Prescribing for the elderly patient: why do we need to exercise caution?

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Introduction

Advancing age is accompanied by pharmacokinetic and pharmacodynamic changes which, together with impairment of homeostatic mechanisms and the effect of coexisting disease, contribute to a significant increase in sensitivity to particular drugs and a corresponding increase in the incidence of adverse drug reactions (ADRs). Increasing medical awareness of these facts has not universally been translated into clinical practice as polypharmacy remains a particular problem amongst elderly people and the degree of polypharmacy increases with advancing age [1, 2]. Such prescribing practice serves to further elevate the risk of drug interactions and ADRs, both directly via the synergistic or antagonistic actions of coprescribed drugs, and indirectly by increasing the likelihood of failed compliance.

Pharmacokinetics

Pharmacokinetics comprises drug absorption, distribution and elimination.

Absorption

Numerous gastrointestinal changes occur with age, e.g. increased gastric pH, delayed gastric emptying, decreased intestinal motility and decreased splanchnic blood flow, but surprisingly drug absorption changes very little [3]. However, the fact that older patients are often taking several medications concurrently (both prescribed and over-the-counter preparations) means that it is particularly important to consider the effects of any coprescribed drugs on absorption. For example antacids or bile acid sequestrants may reduce the absorption of certain drugs.

Distribution

Ageing is accompanied by an increase in body fat, a decrease in lean body mass and a decrease in total body water [4]. Since drug distribution depends largely on body composition these changes result in reduced volume of distribution of water soluble drugs, e.g. digoxin (which may lead to increased initial drug concentration) and increased volume of distribution of lipid soluble drugs, e.g. benzodiazepines (which may lead to increased elimination half-life and prolonged effect). Both types of drug may therefore require reduction in dose and/or dose interval. Drug distribution is also affected by binding to plasma proteins, with highly plasma protein bound drugs tending to have a low volume of distribution (the converse is true for poorly bound drugs). Serum albumin levels have been reported to reduce with

age [5] but this may reflect poor nutrition, chronic illness or debility rather than the effects of the ageing process itself and for the vast majority of drugs any changes in protein binding which do occur are not clinically significant. However, in the case of extensively bound drugs just a small reduction in protein binding may result in a clinically significant increase in free drug concentration. Drugs whose reduced protein binding in elderly people may result in adverse reactions include warfarin, tolbutamide, phenytoin and salicylic acid. Coexisting disease (the incidence of which increases with age) may have a more profound effect on serum albumin concentration than age alone and may therefore alter the pharmacokinetics of an even wider range of protein bound drugs.

Elimination

Elimination of most drugs occurs via metabolism in the liver and/or excretion by the kidneys.

Metabolism

Hepatic metabolism comprises phase 1 reactions (oxidation, reduction and hydroxylation, largely performed by the mixed function oxidases such as cytochrome P450) and phase 2 reactions (conjugation with glucuronate, sulphate or acetate). Phase 2 reactions usually involve conjugation of phase 1 metabolites and appear to be unchanged by the ageing process although they may be impaired in some frail elderly people [6, 7]. Phase 1 reactions however, are reduced, probably due to a combination of reduced hepatic blood flow (35% reduction in hepatic blood flow in the elderly) and reduced hepatic volume (hepatic volume is reduced by 28% in men and 44% in women by the age of 91) [8]. The result is that drug metabolism, particularly first-pass metabolism (e.g. propranolol, labetalol, verapamil, metoclopramide, opioids) may be considerably reduced in elderly people. In addition many other factors including smoking, alcohol consumption, coexisting diseases and certain drugs (e.g. erythromycin, amiodarone) can also inhibit hepatic enzymes and so impair drug metabolism still further.

Excretion

Ageing is accompanied by a number of renal changes [9, 10]. These include both reduced glomerular function (GFR is reduced by 6 to 10% per decade after the age of 40 [11]) and reduced tubular function which means that by the age of 90 there may be a 30 to 40% reduction in overall renal function. This results in reduced clearance of both drugs which are mainly excreted via filtration at the kidney, e.g. digoxin and of drugs which are actively secreted by the renal tubules e.g. penicillin. Dose reduction may therefore be required when prescribing such drugs for older patients.

Renal function may also be adversely affected by the presence of coexisting disease e.g. hypertension, diabetes, congestive cardiac failure, or acute illness such as urinary tract infection and dehydration, all of which are common in elderly people.

Pharmacodynamics

Pharmacodynamics concerns drug action and side effects. The pharmacodynamic changes that occur with ageing are complex and have not been well characterised in humans. They depend upon both receptor density, signal transduction (e.g. via cyclic AMP in the case of β -adrenergic receptors) and intracellular response (e.g. biochemical changes or induction of protein transcription). They may also be affected by diet [12]. Reported changes that occur with ageing include increased response (i.e. sensitivity) to warfarin, benzodiazepines and opiates and reduced inotropic and chronotropic responses to β_1 -adrenergic stimulation [13, 14].

Adverse drug reactions

ADRs increase steadily in incidence with age [15] and are three times more common in those over 90 years than in those under 50. This is due not only to pharmacokinetic and pharmacodynamic changes but also to impairment of homeostatic mechanisms. Those mechanisms that are particularly affected by ageing include baroreceptor responses, control of body sway, thirst, volume regulation, glucose and electrolyte control, and thermoregulation. It is therefore not surprising that elderly people are particularly sensitive to drugs which may cause, respectively, postural hypotension (e.g. antihypertensive or antiparkinsonian medication), ataxia (e.g. benzodiazepines), volume depletion and electrolyte imbalance (e.g. diuretics) or hypothermia (e.g. phenothiazines). The scale of the problem is illustrated by the results of studies which show that 10% or more of elderly patient admissions are due to ADRs [16, 17]. Even in hospitalized patients the incidence of ADRs is in the order of 15% [18]. These are usually type A (dose related) rather than type B (idiosyncratic) which implies that they are largely preventable. Lindley *et al.* found that 50% of cases were actually due to inappropriate prescribing [19].

Coexisting disease

The incidence of chronic disease increases with age and some diseases can have profound effects on pharmacokinetics, pharmacodynamics and sensitivity to certain drugs. Renal impairment and congestive cardiac failure are particularly common in elderly people and are discussed below.

Renal failure results in reduced secretion of drugs which are mainly eliminated via the kidneys resulting in both accumulation of the drug and increased length of time to reach steady state plasma levels (takes approximately 5 half-lives). In addition subtle changes in the structure of albumin may result in reduced binding of acidic drugs leading to increased unbound (i.e. biologically active) drug. Increased meningeal permeability can result in increased sensitivity to certain drugs e.g. opiates, barbiturates, phenothiazines, benzodiazepines.

Congestive cardiac failure results in reduced absorption (due to mucosal oedema, reduced epithelial blood supply and splanchnic vasoconstriction), reduced volume of distribution (due to decreased tissue perfusion) and reduced elimination (due to reduced hepatic blood flow, reduced oxidising capacity as a result of hypoxia, reduced GFR and increased tubular reabsorption).

Polypharmacy

Polypharmacy results in both increased likelihood of drug interactions/ADRs and increased tendency to mistakes in drug compliance. Elderly people constitute the major consumers of prescribed medications in this country with about 70% receiving prescribed drugs. Consequently many surveys of prescribing patterns in elderly people have been performed with the fairly unanimous conclusion that polypharmacy is more common in older people and that the degree of polypharmacy increases with advancing age of the patient [2]. One might argue that this trend is expected due to the fact that the incidence of chronic disease and hence subsequent treatment increases with age. However the fact remains that many elderly patients are on unnecessary medications and evidence suggests that infrequent review of patient medication may be a major contributing factor. For example one community survey of elderly people found that 59% of drugs had been prescribed for more than 2 years and 32% for more than 5 years, the vast majority (88%) were issued by repeat prescription and 40% of the patients had not discussed their treatment with a doctor in the previous 6 months [20].

Compliance

Contrary to popular belief an elderly person whose mental function is intact is no more likely to make mistakes with their medication than a younger person. However polypharmacy does make such errors more likely: in one study the incidence of mistakes increased 15-fold when the number of drugs prescribed was increased from 1 to 4 [21]. Consequently accidental errors in drug compliance are very common in elderly people and some of these errors may actually be due to oversights on part of the doctor or pharmacist, for example a patient with arthritic hands may have difficulty in removing child-proof caps or a patient with poor eyesight may not be able to read the instructions on the drug bottle.

Deliberate non-compliance is also a major problem although not one that is specific to elderly people. It may take the form of failing to take prescribed medication as frequently as directed; taking a larger dose in the mistaken belief that it will be more therapeutic or lead to a faster cure; hoarding drugs for future unauthorised use, or self-prescribing with over-the-counter preparations (OTCs). The causes of deliberate non-compliance are multifactorial but contributing factors include ADRs, inconvenience of taking medication and differing perceptions of what is important by doctor and patient.

More detailed reviews of compliance in elderly people have been published elsewhere [22, 23].

Conclusion

The pharmacokinetic, pharmacodynamic and homeostatic changes that occur with age combine with the effects of chronic disease to make the elderly person particularly sensitive to both the desired and adverse effects of many drugs. This is compounded by an increase in both the incidence and degree of polypharmacy. The result is that both ADRs and poor compliance are particularly common in elderly people.

A rational approach to prescribing for elderly people is therefore essential, particularly in the current climate where an increasing number of drugs are becoming available as OTCs. It is our responsibility, as medical practitioners, to minimize polypharmacy; to simplify drug regimens as much as possible (e.g. by using once daily or combined preparations wherever possible); to pay attention to the correct dose and/or dose interval; to consider possible drug interactions, and to communicate effectively with our patients in terms that they will understand. We should provide patients with clear and simple instructions about how much, how often and for how long they should take each of their medications and ensure that the patient knows exactly why he takes each of his drugs, the importance of taking these medications at the correct times and the importance of continuing treatment uninterrupted. Suggested guidelines to aid rational prescribing for elderly people are shown below

Guidelines for Prescribing for Older People

(adapted from Walley & Scott, 1995) [24]

- 1 Appropriate treatment requires adequate clinical assessment and accurate diagnosis
- 2 Problem orientated prescribing, i.e. treat only the disorders that need to be treated
- 3 Keep drug regimens simple
- 4 Use low doses and increase slowly
- 5 Avoid polypharmacy
- 6 Consider potential drug interactions
- 7 Provide patient with clear instructions, both verbal and in writing
- 8 Review patients and their medications regularly
- 9 If in doubt, don't prescribe

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