a drug in the body and encompasses absorption across the gut wall, first pass metabolism in gut wall and liver, protein binding, distribution throughout the body and elimination by kidney, liver or other routes. Many changes occur with ageing which could theoretically affect these variables (Table 1).

Drug absorption

Although reduced gastric acid production, altered gastric emptying rate and changes in liver and gut blood flow[3-5] may, in theory, affect absorption, age-related changes in absorption across the gut itself are relatively minor, and are probably of limited importance clinically. Some studies have shown that the rate of drug absorption may be slower in the elderly but, in general, age does not seem to be a major influence on the bioavailability of drugs which do not undergo pronounced first pass elimination[6,7].

First pass elimination

Once absorbed from the gut, drugs enter the portal circulation and must pass through the liver before entering the systemic circulation. For polar (water soluble) drugs, which in general are not highly extracted by the liver, first pass metabolism does not greatly affect bioavailability. However, for many lipophilic drugs this first pass through the liver is accompanied by pronounced (sometimes over 90%) extraction, with only 5-10% of the dose reaching the systemic circulation. It is clear that even a small change in hepatic function may result in a large increase in bioavailability in such cases. For example, a fall in extraction from 95-90% would lead to a doubling of bioavailability.

Such changes have been reported for many widely used drugs. Examples include some nitrates; beta-blockers such as propranolol and metoprolol; calcium channel blockers such as nifedipine, verapamil; and so on[8,9]. It should be noted that whilst such changes have been reported even in fit healthy people, they are considerably more marked in the frail and hospitalized elderly.

Table 1. Age-related physiological changes

Change (Ref No.)	*May affect*
Gastric acidity falls (3)	Absorption
Gastric emptying falls (4)	First pass metabolism
Splanchnic blood flow falls (5)	
Body fat increases (6)	Distribution
Body water falls (11)	
Lean body mass falls (6)	
Serum albumin falls (10)	Binding
Liver size falls (23)	Hepatic clearance
Liver blood flow falls (20)	
Glomerular filtration falls (17)	Renal extraction
Renal plasma flow falls (17)	
Renal tubular function falls (18)	

Protein binding and distribution

Many changes occur in body composition with age which could theoretically affect protein binding of drugs and drug distribution to body tissues (Table 1). For example, plasma albumin falls significantly even in the fit elderly[10]. This means that the free fraction of drugs which are heavily bound to albumin (e.g. phenytoin, or warfarin) rises with age. During acute administration this will lead to greater pharmacological activity of the drug. However, a raised free fraction will also result in an increased clearance allowing a new steady-state to be maintained. Total plasma drug concentrations may be lower, but free drug plasma concentrations remain the same since these are determined by hepatic or renal clearance of free drugs.

Age-related changes in distribution also occur. For example, body water falls with ageing[11]. This means that water-soluble drugs are less widely distributed in the elderly than the young, and plasma concentrations per unit dose are relatively higher. A good example of this is seen in the case of alcohol (ethanol) whose distribution volume falls and blood concentrations per unit dose rise with age[12].

In contrast, for lipid-soluble drugs, distribution is more extensive resulting in lower plasma concentrations. The importance of an increased distribution volume lies principally in its effect on half-life and therefore duration of action. Increased distribution volume in the presence of unaltered clearance, results in a lengthening of half-life. This may be particularly important in the case of hypnotic drugs where a 'hangover' effect may become apparent in the elderly[13-16].

Renal clearance

It has been known for many years that, in general, the renal clearance of drugs falls with age, and it is common clinical practice to reduce the dose of renally excreted drugs such as digoxin in the elderly. Parameters that have been shown to decline with age include glomerular filtration rate[17], renal plasma flow[17] and various measures of tubular function[18]. However, it is now known that the age-related fall in renal function is very variable between individuals, and longitudinal studies show that whilst many elderly patients have significantly lowered glomerular filtration rate (perhaps one-quarter of the 'normal' adult value), some elderly people experience a much smaller decrement: a few elderly people maintain essentially normal renal function[19].

This inter-individual variability in the response to the ageing process is a common feature of many physiological functions and in this case highlights the need to tailor drug therapy to the individual patient rather than relying on strict guidelines.

Hepatic clearance

Numerous *in vivo* studies have shown impaired clearance of drugs which are eliminated by the liver in elderly populations, resulting in a propensity to develop type A adverse events.

The hepatic clearance (CL_H) of a drug can be defined as:

$$CL_H = Q.\frac{Ca - Cv}{Ca} = Q \cdot E$$

where Ca and Cv are the arterial and venous concentrations of the drug, Q is hepatic blood flow, and E is the steady-state extraction ratio. Thus, with high extraction drugs, CL_H approaches and is determined by liver blood flow. With low-extraction drugs, when E is small, hepatic clearance is limited by uptake and enzyme activity. Liver size is obviously important for the elimination of both groups of drugs. Age-related changes in many of these variables have been reported. For example, liver blood flow (as measured by indocyanine clearance) may fall by as much as 40% or more between the ages of 20-90 years; a slightly lesser but still significant fall (25-35%) in liver size has been reported, even allowing for changes in body weight[20].

The situation with regard to drug metabolizing enzymes has been less clear for many years. In the early 1960s studies using ageing male rodents reported that the activities of the critical drug metabolizing enzymes, the microsomal monooxygenase system, fell significantly in the old animals[21]. These data were extrapolated to humans. However, direct measurements of various parts of the microsomal monooxygenase system have now shown that any age-related fall in humans (and indeed non-human primates) is minimal, if it occurs at all[22].

Similarly, the activities of glucuronyl transferases and sulpho-transferases do not change significantly with age in either humans or rodents[23,24]. Other enzyme systems including those responsible for acetylation and hydrolysis, esterases for example[25], are also unaffected.

The above comments apply to healthy elderly individuals. In the frail and hospitalized elderly, as defined by Woodhouse *et al.*[26], the activities of certain conjugating enzymes and esterases at least are significantly depressed, again reflecting the increased propensity of this sub-population to type A adverse drug reactions[27].

Ageing and the environment

It has been suggested that one reason why old people suffer adverse drug reactions is that they are unable to increase the activities of drug metabolizing enzymes in response to inducing stimuli. For example, the half-life of marker drugs such as phenazone has been shown to decline significantly in the young after exposure to inducing agents; this did not seem to occur in the elderly. However, some recent data has challenged this. Our own studies using an isolated peripheral blood monocyte model have failed to show impaired induction of the microsomal monooxygenase aryl hydrocarbon hydroxylase in response to *in vitro* stimulation with polycyclic hydrocarbons[28]. Similarly, we have failed to show either a decreased sensitivity of the cell to an inducing stimulus with age[29], or a reduced rate of enzyme induction[30]. Further work is required before the true relationship between the ageing process and induction of drug metabolism is fully understood.

Ageing and injury in the elderly

It is a common clinical experience that all patients who undergo surgery or trauma are particularly likely to suffer adverse drug reactions. There may be many reasons for this, but it has recently been shown that the activities of at least one drug metabolizing enzyme (plasma aspirin esterase) falls markedly at the time of hip fracture, or after elective hip replacement surgery[31]. Were this to be reflected in other pathways of drug metabolism, it could have great clinical significance.

Discussion

(1) Drug absorption across the gut is probably not affected to a clinically important degree by ageing.
(2) First pass metabolism is impaired even in healthy elderly people. This is much more pronounced in frail elderly patients resulting in greater bioavailability of highly extracted drugs.
(3) Drug binding to albumin decreases with age resulting in a higher free fraction of drug. This is important for acute dosage, but is less important at steady-state when new 'normal' free drug concentrations are achieved.
(4) Tissue distribution of drugs alters with age. This is particularly important for lipid-soluble drugs where an apparent increased volume of distribution may lead to a prolongation of half life and, therefore, duration of effect.
(5) Renal function falls with ageing. Reduced renal clearance of many drugs is the result, leading in some cases to toxicity. However, this change is not universal and drug dosage must be tailored to the individual patient.
(6) Hepatic clearance of drugs falls with ageing, largely due to a fall in liver size and blood flow. In healthy elderly people the activities of drug metabolizing enzymes do not appear to be affected. However, in the frail elderly, in those who have suffered injury or have undergone surgery, enzyme activity may be significantly depressed resulting in higher blood concentrations and an increased risk of adverse reactions.

(7) The relationship between age and enzyme induction remains unclear, but it is probably unlikely to be of major clinical importance in the elderly.

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