Pharmacokinetics and pharmacodynamics in the elderly

P Midlöv*

Abstract

Introduction
Pharmacotherapy in the elderly is one of the most challenging aspects of patient care. It is important to understand the pharmacological properties of drugs in elderly patients. Different parts of pharmacokinetics such as distribution, metabolism and renal elimination are affected by age. Renal elimination may be measured or estimated (glomerular filtration rate), whereas other changes are difficult to measure. Pharmacodynamic changes with aging affect both beneficial and adverse effects in many organs.

These age-related changes make elderly patients at greater risk of adverse drug effects. Adjustment in choice of drugs and dosage is advisable. Starting at a low dose and titrating slowly followed by careful evaluation of effects may minimise the risk of adverse effects. It is important to choose the lowest dose required for clinical effect. The aim of this review was to discuss pharmacokinetics and pharmacodynamics in the elderly.

Conclusion

Elderly patients are at greatest risk of adverse drug effects. Optimizing a dosage regimen for an individual patient is important for all patients. Drug dosage should, if possible, be adjusted to the individual organ function.

Introduction

Pharmacotherapy in the elderly is one of the most challenging aspects of patient care. The increased risk of drug–drug interactions and adverse drug effects compared with younger patients makes use of pharmacologic agents in the elderly much more difficult.

Usually, elderly is defined by a chronological age of 65 years or older. One should be aware of the great variability in pharmacokinetics and pharmacodynamics in the elderly. The variability seen in younger persons is much increased in the elderly. Hence, drug treatment in elderly patients should be monitored carefully.

Drugs have been tested primarily in healthy younger persons because they are likeliest to yield results uncomplicated by concomitant other drugs or diseases. Clinicians, therefore, have to make decisions in the absence of evidence-based knowledge. Studies on drug safety are also often done on younger patients with a single medical condition receiving few or no other drugs. This is despite the fact that adverse drug reactions (ADRs) are more frequent and more serious in the elderly. Limited data are available especially in the very old.

Older people should be our focus when studying and reducing drug-related problems (DRPs). A DRP is defined as an event or circumstance involving drug treatment that actually or potentially interferes with a patient’s experiencing an optimum outcome of medical care. According to this definition, DRPs include (ADRs), but also overdosage, subtherapeutic dosage, noncompliance and drug–drug interactions.

Older people are vulnerable to DRPs for several reasons, including physiological alterations that affect pharmacodynamics and pharmacokinetics, resulting in enhanced and prolonged drug effects; increased prevalence of chronic diseases and concomitant use of other medications. Another complicating fact is that the physician is not always aware of what medications the patient is taking. The focus of this review is, however, on pharmacokinetics and pharmacodynamics in the elderly.

Discussion

Age-related physiological alterations

Elderly persons have lower physiological reserves in most organs compared to younger adults, with aging negatively affecting homeostatic mechanisms. Together with the alterations in pharmacodynamics and pharmacokinetics, this increases the risk of ADRs.

Pharmacodynamics

Pharmacodynamics affects not only therapeutic effects but also toxic and adverse effects. Pharmacodynamics depends on the concentration of the drug at the receptor; the response at the receptor, postreceptor events within cells and homeostatic mechanisms. All these parts of pharmacodynamics may be affected with aging. The study of these changes is complicated since the effect of many drugs is also affected by reduced drug clearance in the elderly. Therefore, there is relatively little information about the effect of aging on pharmacodynamics.

Usually, there is an increased sensitivity to the effects of drugs but for some drugs there is a decrease in responsiveness. The same plasma concentration of a drug may be associated with a higher risk of adverse effects in older patients compared to younger patients. All organ systems are affected by these changes.
Critical review

Cardiovascular effects

The effect of β-adrenergic agonists is decreased in the elderly\(^3\). This may result in a decreased effect of beta-blockers on heart rate and stroke volume.

For most other cardiovascular drugs, the elderly have higher risk of adverse events. A common adverse effect in the elderly is orthostatic hypotension due to decreased arterial compliance and baroreceptor reflex response\(^4\). Not only cardiovascular drugs may cause orthostatic hypotension but also, for example, antipsychotic drugs and drugs for Parkinson's disease.

Aging is also associated with other cardiovascular effects, for example, enhanced susceptibility to digoxin toxicity\(^5\).

Effects on central nervous system

Aging is associated with structural and neurochemical changes in the central nervous system (CNS). Due to less effective blood-brain barrier, the brain may be exposed to higher drug levels in the elderly\(^6\).

Several drugs may cause confusion in the elderly. Antipsychotics, anticholinergics and benzodiazepines are common examples. Elderly are more susceptible to adverse effects of benzodiazepines at a given plasma level\(^7\). This increased susceptibility as well as alterations in distribution (described below) make benzodiazepines inappropriate in old patients.

The acetylcholine neurotransmission may be affected at several levels\(^8\). Drugs with anticholinergic effects, for example, drugs for urinary incontinence, cause CNS effects more often in the elderly. Anticholinergic drugs may induce delirium or increase delirium symptom severity in elderly patients\(^9,10\). Another example is that elderly patients with epilepsy have a therapeutic response to antiepileptic medications at lower plasma levels and a higher incidence of adverse effects\(^11\).

Electrolytes

There is a decline in electrolyte homeostatic mechanisms with aging\(^12\). The ability to cope with sudden changes in electrolyte levels is reduced. Old patients have a greater susceptibility to adverse drug effects, for example, hyperkalaemia or hyponatremia. Such adverse effects are quite common. Many different drugs may cause disturbances in electrolyte levels and the clinician has to be aware of this.

Pharmacokinetics

Pharmacokinetic alterations are easier to measure since they affect the plasma concentration of the drug. However, for most drugs pharmacokinetic alterations are seldom measured in clinical practice. The bioavailability of a drug depends on many factors including absorption, distribution, metabolism and elimination. For many drugs, the facts about pharmacokinetics are based on studies on younger adults although mainly elderly patients will use these drugs\(^13\).

The elimination half-life \(t_{1/2}\) of a medication is determined by the volume of distribution \(V_d\) in a given individual divided by its clearance \(Cl\).

This can be expressed as: \(t_{1/2} = 0.693 \times V_d / CI\).

Clearance is mainly hepatic metabolism and renal elimination. The half-life of a medication will increase if clearance decreases or if the volume of distribution is increased.

### Table 1: Physiological alterations with aging that may affect pharmacokinetics

| Pharmacokinetic | Change | Change due to | Clinical importance | Drugs that may be affected (examples) |
|-----------------|--------|---------------|---------------------|--------------------------------------|
| Absorption      | Maybe slowed but the absorbed share is most often not affected | Decreased function of ventricle, intestines and the blood flow to the intestines | Little | Vancomycin, amiodarone, diazepam and flunitrazepam may have increased plasma half-life |
| Distribution    | Decreased volume of distribution of hydrophilic drugs and increased volume of distribution of lipophilic drugs | Decline in fat-free mass and increase in body fat with aging | Important for some drugs | Water-soluble drugs as digoxin and lithium have higher peak plasma concentrations and shorter half-lives |
| Metabolism      | Hepatic metabolism maybe reduced | Decreased hepatic blood flow and liver mass | Important for several drugs | Amlodipine, dilizazem, ropinirole, and theophylline |
| Renal elimination | Renal elimination is reduced | Decreased glomerular filtration rate | Very important | Digoxin, gabapentin, glipizide and hydrochlorothiazide |

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Critical review

Drug absorption

Uptake of drugs administered orally depends on the function of ventricle, intestines and blood-flow to the intestines. Most medications are passively absorbed. In most cases, this is not significantly affected by aging. Diseases that affect gastrointestinal organs or their vasculature may of course affect the absorption of oral drugs.

The absorption rate of drugs administered via transdermal or transmucosal routes may be affected in the elderly because of reduced tissue blood perfusion.

Distribution of drugs

When a drug enters the systemic circulation it will be distributed throughout the body. There is a decline in fat-free mass and body water, whereas there is an increase in body fat in the elderly.

With a decrease in body water, hydrophilic drugs have higher peak plasma concentrations and shorter half-life in the elderly. The elimination half-life of lipid-soluble drugs on the other hand is increased leading to an accumulation of these drugs. Since many drugs that can affect the brain are lipid-soluble, physicians must be aware of the increased risk of cerebral adverse effects in elderly patients.

Drug metabolism

The liver is the most important site of drug metabolism. Aging is associated with a reduction in liver mass and in hepatic blood flow. Age-related changes in the liver have a major impact on hepatic clearance that in turn influences variability in response to medicines in the elderly. Liver metabolism depends on the function and capacity of drug-metabolizing enzymes in the liver and hepatic blood flow. The delivery of drugs to the drug metabolising enzymes within hepatocytes depends on hepatic blood flow and this is known to decrease with age.

There is great inter-individual variability and chronological age is a relatively poor predictor of hepatic clearance.

Renal elimination

Many drugs, including metabolites, are excreted by the kidney. Therefore, dosage adjustment must be made based on renal function.

Renal function is most often assessed by measuring the glomerular filtration rate (GFR). In a healthy young adult, GFR is 100–130 mL/min/1.73 m². Starting from 40 to 50 years of age, GFR appears to decrease approximately 10 mL/min/1.73 m² per decade. The decline in GFR is due to a reduced number of functioning glomeruli. There are, however, great inter-individual differences in this decline and it is, therefore, necessary to estimate GFR before initiating drug treatment in the elderly.

Unfortunately, direct measurement of GFR using exogenous markers—the gold standard method—is both cumbersome and costly. Therefore, other techniques are often used to estimate GFR. Plasma creatinine is the most commonly used marker of renal function. However, it does not reflect GFR precisely since it is influenced by muscle mass, physical activity, protein intake and active secretion of creatinine by the proximal tubule, among other things.

Plasma cystatin C has been suggested as an alternative endogenous biomarker of GFR. However, it too seems to have some limitations. It is, for example, affected by thyroid dysfunction and treatment with glucocorticoids. According to a recent systematic review of the literature, the best way to estimate GFR is to use the mean value of estimated GFR based on both creatinine and cystatin C. For patients over 80 years of age, the evidence is, however, not sufficient on how to estimate GFR.

Drug-drug interactions

Numerous drug–drug interactions have been identified. These interactions can affect pharmacokinetics or pharmacodynamics. Pharmacokinetic interactions one drug changes the absorption, distribution, metabolism or elimination of another drug. Pharmacodynamic interactions occur when one drug changes the response to another drug.

Drug–drug interactions play an important role in patient safety. The risk of drug–drug interactions increases with age and the number of drugs used. Most often drug–drug interactions are preventable.

Some common drug–drug interactions in elderly patients are described in Table 2.

| Drug 1                        | Drug 2                        | Potential outcome                                      |
|-------------------------------|-------------------------------|--------------------------------------------------------|
| Angiotensin converting enzyme | Non-steroidal anti-inflammatory drugs | Hypokalaemia, decline in renal function                |
| Ciprofloxacin                 | Olanzapine                    | Ciprofloxacin inhibits CYP1A2. As a result plasma-concentration of olanzapine increases |
| Digoxin                       | Furosemide                    | Hypokalaemia may increase risk for digitalis-intoxication |
| Nitroglycerin                 | Sildenafil                    | Increased risk of severe hypotension                    |
| Spironolactone                | Potassium chloride            | Hyperkalaemia                                           |
| Verapamil                     | Atenolol                      | Bradycardia and hypotension                            |
| Warfarin                      | Acetylsalicylic acid          | Increased risk of bleeding                              |
Drug–disease interactions
The inter-individual variability in susceptibility to drugs is at least partly explained by differences in multi-morbidity. Diseases that affect the kidneys make the elderly patient more susceptible to ADR due to reduction in renal elimination. Liver diseases as well as cardiac diseases that affect hepatic blood flow may affect drug metabolism. In the same way, diseases that affect other organ systems may make elderly patients even more susceptible to drugs. A few, of the numerous, examples are presented in Table 3.

Drug–food interactions
Drug–food interaction adds variability to effects and adverse effects of drugs.

For example, warfarin is known for its drug–food interactions. Warfarin has a narrow therapeutic interval and food with a high K-vitamin content counteract the effects of warfarin. Other examples are grapefruit juice that inhibits the metabolism of cyclosporine and non-selective monoamine oxidase (MAO) inhibitor with food rich in tyramine. Some fermented and stored products (e.g. some cheese, sausages, red wine) contain tyramine that is metabolised to noradrenaline, which in conjunction with MAO inhibitors may block MAO and cause a hypertensive crisis. Selgiline and moclobemide are examples of MAO inhibitors.

Adverse drug effects
Adverse drug effects can mimic clinical syndromes in geriatrics. Instead of adding a medication, the clinician should consider the possibility of adverse effects and maybe withdraw a medication. The risk of ADRs is increased for several reasons in the elderly. The changes in pharmacokinetics and pharmacodynamics, the high number of medications and multi-morbidity contribute to this increased risk of ADR. The symptoms of ADR may be harder to detect and misinterpreted as symptoms from a disease or even as ‘normal aging’ in the elderly.

It is important to recognise that adverse effects can occur with drugs and drug dosages unlikely to cause adverse effects in younger adults. ADRs are mostly preventable including the more severe ADRs. Closer monitoring and thorough evaluation of pharmacotherapy is important to be able to prevent ADR.

| Drug                        | Disease                | Potential outcome                        |
|-----------------------------|------------------------|------------------------------------------|
| Anticholinergic drugs       | Dementia               | Delirium                                 |
| Antipsychotics              | Parkinson’s disease    | Worsening of Parkinson’s disease symptoms |
| Aspirin                     | Peptic ulcer disease   | Gastrointestinal bleeding                |
| First-generation calcium channel blockers | Congestive heart failure | Worsening of heart failure |
| Non-steroidal anti-inflammatory drugs | Decreased renal function | Renal failure                            |
| Non-steroidal anti-inflammatory drugs | Heart failure         | Worsening of heart failure               |
| Thiazides                   | Gout                   | Worsening of gout                        |
| Tricyclic antidepressants   | Epilepsy               | Lower seizure threshold (more so if toxic levels of Tricyclic antidepressant) |

Adverse drug withdrawal events
Adverse drug withdrawal events (ADWE) may be caused by a physiological withdrawal reaction but it is also possible that an underlying disease is worsened. Known ADWEs occur after abrupt discontinuation of benzodiazepines or alcohol. It has been shown that ADWEs are common in nursing home residents. Knowledge of ADWE is often sparse and drug discontinuation guidelines may be useful.

Conclusion
Elderly patients are at greatest risk of adverse drug effects. Optimizing a dosage regimen for an individual patient is important for all patients. Drug dosage should, if possible, be adjusted to the individual organ function. Sometimes organ function may be quantified, for example, GFR but that is not always the case. Changes in pharmacodynamics most often result in an increased sensitivity. Adjustment in choice of drugs and dosage is advisable especially for drugs with CNS effects. Starting at a low dose and titrating slowly followed by careful evaluation of effects may minimise the risk of adverse effects. It is important to choose the lowest dose required for clinical effect.

The typical frail elderly patient has multiple diagnoses, is taking several different medications, and has reduced renal function, increased body fat levels and reduced homeostasis. It is important to be aware of the increased risk of ADRs in frail elderly patients. More studies should focus on this neglected patient group.

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