Pharmacokinetics: optimising safe and effective prescribing

SUSAN MAYOR

This article goes back to basics with an update on pharmacokinetics, examining how underlying processes in the body influence the clinical effects and risk of side-effects of drugs that GPs commonly prescribe.

More than one in 20 hospital admissions are associated with adverse drug reactions with most being avoidable, according to a large UK study,¹ and a Scottish general practice study warned that 14% of patients had received at least one prescription likely to cause adverse drug effects in the previous year.² This article provides an update on pharmacokinetics and how to ensure that drugs get to the right place, at the right dose for the right duration to achieve a therapeutic effect, with viewpoints from primary care prescribing experts on practical steps to optimise safe and effective prescribing.

What is pharmacokinetics?

Effective medicines are some of the most important ‘power tools’ in a GP’s toolbox for treating disease and improving health. But, as with any power tool, they bring potential risks. Being clear on how to use a drug effectively and safely in individual patients helps ensure the drug reaches the right place in the body to achieve a therapeutic effect, at the right concentration, for the right amount of time.

Understanding pharmacokinetics, or what the patient’s body does to a drug – in contrast to pharmacodynamics, which describes what a drug does to the body – is a fundamental step in using drugs effectively and safely. “Pharmacokinetics are relevant to both the efficacy and safety of medicines,” points out Dr Rupert Payne, consultant senior lecturer in primary health care at the University of Bristol. “Understanding pharmacokinetics is central to key therapeutic concepts such as drug half-life, loading doses and therapeutic monitoring, and can help prescribers optimise medication regimens for individual clinical circumstances.”

Pharmacokinetics describes how a drug moves into, through and out of the body, tracking its absorption, distribution, metabolism and excretion (or ADME, for short), which together control the concentration of the drug in the body over time (see Table 1).
Absorption is the process by which a drug enters the systemic circulation following administration by mouth, inhalation, through the skin either by subcutaneous or transdermal routes, or by injection.

Distribution is a reversible process by which a drug moves from the blood to other tissues and depends on the drug’s protein binding and ability to cross cell membranes.

Metabolism of drugs occurs mainly in the liver by processes involving oxidation and conjugation. The enzymes catalysing oxidation collectively constitute cytochrome P450. Conjugation involves adding an endogenous group (such as glucuronic acid) to the active drug or its oxidative metabolite, rendering it inactive. Lipid-soluble drugs have to be converted to more water-soluble metabolites before they can be excreted in the bile and/or urine.

Excretion removes drugs from the body. Water-soluble drugs are generally excreted by the kidneys but can also be excreted by hepatocytes into the bile, usually in conjugated form.

Table 1. Pharmacokinetics: the key processes controlling drug concentrations in the body

<table>
<thead>
<tr>
<th>Process</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>The process by which a drug enters the systemic circulation following</td>
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</tr>
<tr>
<td>Metabolism</td>
<td>The process by which drugs are metabolised within the body.</td>
</tr>
<tr>
<td>Excretion</td>
<td>The process by which drugs are removed from the body.</td>
</tr>
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Table 2. Examples of drugs that can cause problems due to their pharmacokinetics

- Digoxin
- Warfarin
- Morphine and morphine preparations
- Fentanyl
- Amiodarone
- Phenytoin
- Lithium
- Benzodiazepines (in older people)
- Simvastatin

The practical implications

Pharmacokinetics can sound rather dry, but understanding the basic principles can help prescribers to be clear about:

- What dose of a drug to give to a particular patient
- How frequently to give a drug
- How to change the dose/route in particular situations
- How some drug interactions occur (and, more importantly, how to avoid them).

Understanding pharmacokinetics underpins selection of the dose and dosing interval for a drug to ensure that the target tissues are exposed to effective drug concentrations for a sufficient length of time.

“Pharmacokinetics are an important issue for GPs. Most of us probably don’t think about how we use drugs in terms of pharmacokinetic concepts but they explain why drug dosing intervals matter and why we need to take account of how drugs are metabolised,” says Dr Martin Duerden, a GP in Conwy, clinical adviser on prescribing to the RCGP and senior clinical lecturer at the University of Bangor. “It is really useful to have a basic understanding of how long it takes for drugs to work, which is based on pharmacokinetics. It is also important to know the point at which to assess a patient’s response to a drug and when we might need to adjust the dose according to that response.”

Drug-related factors affecting pharmacokinetics

The physicochemical properties of a drug, including its solubility and permeability, affect its absorption. Lipid-soluble drugs are absorbed rapidly while absorption of water-soluble drugs is slower. In terms of drug distribution throughout the body, some drugs bind to circulating proteins (usually albumin) but have to be unbound to have a pharmacological effect. Protein binding is clinically important only for drugs that are highly protein bound (>90%), such as phenytoin and warfarin, which results in minimal distribution into the tissues.

Drugs with long half-lives (the time it takes for the concentration in the body to be reduced by half) or narrow therapeutic index (the gap between the therapeutic and toxic doses) can also cause problems because of the increased risk of adverse effects. “Warfarin, amiodarone and the benzodiazepines, which are very commonly used in clinical practice, can be problematic because they have very long half-lives and narrow therapeutic indices,” points out Dr Duerden. “Digoxin and paracetamol also have relatively narrow therapeutic indices,” adds Dr Payne, noting that these drugs are also very frequently used in daily clinical practice.

Table 2 lists some of the drugs that can cause particular problems due to their pharmacokinetics. Caution is also needed with drugs that inhibit or induce enzymes in cytochrome P450 systems, such as the antiepileptics phenytoin and carbamazepine (see Table 3). Their use can result in unanticipated adverse reactions or therapeutic failures with drugs that are metabolised by the same enzyme systems. Interactions with warfarin, antidepressants, antiepileptic drugs and statins often involve cytochrome P450 enzymes.

Drug interactions were responsible for more than one in every six (16.6%) of adverse drug reactions that resulted in hospital admissions in a large UK study. These interactions included aspirin with warfarin causing gastrointestinal bleeding, and renal failure associated with the use of combinations of diuretics or concomitant use of diuretics and ACE inhibitors.

Patient-related factors that affect drug pharmacokinetics

A patient’s age, co-morbidities, other drugs they are taking and environmental factors such as food can all affect the efficiency of the processes underpinning drug metabolism.

Ageing

Age has a major effect on how the body handles drugs, with frailty and old age being a common cause of problems with prescription drugs. “As patients get older their ability to metabolise and excrete drugs is reduced. Therefore, drugs that might have seemed appropriate at a standard dose when they were younger start to cause problems,” explains Dr Duerden. Renal function decreases with age, which affects drug excretion, and liver function also falls, so drugs...
are metabolised more slowly. Both of these factors can cause increased blood levels of drugs, which can lead to side-effects. “For example, as people get older their ability to excrete benzodiazepines is considerably reduced, so the effects of the drug are increased and patients may suffer dizziness, feel unsteady or become confused. Suddenly, a drug that was well tolerated when younger leads to falls, fractures and possible hospital admissions,” he notes.

The bioavailability of drugs that undergo extensive first-pass metabolism (where the concentration of the drug is greatly reduced before it enters the general circulation, see Figure 1), such as propranolol and labetalol, can be significantly increased with ageing. In contrast, several ACE inhibitors including enalapril and perindopril are pro-drugs and have to be activated in the liver, which can be slowed or reduced with ageing.

Co-morbidities
A patient’s co-morbidities are increasingly recognised as having an important role in drug effects. “GPs prescribe more treatments because of these co-morbidities and you increase the chances of pharmacokinetic problems and drug interactions with treatments,” points out Dr Duerden. “Not only that but there is also the risk of giving a drug that might interact with one of the patient’s diseases – so-called drug-disease interactions.” A study in Scottish general practice showed the patient characteristic most strongly associated with high risk prescribing was the number of drugs prescribed.2

Patient behaviours
Dietary habits and how drugs are taken can also affect pharmacokinetics. “The absorption and metabolism of medicines can be affected by dietary habits, with some medications, such as fluoxacillin, being absorbed best on an empty stomach,” explains Dr Payne. Absorption can be slowed by a heavy meal or by other drugs that reduce gastric emptying including opiates, tricyclic antidepressants and anticholinergic drugs. “Certain foodstuffs can lead to drug interactions – such as that between grapefruit juice (which inhibits its cytochrome P450 3A4) and statins,” he adds. “And the use of indigestion remedies can lead to premature dissolution of enteric-coated products by increasing gastric pH, or can lead to chelation of elements such as calcium, reducing absorption.”

How patients use medicines can also affect their pharmacokinetics. Patients may inadvertently alter the formulation of medications by opening or cutting enteric-coated drugs or modified-release preparations. “Cutting patches can sometimes be done, depending on patch type, but may adversely affect their adhesiveness. In the case of reservoir patches, such as fentanyl, it can potentially lead to harmful immediate drug release,” warns Dr Payne.

What measures can improve the safety of prescribing?
Researchers from the large UK study on adverse drug reactions recommend that focusing particularly on prescribing in the elderly is a key step for improving safe prescribing.1 “The most important tip, particularly with elderly patients, is...
to think about starting low and going slow in terms of drug dose. Always remember that you are more likely to see problems related to poor drug metabolism and excretion in older people,” cautions Dr Duerden. Checking the BNF (which is updated monthly online) and the summary of product characteristics for a drug is helpful where there may be any concerns about potential adverse drug effects or interactions.

“It is also worth asking patients about medication adherence,” suggests Dr Payne. “For an individual who struggles with an excessive pill burden, can a once-daily preparation, such as a modified-release formulation or an alternative drug with a longer half-life, be used instead?” he says. Simple measures, including regular review of patients’ prescriptions, use of computerised prescribing and working in co-operation with local pharmacists can also help to ensure patients understand how to take their medicines correctly and avoid drug interactions.1

References

Declaration of interests
None to declare.

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POEMs

One-third of adults with diagnosed asthma can be weaned off all asthma meds

Clinical question:
How many adults with physician-diagnosed asthma can safely taper off their asthma medications?

Bottom line:
This study found that current asthma was ruled out after repeated testing in one-third of adults with physician-diagnosed asthma. Patients ruled out for current asthma were less likely to be using asthma medications or daily-controlling medications and less likely to have undergone testing for airflow limitation at the time of initial diagnosis. After one year of follow-up, 2.9% of the patients who tapered off their asthma medications presented with respiratory symptoms and resumed treatment. (LOE=1b)

Reference:

Study design: Cohort (prospective).

Synopsis:
These investigators randomly dialled both landline and mobile phones in Canada to identify a true cohort of adults, 18 years or older, with physician-diagnosed asthma within the previous five years. Exclusion criteria included pregnancy, smoking history greater than 10 pack-years, or the use of long-term oral steroids. Review of medical records allowed collection of data on the determination of the original diagnosis of asthma.

All participants (n=701) underwent assessment with baseline spirometry and continued symptom monitoring using standard tools, as well as serial bronchial challenge testing. Patients using daily medications and not confirmed to have asthma with either baseline spirometry or serial bronchial challenge testing had their medications gradually tapered off over four study visits. Patients with continued negative test results for asthma were followed up clinically and with repeated bronchial challenges over one year. Two pulmonologists independently reviewed all medical records to determine agreement with the final diagnosis for all participants. Discrepancies were resolved by consensus agreement with a third reviewer.

A total of 613 patients (87.4%) completed the study assessment procedures. Of these, 203 (33.1%) had a diagnosis of current asthma ruled out. Patients ruled out for current asthma were less likely to be using asthma medications or daily asthma-controlling medications and less likely to have spirometry or bronchial challenge testing performed at the time of initial diagnosis. After one year of follow-up, six patients (2.9%) in the group who were ruled out for current asthma and tapered off their asthma medications presented with respiratory symptoms and resumed treatment. In 12 patients, a serious alternative respiratory diagnosis – including ischemic heart disease, subglottic stenosis, and bronchiectasis – was made.