Dimension in a Quarter: Part 1 *Pharmacotherapy*

Matthew Young

This is the first in a series of articles that seek to provide some of the theoretical knowledge required to underpin the *Podiatry Competency Framework For Integrated Diabetic Foot Care* (TriePodD-UK, 2012). The information contained in this article is aimed at a Level D (specialist podiatrist or clinician), but is also relevant to the lower or higher levels. The first dimension to be examined is Dimension 4: Pharmacotherapy. Please note that, before prescribing or adjusting any medication, always refer to an up-to-date reference source, such as the British National Formulary and/or the Summary of Product Characteristics for the relevant drug information, including doses, side effects, contraindications, and interactions.

Independent nonmedical prescribing is already a reality for nurses and is also planned for podiatrists. Experience suggests that this will apply mainly to secondary care centres, particularly where there are multidisciplinary teams to mentor the process in the first instance. Within these centres, diabetes foot care is a logical choice for independent prescribing as so many drugs are used in the management of the condition and particularly with antibiotic therapy as delays in waiting for a prescription can be costly in terms of lives and limbs.

However, although not everyone will want to be an independent prescriber, any clinician working in this specialty should understand the drugs their patients are taking, why they are taking them and what potential problems can arise. This will help clinicians recognise problems should they occur. For this reason, pharmacotherapy is a core dimension in the competency framework. This article is an introduction to the theoretical knowledge required to understand the drug therapy taken by people with diabetes and includes information for Dimension 4, Level D/E (TriePodD-UK, 2012), including:

- Awareness of the modes of action and effects of relevant medicines, including pharmacokinetics and pharmacodynamics.
- Awareness of the potential for unwanted effects (e.g. allergic reactions, drug interactions, precautions, contraindications, etc).
- Development of an up-to-date knowledge of relevant products – including formulations, doses, and costs – in the British National Formulary (BNF) drug tariff.
- Awareness of the potential misuses of relevant medicines.
- Awareness of non-treatment, non-drug and drug treatment options (including preventative measures and referrals for non-drug interventions).
- Awareness that patient-specific factors (e.g. age, renal impairment) impact the pharmacokinetics and pharmacodynamics of relevant medicines and that regimens may need to be adjusted based on these factors.

Drugs and diabetic foot disease

People with diabetic foot disease have some of the most complex drug regimens of any condition. The main drug therapy areas for patients requiring diabetic foot care are:

- Diabetes medications – see also Dimension 1.4
- Cardiovascular medications, including blood pressure and risk factor modification

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Article points

1. Independent nonmedical prescribing will be required of podiatrists, mainly within secondary care centres.
2. Theoretical knowledge is vital for practitioners to thoroughly understand the drug therapy taken by diabetes foot patients.
3. When prescribing drugs, it is essential to be aware of the potential for unwanted effects, such as allergic reactions and drug interactions.

Key words

- Pharmacodynamic
- Pharmacokinetic
- Pharmacotherapy

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- Antibiotics – see also Dimension 8.5
- Painful neuropathy medications – see also Dimension 6.5
- Transplant medications.

Patients may also be taking medications for respiratory, gastrointestinal, renal disorders, and many other conditions. In 2005, the average number of different medications taken by people with diabetes per day was 8.9 (standard deviation 3.4). More than 90% had the potential for at least one moderately severe drug–drug interaction, and up to 40% had the potential for at least one severe drug-drug interaction (Ibrahim et al, 2005). The number of drugs available to manage diabetes has increased since 2005 and perhaps, at least from an interaction perspective, it is fortunate that people with diabetes do not take their medication all the time (Miccoli et al, 2011). Promoting adherence to medication is also a vital part of pharmacotherapy and will be discussed in a future issue of *The Diabetic Foot Journal*.

It is important to check for any herbal remedies or supplements that a patient may be taking. These also have the potential for interactions with prescribed drugs. A notable example is St John's Wort, which interacts with many drugs, including statins, blood pressure therapies, and amitriptyline, which are taken by many people with diabetic foot disease.

An article published next quarter will provide specific examples of real-life situations in diabetic foot care practice.

Pharmacokinetics and pharmacodynamics

The term "pharmacodynamics" describes the mechanism of action of a given drug. The majority of drugs either:

- Increase or inhibit normal physiological biochemical processes
- Inhibit pathological processes
- Inhibit the vital processes of infective or parasitic organisms.

Most actions occur through interaction with cellular receptors, typically by either increasing (agonism) or decreasing (inverse agonism) receptor activity. Some occupy receptors and block them (antagonism) and while others influence chemical processes up or down through direct interaction with enzyme-mediated reactions. These actions can be permanent or more usually competitive effects, which are then dose dependent Aspirin has both actions. Low doses of aspirin are enough to irreversibly block cyclo-oxygenase1, while higher doses block both COX-2 and COX-3 inhibitors reversibly. COX-1 inhibition is responsible for the beneficial effects of reducing platelet aggregation. COX-2 and COX-3 inhibition are responsible for anti-inflammatory effects and most of the side effects.

Adverse drug reactions can also occur independently of the known mechanism of action of the drug. Unpredictable side effects include allergic reactions and are often more serious than the predictable ones. All suspected adverse drug reactions – even minor ones – in new drugs and all serious reactions, even in established drugs, should be reported using the yellow card scheme (Medicines and Healthcare products Regulatory Agency, the Yellow Card Scheme [see *https://yellowcard.mhra.gov.uk/*]).

A drug's mechanism of action can result in desired activities, such as angiotensin-converting-enzyme (ACE) inhibitors that interrupt ACE and promote vasodilatation, while lowering blood pressure. They can also have undesired effects, such as in the case of beta-blockers that worsen asthma by inhibiting sympathetic bronchodilatation.

Sometimes the action may deliberately cause cell death through genetic damage or blocking of vital processes, but this is exploited in the action of cytotoxic drugs for chemotherapy or in many antibiotics.

Pharmacokinetics describes the absorption, distribution and elimination of a drug in the body. (*Figure 1*).

Absorption

Most drugs are delivered by the oral route and diabetes can affect this in a number of ways. Slow gastric emptying, impaired bowel functioning (either slow or rapid), particularly with autonomic neuropathy, which is common in people with diabetic foot disease, can alter the absorption of a drug and potentially render it ineffective.

Drugs with low levels of absorption or those that are subject to very high levels of first pass metabolism have a low bioavailability from

the gut and are delivered by alternative routes, including:

- *Buccal:* To avoid first-pass metabolism (e.g. glyceryl trinitrate), or can be used if the stomach is not working (e.g. buccal prochlorperazine for vomiting).
- *Transdermal:* Most drugs need to be formulated specifically to be absorbed through the skin. Patches can provide a slow, steady absorption of a drug, such as long-acting painkillers like fentanyl patches, or hormones, such as oestrogen or testosterone. Repeated applications to the same place increase absorption and sites should be rotated. Topical applications of iodine, corticosteroid creams, and nonsteroidal gels can occasionally have a significant absorption and systemic effects.
- *Rectal and vaginal:* Rectal delivery of drugs is often used if the oral route is not viable. Also, local treatments can be applied directly to these areas to minimise systemic effects, such as clotrimazole pessaries.
- *Inhaled drugs:* These are mainly reserved for local treatments for lung disorders, including bronchodilators, but inhaled antibiotics are sometimes used to get high lung concentrations if systemic side effects are encountered by the patient, while inhaled anaesthetic agents are still used on a regular basis.

Drugs that cannot be reliably absorbed through any of the above routes are usually delivered via injection. Typical examples include insulin, which, despite a brief attempt at inhaled delivery, is still only effective by direct injection to the skin or vein. These can also be affected by local changes, such as poor blood flow when dehydrated, or barriers, such as lipohypertrophy, which can make subcutaneous insulin absorption vary widely.

Poor oral absorption can occasionally be exploited to deliver drugs to the bowel. For example, vancomycin when administered orally is poorly absorbed, but is used to treat C.*difficile* in the colon, yet it must be used intravenously for the treatment of foot infections.

As the kidneys or liver reduce in function due to age or comorbidities, drug metabolism and elimination can be impaired. Common problems include hypoglycaemia with accumulating sulphonylureas in the elderly and the accumulation of opiates in those with liver or renal disease, causing over-sedation.

Distribution

Once absorbed, most drugs bind to plasma proteins for distribution around the bloodstream. However, these proteins might be reduced in chronic poor health or in diabetic nephropathy – both are more common in people with diabetic foot disease. Competition from other drugs may also interfere with this protein binding, displacing the drug into the circulation. Displacement may lead to increased unbound (free) drug levels, which may then increase the effects of a drug and significantly increase the side effects, but it is likely that other mechanisms, such as altered drug clearance, are as, or more, likely to account for these reactions (Rolan, 1994).

Most drugs are then distributed through the target tissue. Depending on their degree of protein binding, or their affinity for fats or water, the apparent volume of distribution of a drug varies. This may also affect the time taken to reach a steady state and the dose required. Another feature of aging is that the volume of distribution of a drug changes and dose adjustment may be required. Similarly, body size has an effect on many drugs

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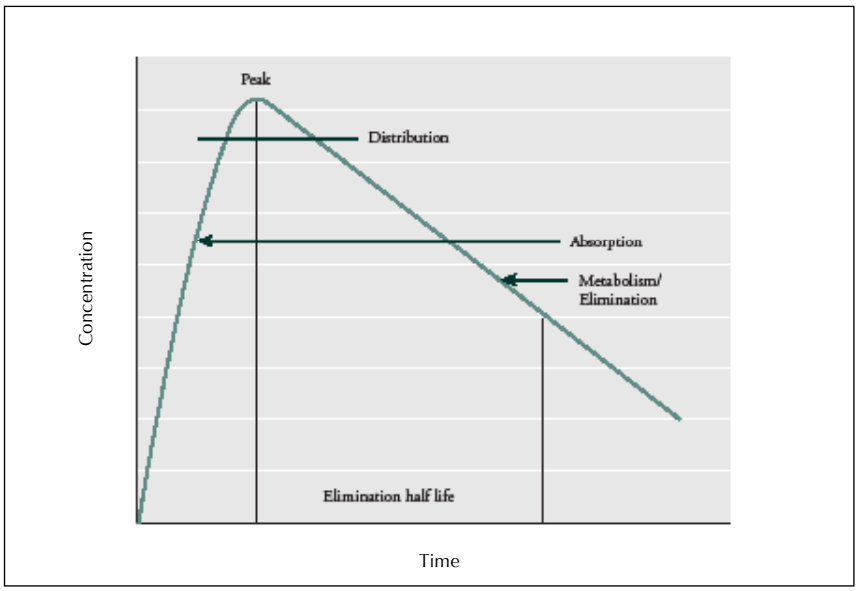

Figure 1. A schematic representation of concentration over time of a single drug dose.

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that are dosed per kilogram, such as gentamicin, or dose adjusted for weight, such as paracetamol, where the maximum single dose is 500 mg in adults under 50 kg, and even less in children.

Elimination

Drugs absorbed from the gut pass through the liver and many are metabolised in first-pass metabolism. Liver dysfunction or interference from drugs which inhibit first pass metabolism can significantly increase effective drug levels and, again, worsen adverse effects. Conversely, other drugs that induce the first pass metabolism enzymes, most notably the cytochrome P450 system, may reduce effective concentrations and lead to therapeutic failure.

For a small number of drugs, such as tramadol, aspirin and enalapril, first-pass (and subsequent) metabolism produces an active metabolite, which is more potent than the original drug and the impact of the liver metabolism changes described above are reversed.

Liver metabolism forms a significant part of the elimination of many drugs. Other drugs are eliminated unchanged from the body. Drugs can be eliminated from the gut unabsorbed or, if through the liver, excreted in bile and eliminated through enterohepatic circulation. Active drug, active metabolites, and inactive metabolites are mainly eliminated through the kidney and the decline in renal function that comes with age and diabetic nephropathy, which is very common in people with diabetic foot disease, can have a major impact on the way drugs are handled, requiring a significant dose adjustment or the avoidance of many drugs altogether.

The small amounts of drug eliminated in sweat, tears, skin, and hair are not enough to impact drug metabolism, but are used for monitoring, particularly of drugs of abuse. Lung excretion is measurable for inhaled anaesthetics and alcohol.

Although not usually a major issue in people with diabetic foot disease – as they are typically older – transplacental and breast milk elimination of drugs can produce significant effects in the children of mothers with diabetes and should be considered for every woman of child-bearing age.

Maintaining drug levels in the body: Half–life, concentration, and dosing

The main objective of administering any drug is to produce a therapeutically appropriate level in the blood for as long as required. This is determined by two key factors, namely the rate of absorption and the rate of elimination. If the levels are too low, the drug will be ineffective, but if the levels are too high, the drug may become toxic.

Most drugs have a minimum effective concentration (MEC) and a maximum safe concentration (MSC). The difference between them is the therapeutic window. The therapeutic index (TI) quantifies the therapeutic window and is defined as the ratio of MEC to MSC where:

$$TI = MSC \div MEC$$

A large TI means a drug is likely to be safer and does not require strict dose monitoring. Examples of drugs with large TIs are phenoxymethyl and benzyl penicillin, of which massive doses can be used in serious infections – over 10 times normal treatment doses. However, given normal patient physiological variation, drugs with a small TI (e.g. heparin, warfarin, digoxin, lithium, or vancomycin) require regular monitoring to ensure they remain within the therapeutic window.

Knowing the TI does not determine what drug dosage to administer; it does not allow for the variation in absorption or the rate of elimination that determine the effective duration of action for a drug.

Half-life refers to the time over which the concentration of a drug will decrease by half. The longer the half-life, the longer the drug will remain in the circulation, and vice versa. Drugs with a short half-life can be administered once or twice a day. Some drugs with short half-lives may be altered – typically a physical or chemical alterations – in the delivery system, such as capsules that produce a more controlled release in the gut and prolong absorption to provide extended drug levels in the body.

Within an individual over the medium term, elimination of a particular drug is constant as drugs are metabolised by the liver and excreted by the kidneys (if functioning normally) at

a continual rate. However, in general, administration tends to be episodic, except for drugs with very rapid elimination where a constant infusion is required to keep a steady state. Examples of this are intravenous insulin infusions for managing ketoacidosis, or nitrates for heart failure.

Drugs with a half-life of 5–7 hours typically need to be administered four times a day, those with a half-life of 10–14 hours, twice a day, etc. However, if a drug has a large TI, a larger dose may be safely given at less frequent intervals.

For most drugs, it takes around five half-life cycles to reach a steady state (*Figure 2*). For this reason, with drugs such as digoxin or warfarin, a loading dose is sometimes used to speed up the time to reach a steady state and produce long-term therapeutic effects. Long-acting insulins, such as glargine, which have an effective half-life of around a day, will take 4–5 days to reach a steady state and, therefore, daily variation in the dose of these insulins will not have a meaningful effect.

In the next issue, we will look at how these principles apply to specific drugs in the care of patients with diabetic foot disease. ■

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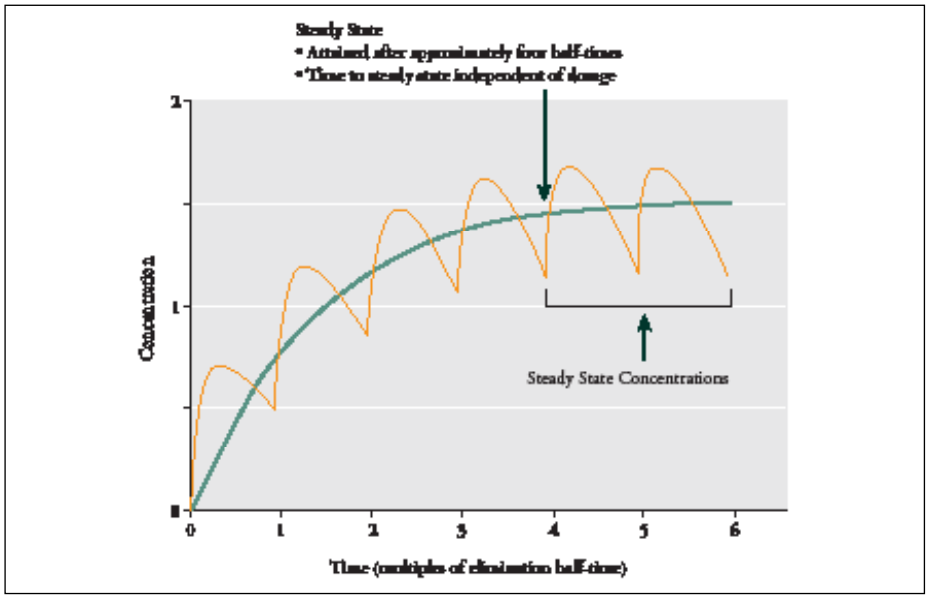

Figure 2. A schematic representation of repeated drug dosing to reach a steady state.

CPD activity

To undertake this CPD activity, you should read the preceding article before answering the multiple choice questions below, but not all answers are contained in the text. An up-to-date British National Formulary should be referred to in answering the following questions. The answers are listed at the bottom of the page.

Classify each of the following statements as true or false (there may be more than one true statement in each question).

1. When taking aspirin...
A. Larger doses are better for preventing vascular events
B. Larger doses are needed for reducing pain and inflammation
C. Bleeding is a predictable side-effect
D. Aspirin-induced asthma in susceptible individuals is an allergic reaction

2. When considering the pharmacokinetics...
A. Diabetic gastroparesis impairs drug absorption
B. Oral vancomycin is effective for systemic infections
C. Grapefruit juice has a major effect on many drugs by inhibiting the cytochrome P450 system
D. Age-related renal impairment alone does not affect drug metabolism.

3. When considering drug elimination...
A. All drugs undergo both significant liver and renal elimination
B. Protein binding alters the rate at which a drug is metabolised and eliminated
C. Doubling the dose of phenytoin typically doubles the blood concentration
D. Steady drinking can reliably keep your blood alcohol level under the legal limit.

4. Adverse drug reactions...
A. Can usually be predicted from the action of the drug
B. Can arise from interactions with other drugs
C. Are usually predictable if serious
D. Should be reported to the Medicines and Healthcare products Regulatory Agency only if serious

5. Diabetic foot patients...
A. Should have a detailed drug history as part of their assessment, including supplements and herbal drugs
B. Are likely to be taking more than eight medications
C. Are at increased risk of drug interactions
D. Are at increased risk of adverse effects due to changes in drug handling

Answers
Q1: A, false; B, true; C, true; D, false.
Q2: A, true; B, false; C, true; D, false.
Q3: A, false; B, true; C, false; D, false.
Q4: A, true; B, true; C, false; D, false.
Q5: A–D, true.