Guide to Good Prescribing

A practical manual

World Health Organization
Action Programme on Essential Drugs
Geneva

A uthors

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W hy you need this book

At the start of clinical training most medical students find that they don't have a very clear idea of how to prescribe a drug for their patients or what information they need to provide. This is usually because their earlier pharmacology training has concentrated more on theory than on practice. The material was probably 'drug-centred', and focused on indications and side effects of different drugs. But in clinical practice the reverse approach has to be taken, from the diagnosis to the drug. Moreover, patients vary in age, gender, size and sociocultural characteristics, all of which may affect treatment choices. Patients also have their own perception of appropriate treatment, and should be fully informed partners in therapy. All this is not always taught in medical schools, and the number of hours spent on therapeutics may be low compared to traditional pharmacology teaching.

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behaviour of their clinical teachers, or existing standard treatment guidelines, without explanation as to *why* certain treatments are chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centred, and although clinical textbooks and treatment guidelines are disease-centred and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

The result of this approach to pharmacology teaching is that although pharmacological knowledge is acquired, practical prescribing skills remain weak. In one study, medical graduates chose an inappropriate or doubtful drug in about half of the cases, wrote one-third of prescriptions incorrectly, and in two-thirds of cases failed to give the patient important information. Some students may think that they will improve their prescribing skills *after* finishing medical school, but research shows that despite gains in general experience, prescribing skills do not improve much after graduation.

Bad prescribing habits lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, distress and harm to the patient, and higher costs. They also make the prescriber vulnerable to influences which can cause irrational prescribing, such as patient pressure, bad example of colleagues and high-powered salesmanship. Later on, new graduates will copy them, completing the circle. Changing existing prescribing habits is very difficult. So good training is needed *before* poor habits get a chance to develop.

This book is primarily intended for undergraduate medical students who are about to enter the clinical phase of their studies. It provides step by step guidance to the process of rational prescribing, together with many illustrative examples. It teaches skills that are necessary throughout a clinical career. Postgraduate students and practising doctors may also find it a source of new ideas and perhaps an incentive for change.

Its contents are based on ten years of experience with pharmacotherapy courses for medical students in the Medical Faculty of the University of Groningen (Netherlands). The draft has been reviewed by a large body of international experts in pharmacotherapy teaching and has been further tested in medical schools in Australia, India, Indonesia, Nepal, Netherlands, Nigeria and the USA (see Box 1).

Box 1:   Field test of the Guide to Good Prescribing in seven universities

The impact of a short interactive training course in pharmacotherapy, using the Guide to Good Prescribing, was measured in a controlled study with 219 undergraduate medical students in Groningen, Kathmandu, Lagos, Newcastle (Australia), New Delhi, San Francisco and Yogyakarta. The impact of the training course was measured by three tests, each containing open and structured questions on the drug treatment of pain, using patient examples. Tests were taken before the training, immediately after, and six months later.

After the course, students from the study group performed significantly better than controls in all patient problems presented ($p < 0.05$). This applied to all old and new patient problems in the tests, and to all six steps of the problem solving routine. The students not only remembered how to solve a previously discussed patient problem (retention effect), but they could also apply this knowledge to other patient problems (transfer effect). At all seven universities both retention and transfer effects were maintained for at least six months after the training session.

This manual focuses on the *process* of prescribing. It gives you the tools to think for yourself and not blindly follow what other people think and do. It also enables you to understand why certain national or departmental standard treatment guidelines have been chosen, and teaches you how to make the best use of such guidelines. The manual can be used for self-study, following the systematic approach outlined below, or as part of a formal training course.

Part 1: The process of rational treatment
This overview takes you step by step from problem to solution. Rational treatment requires a logical approach and common sense. After reading this chapter you will know that prescribing a drug is part of a process that includes many other components, such as specifying your therapeutic objective, and informing the patient.

Part 2: Selecting your P-drugs

This section explains the principles of drug selection and how to use them in practice. It teaches you how to choose the drugs that you are going to prescribe regularly and with which you will become familiar, called P(ersonal)-drugs. In this selection process you will have to consult your pharmacology textbook, national formulary, and available national and international treatment guidelines. After you have worked your way through this section you will know how to select a drug for a particular disease or complaint.

Part 3: Treating your patients

This part of the book shows you how to treat a patient. Each step of the process is described in separate chapters. Practical examples illustrate how to select, prescribe and monitor the treatment, and how to communicate effectively with your patients. When you have gone through this material you are ready to put into practice what you have learned.

Part 4: Keeping up-to-date

To become a good doctor, and remain one, you also need to know how to acquire and deal with new information about drugs. This section describes the advantages and disadvantages of different sources of information.

Annexes

The annexes contain a brief refresher course on the basic principles of pharmacology in daily practice, a list of essential references, a set of patient information sheets and a checklist for giving injections.

> *A word of warning*
>
> Even if you do not always agree with the treatment choices in some of the examples it is important to remember that prescribing should be part of a logical deductive process, based on comprehensive and objective information. It should not be a knee-jerk reflex, a recipe from a 'cook-book', or a response to commercial pressure.

Drug names

In view of the importance that medical students be taught to use generic names, the International Nonproprietary Names (INNs) of drugs are used throughout the manual.

Comments

The WHO Action Programme on Essential Drugs would be very glad to receive comments on the text and examples in this manual, as well as reports on its use. Please write to: The Director, Action Programme on Essential Drugs, World Health Organization, 1211 Geneva 27, Switzerland. Fax 41-22-7914167.

Part 1: Overview

As a first introduction to the rest of the book, this section presents an overview of the logical prescribing process. A simple example of a taxi driver with a cough is followed by an analysis of how the patient's problem was solved. The process of choosing a first-choice treatment is discussed first, followed by a step by step overview of the process of rational treatment. Details of the various steps are given in subsequent chapters.

Chapter 1 page

C hapter 1

The process of rational treatment

This chapter presents a first overview of the process of choosing a drug treatment. The process is illustrated using an example of a patient with a dry cough. The chapter focuses on the principles of a stepwise approach to choosing a drug, and is not intended as a guideline for the treatment of dry cough. In fact, some prescribers would dispute the need for any drug at all. Each of the steps in the process is discussed in detail in subsequent chapters.

A good scientific experiment follows a rather rigid methodology with a definition of the problem, a hypothesis, an experiment, an outcome and a process of verification. This process, and especially the verification step, ensures that the outcome is reliable. The same principles apply when you treat a patient. First you need to define carefully the patient's **problem** (the **diagnosis**). After that, you have to specify the **therapeutic objective**, and to **choose a treatment** of proven efficacy and safety, from different alternatives. You then **start the treatment**, for example by writing an accurate prescription and providing the patient with clear **information and instructions**. After some time you **monitor the results** of the treatment; only then will you know if it has been successful. If the problem has been solved, the treatment can be **stopped**. If not, you will need to re-examine all the steps.

> **Example: patient 1**
> *You sit in with a general practitioner and observe the following case. A 52-year old taxi-driver complains of a sore throat and cough which started two weeks earlier with a cold. He has stopped sneezing but still has a cough, especially at night. The patient is a heavy smoker who has often been advised to stop. Further history and examination reveal nothing special, apart from a throat inflammation. The doctor again advises the patient to stop smoking, and writes a prescription for codeine tablets 15 mg, 1 tablet 3 times daily for 3 days.*

Let's take a closer look at this example. When you observe experienced physicians, the process of choosing a treatment and writing a prescription seems easy. They reflect for a short time and usually decide quickly what to do. But don't try to imitate such behaviour at this point in your training! Choosing a treatment is more difficult than it seems, and to gain experience you need to work very systematically.

In fact, there are two important stages in choosing a treatment. You start by considering your 'first-choice' treatment, which is the result of a selection process done earlier. The second stage is to verify that your first-choice treatment is suitable for this particular patient. So, in order to continue, we should define our first-choice treatment for dry cough.

What is your first-choice treatment for dry cough?

Rather than reviewing all possible drugs for the treatment of dry cough every time you need one, you should decide, in advance, your first-choice treatment. The general approach in doing that is to specify your therapeutic objective, to make an inventory of possible treatments, and to choose your 'P(ersonal) treatment', on the basis of a comparison of their efficacy, safety, suitability and cost. This process of choosing your P-treatment is summarized in this chapter and discussed in more detail in Part 2 of this manual.

Specify your therapeutic objective

In this example we are choosing our P-treatment for the suppression of dry cough.

Make an inventory of possible treatments

In general, there are four possible approaches to treatment: information or advice; treatment without drugs; treatment with a drug; and referral. Combinations are also possible.

Cartoon 1

For dry cough, **information and advice** can be given, explaining that the mucous membrane will not heal because of the cough and advising a patient to avoid further irritation, such as smoking or traffic exhaust fumes. Specific **non-drug treatment** for this condition doesn't exist, but there are a few **drugs** to treat a dry cough. You should make your personal selection while still in medical school, and then get to know these 'P(ersonal) drugs' thoroughly. In the case of dry cough an opioid cough suppressant or a sedative antihistamine could be considered as potential P-drugs. The last therapeutic possibility is to **refer** the patient for further analysis and treatment. For an initial treatment of dry cough this is not necessary.

In summary, treatment of dry cough may consist of advice to avoid irritation of the

lungs, and/or suppression of the cough by a drug.

Choose your P-treatment on the basis of efficacy, safety, suitability and cost

The next stage is to compare the various treatment alternatives. To do this in a scientific and objective manner you need to consider four criteria: efficacy, safety, suitability and cost.

If the patient is willing and able to follow advice to avoid lung irritation from smoking or other causes, this will be therapeutically effective, since the inflammation of the mucous membrane will subside within a few days. It is also safe and cheap. However, the discomfort of nicotine withdrawal may cause habituated smokers to ignore such advice.

Opioid cough depressants, such as codeine, noscapine, pholcodine, dextromethorfan and the stronger opiates such as morphine, diamorphine and methadone, effectively suppress the cough reflex. This allows the mucous membrane to regenerate, although the effect will be less if the lungs continue to be irritated. The most frequent side effects are constipation, dizziness and sedation. In high doses they may even depress the respiratory centre. When taken for a long time tolerance may develop. Sedative antihistamines, such as diphenhydramine, are used as the cough depressant component of many compound cough preparations; all tend to cause drowsiness and their efficacy is disputed.

Weighing these facts is the most difficult step, and one where you must make your own decisions. Although the implications of most data are fairly clear, prescribers work in varying sociocultural contexts and with different treatment alternatives available. So the aim of this manual is to teach you **how**, and not **what**, to choose, within the possibilities of your health care systems.

In looking at these two drug groups one has to conclude that there are not many alternatives available for treating dry cough. In fact, many prescribers would argue that there is hardly any need for such drugs. This is especially true for the many cough and cold preparations that are on the market. However, for the sake of this example, we may conclude that an unproductive, dry cough can be very inconvenient, and that suppressing such a cough for a few days may have a beneficial effect. On the grounds of better efficacy we would then prefer a drug from the group of opioids.

Within this group, codeine is probably the best choice. It is available as tablets and syrup. Noscapine may have teratogenic side effects; it is not included in the British National Formulary but is available in other countries. Pholcodine is not available as tablets. Neither of the two drugs are on the WHO Model List of Essential Drugs. The stronger opiates are mainly indicated in terminal care.

On the basis of these data we would propose the following first-choice treatment (your P-treatment). For most patients with a dry cough after a cold, advice will be effective if it is practical and acceptable for the patient's circumstances. Advice is certainly safer and cheaper than drugs, but if the patient is not better within a week, codeine can be prescribed. If the drug treatment is not effective after one week, the diagnosis should be reconsidered and patient adherence to treatment verified.

Codeine is our P-drug for dry cough. The standard dose for adults would be 30-60 mg 3-4 times daily (British National Formulary). Noscapine and pholcodine could be an alternative.

The process of rational prescribing

Now that we have defined our P-treatment for dry cough, we can review the process of rational prescribing as a whole. This process consists of six steps, each of which is discussed briefly, using the example of our patient with a dry cough. Each step is explained in detail in Part 3.

Step 1: Define the patient's problem

The patient's problem can be described as a persistent dry cough and a sore throat. These are the symptoms that matter to the patient; but from the doctor's viewpoint there might be other dangers and concerns. The patient's problem could be translated into a working diagnosis of persistent dry cough for two weeks after a cold. There are at least three possible causes. The most likely is that the mucous membrane of the bronchial tubes is affected by the cold and therefore easily irritated. A secondary bacterial infection is possible but unlikely (no fever, no green or yellowish sputum). It is even less probable that the cough is caused by a lung tumour, although that should be considered if the cough persists.

Step 2: Specify the therapeutic objective

Continuous irritation of the mucous membranes is the most likely cause of the cough. The first therapeutic objective is therefore to stop this irritation by suppressing the cough, to enable the membranes to recover.

Step 3: Verify whether your P-treatment is suitable for this patient

You have already determined your P(ersonal) treatment, the most effective, safe, suitable and cheap treatment for dry cough in general. But now you have to verify whether your P-treatment is also suitable for this particular patient: is the treatment also **effective** and **safe** in this case?

In this example there may be reasons why this advice is unlikely to be followed. The patient will probably not stop smoking. Even more important, he is a taxi-driver and cannot avoid traffic fumes in the course of his work. So although advice should still be given, your P-drug should also be considered, and checked for suitability. Is it effective, and is it safe?

Codeine is effective, and it is not inconvenient to take a few tablets every day. However, there is a problem with safety because the patient is a taxi-driver and codeine has a sedative effect. For this reason it would be preferable to look for a cough depressant which is not sedative.

Our two alternatives within the group of opiates (noscapine, pholcodine) share the same side effect; this is often the case. The antihistamines are even more sedative and probably not effective. We must therefore conclude that it is

probably better not to prescribe any drug at all. If we still consider that a drug is needed, codeine remains the best choice but in as low a dosage as possible, and for a few days only.

Step 4: Start the treatment

The advice should be given first, with an explanation of why it is important. Be brief and use words the patient can understand. Then codeine can be prescribed: R/codeine 15 mg; 10 tablets; 1 tablet 3 times daily; date; signature; name, address and age of the patient, and the insurance number (if applicable). Write clearly!

Step 5: Give information, instructions and warnings

The patient should be informed that codeine will suppress the cough, that it works within 2-3 hours, that it may cause constipation, and that it will make him sleepy if he takes too much of it or drinks any alcohol. He should be advised to come back if the cough does not go within one week, or if unacceptable side effects occur. Finally he should be advised to follow the dosage schedule and warned not to take alcohol. It's a good idea to ask him to summarize in his own words the key information, to be sure that it is clearly understood.

Step 6: Monitor (stop) the treatment

If the patient does not return, he is probably better. If there is no improvement and he does come back there are three possible reasons: (1) the treatment was not effective; (2) the treatment was not safe, e.g. because of unacceptable side effects; or (3) the treatment was not convenient, e.g. the dosage schedule was hard to follow or the taste of the tablets was unpleasant. Combinations are also possible.

If the patient's symptoms continue, you will need to consider whether the diagnosis, treatment, adherence to treatment and the monitoring procedure were all correct. In fact the whole process starts again. Sometimes there may be no end solution to the problem. For example, in chronic diseases such as hypertension, careful monitoring and improving patient adherence to the treatment may be all that you can do. In some cases you will change a treatment because the therapeutic focus switches from curative to palliative care, as in terminal cancer or AIDS.

Conclusion

So, what at first seems just a simple consultation of only a few minutes, in fact requires a quite complex process of professional analysis. What you should *not* do is copy the doctor and memorize that dry cough should be treated with 15 mg codeine 3 times daily for three days - which is not always true. Instead, build your clinical practice on the core principles of choosing and giving a treatment, which have been outlined. The process is summarized below and each step is fully described in the following chapters.

Summary

The process of rational treatment

> **Step 1:** **Define the patient's problem**
>
> **Step 2:** **Specify the therapeutic objective**
> What do you want to achieve with the treatment?
>
> **Step 3:** **Verify the suitability of your P-treatment**
> Check effectiveness and safety
>
> **Step 4:** **Start the treatment**
>
> **Step 5:** **Give information, instructions and warnings**
>
> **Step 6:** **Monitor (and stop?) treatment**

Part 2: Selecting your P(ersonal) drugs

This section teaches you how to choose your personal selection of drugs (called P-drugs). It explains the principles of drug selection and how to use them in practice. Chapter 2 explains why you should develop your own list of P-drugs. It also tells you how *not* to do it. Chapter 3 gives a detailed example of selecting P-drugs in a rational way. Chapter 4 provides the theoretical model with some critical considerations, and summarizes the process. Chapter 5 describes the difference between P-drug and P-treatment: not all health problems need treatment with drugs.

When selecting your P-drugs you may need to revise some of the basic principles of pharmacology, which are summarized in Annex 1.

Chapter 5

C hapter 2

Introduction to P-drugs

As a doctor you may see 40 patients per day or more, many of whom need treatment with a drug. How do you manage to choose the right drug for each patient in a relatively short time? By using *P-drugs*! P-drugs are the drugs you have chosen to prescribe regularly, and with which you have become familiar. They are your priority choice for given indications.

The P-drug concept is more than just the name of a pharmacological substance, it also includes the dosage form, dosage schedule and duration of treatment. P-drugs will differ from country to country, and between doctors, because of varying availability and cost of drugs, different national formularies and essential drugs lists, medical culture, and individual interpretation of information. However, the principle is universally valid. P-drugs enable you to avoid repeated searches for a good drug in daily practice. And, as you use your P-drugs regularly, you will get to know their effects and side effects thoroughly, with obvious benefits to the patient.

P-drugs, essential drugs and standard treatment guidelines

You may wonder what the relation is between your set of P-drugs and the WHO Model List of Essential Drugs or the national list of essential drugs, and existing standard treament guidelines.

In general, the list of drugs registered for use in the country and the national list of essential drugs contain many more drugs than you are likely to use regularly. Most doctors use only 40-60 drugs routinely. It is therefore useful to make your own selection from these lists, and to make this selection in a rational way. In fact, in doing so you are preparing your own essential drugs list. Chapter 4 contains detailed information on the process of selection.

Institutional, national and international (including WHO) standard treatment guidelines have been developed to deal with the most common conditions, such as acute respiratory tract infections, diarrhoeal diseases and sexually transmitted diseases. They are based on good scientific evidence and consensus between experts. For these reasons they are a valuable tool for rational prescribing and you should consider them very carefully when choosing your P-drugs. In most cases you will want to incorporate them in your practice.

P-drugs and P-treatment

There is a difference between P-drugs and P-treatment. The key point is that not all diseases need to be treated with a drug. Not every P-treatment includes a P-drug! The concept of choosing a P-treatment was already introduced in the previous chapter. The process of choosing a P-drug is very similar and will be discussed in the following chapters.

How <u>not</u> to compile your list of P-drugs

Instead of compiling your own list, one of the most popular ways to make a list of P-drugs is just to copy it from clinical teachers, or from existing national or local treatment guidelines or formularies. There are four good reasons **not** to do this.

✦ You have final responsibility for your patient's well-being and you cannot pass this on to others. While you can and should draw on expert opinion and consensus guidelines, you should always think for yourself. For example, if a recommended drug is contraindicated for a particular patient, you have to prescribe another drug. If the standard dosage is inappropriate, you must adapt it. If you do not agree with a particular drug choice or treatment guideline in general, prepare your case and defend your choice with the committee that prepared it. Most guidelines and formularies are updated regularly.

✦ Through developing your own set of P-drugs you will learn how to handle pharmacological concepts and data. This will enable you to discriminate between major and minor pharmacological features of a drug, making it much easier for you to determine its therapeutic value. It will also enable you to evaluate conflicting information from various sources.

✦ Through compiling your own set of P-drugs you will know the alternatives when your P-drug choice cannot be used, for example because of serious side effects or contraindications, or when your P-drug is not available. The same applies when a recommended standard treatment cannot be used. With the experience gained in choosing your P-drugs you will more easily be able to select an alternative drug.

✦ You will regularly receive information on new drugs, new side effects, new indications, etc. However, remember that the latest and the most expensive drug is not necessarily the best, the safest or the most cost-effective. If you cannot effectively evaluate such information you will not be able to update your list, and you will end up prescribing drugs that are dictated to you by your colleagues or by sales representatives.

C hapter 3

Example of selecting a P-drug: angina pectoris

Example: patient 2

You are a young doctor, and one of your first patients is a 60-year old man, with no previous medical history. During the last month he has had several attacks of suffocating chest pain, which began during physical labour and disappeared quickly after he stopped. He has not smoked for four years. His father and brother died of a heart attack. Apart from occasionally taking some aspirin he has not used any medication in the past year. Auscultation reveals a murmur over the right carotid artery and the right femoral artery. Physical examination reveals no other abnormalities. Blood pressure is 130/85, pulse 78 regular, and body weight is normal.

You are fairly sure of the diagnosis, angina pectoris, and explain the nature of this disease to him. The patient listens carefully and asks: 'But, what can be done about it?'. You explain that the attacks are usually self-limiting, but that they can also be stopped by drugs. He responds 'Well, that's exactly what I need.' You tend to agree that he might need a drug, but which? Atenolol, glyceryl trinitrate, furosemide, metoprolol, verapamil, haloperidol (no, no that's something else) all cross your mind. What to do now? You consider prescribing Cordacor®[1], because you have read something about it in an advertisement. But which dose? You have to admit that you are not very sure.

Later at home you think about the case, and about your problem in finding the right drug for the patient. Angina pectoris is a common condition, and you decide to choose a P-drug to help you in the treatment of future cases.

Choosing a P-drug is a process that can be divided into five steps (Table 1). Many of these are rather similar to the steps you went through in treating the patient with cough in Chapter 1. However, there is an important difference. In Chapter 1 you have chosen a drug for an individual patient; in this chapter you will choose a drug of first choice for a common condition, without a specific patient in mind.

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[1] A fictitious brandname

Each of the steps is discussed in detail below, following an example of choosing a P-drug for angina pectoris.

Table 1:	Steps in choosing a P-drug	
	i	Define the diagnosis
	ii	Specify the therapeutic objective
	iii	Make an inventory of effective groups of drugs
	iv	Choose an effective group according to criteria
	v	Choose a P-drug

Step i: Define the diagnosis

Angina pectoris is a symptom rather than a diagnosis. It can be subdivided into classic angina pectoris or variant angina pectoris; it may also be divided into stable and unstable. Both aspects have implications for the treatment. You could specify the diagnosis of patient 2 as stable angina pectoris, caused by a partial (arteriosclerotic) occlusion of the coronary arteries.

Step ii: Specify the therapeutic objective

Angina pectoris can be prevented and treated, and preventive measures can be very effective. However, in this example we limit ourselves to treatment only. In that case the therapeutic objective is to stop an attack as soon as it starts. As angina pectoris is caused by an imbalance in oxygen need and supply in the cardiac muscle, either oxygen supply should be increased or oxygen demand reduced. It is difficult to increase the oxygen supply in the case of a sclerotic obstruction in the coronary artery, as a stenosis cannot be dilated with drugs. This leaves only one other approach: to reduce the oxygen need of the cardiac muscle. Since it is a life-threatening situation this should be achieved as soon as possible.

This therapeutic objective can be achieved in four ways: by decreasing the preload, the contractility, the heart rate or the afterload of the cardiac muscle. These are the four pharmacological sites of action.[2]

Step iii: Make an inventory of effective groups of drugs

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[2] If you do not know enough about pathophysiology of the disease or of the pharmacological sites of action, you need to update your knowledge. You could start by reviewing your pharmacology notes or textbook; for this example you should probably also read a few paragraphs on angina pectoris in a medical textbook.

The first selection criterion for any group of drugs is **efficacy**. In this case the drugs must decrease preload, contractility, frequency and/or afterload. There are three groups with such an effect: nitrates, beta-blockers and calcium channel blockers. The sites of action are summarized in Table 2.

Table 2: Sites of action for drug groups used in angina pectoris				
	Preload	Contractility	Frequency	Afterload
Nitrates	++	-	-	++
Beta-blockers	+	++	++	++
Calcium channel blockers	+	++	++	++

Step iv: Choose an effective group according to criteria

The pharmacological action of these three groups needs further comparison. During this process, three other criteria should be used: **safety**, **suitability** and **cost of treatment**. The easiest approach is to list these criteria in a table as in Table 3. Of course, efficacy remains of first importance. Cost of treatment is discussed later.

Efficacy is not based on pharmacodynamics alone. The therapeutic objective is that the drug should work as soon as possible. Pharmaco*kinetics* are therefore important as well. All groups contain drugs or dosage forms with a rapid effect.

Safety

All drug groups have side effects, most of which are a direct consequence of the working mechanism of the drug. In the three groups, the side effects are more or less equally serious, although at normal dosages few severe side effects are to be expected.

Suitability

This is usually linked to an individual patient and so not considered when you make your list of P-drugs. However, you need to keep some practical aspects in mind. When a patient suffers an attack of angina pectoris there is usually nobody around to administer a drug by injection, so the patient should be able to administer the drug alone. Thus, the dosage form should be one that can be handled by the patient and should guarantee a rapid effect. Table 3 also lists the available dosage forms with a rapid effect in the three drug groups. All groups contain drugs that are available as injectables, but nitrates are also available in

sublingual forms (sublingual tablets and oromucosal sprays). These are equally effective and easy to handle, and therefore have an advantage in terms of practical administration by the patient.

Cost of treatment

Prices differ between countries, and are more linked to individual drug products than to drug groups. In Table 4, indicative prices for drugs within the group of nitrates, as given in the British National Formulary of March 1994, have been included for the sake of the example. As you can see from the table, there are considerable price differences within the group. In general, nitrates are inexpensive drugs, available as generic products. You should check whether in your country nitrates are more expensive than beta-blockers or calcium channel blockers, in which case they may lose their advantage.

Table 3:	Comparison between the three drug groups used in angina pectoris	
Efficacy	Safety	Suitability
Nitrates		
Pharmacodynamics	*Side effects*	*Contraindictions*
Peripheral vasodilatation	Flushing, headaches, temporary tachycardia	Cardiac failure, hypotension, raised intracranial pressure
Tolerance (especially with constant blood levels)	Nitrate poisoning due to long-lasting oral dosage	Anaemia
Pharmacokinetics		
High first pass metabolism		
Varying absorption in the alimentary tract (less in mononitrates)		
		Fast effect dosage forms:
Glyceryl trinitrate is volatile: tablets cannot be kept long		Injection, sublingual tablet, oromucosal spray
Beta-blockers		
Pharmacodynamics	*Side effects*	*Contraindications*
Reduced heart contractility	Hypotension, congestive heart failure	Hypotension, congestive heart failure
Reduced heart frequency	Sinus bradycardia, AV block	Bradycardia, AV block, sick sinus syndrome
Bronchoconstriction, muscle vasoconstriction, inhibited glycogenolysis	Provocation of asthma Cold hands and feet Hypoglycaemia	Asthma Raynaud's disease Diabetes
Less vasodilatation in penis	Impotence	

Pharmacokinetics		
Lipophilicity increases passage through blood-brain barrier	Drowsiness, decreased reactions, nightmares	Liver dysfunction
		Fast effect dosage forms: Injection
Calcium channel blockers		
Pharmacodynamics	*Side effects*	*Contraindictions*
Coronary vasodilatation		
Peripheral vasodilatation (afterload)	Tachycardia, dizziness, flushing, hypotension	Hypotension
Reduced heart contractility	Congestive heart failure	Congestive heart failure
Reduced heart frequency	Sinus bradycardia, AV block	AV block, sick sinus syndrome
		Fast effect dosage forms: Injection

Table 4:   Comparison between drugs within the group of nitrates

	Efficacy	Safety	Suitability	Cost/100 (£)*
Glyceryl trinitrate	NB: volatile			
Sublingual tab 0.4-1mg	0.5-30 min	No difference	No difference	0.29 - 0.59
Oral tab 2.6mg, cap 1-2.5mg	0.5-7 hours	between	between	3.25 - 4 28
Transdermal patch 16-50mg	1-24 hours	individual	individual	42.00 - 77.00
	NB: tolerance	nitrates	nitrates	
Isosorbide dinitrate				
Sublingual tab 5mg	2-30 min			1.45 - 1.51
Oral tab 10-20 mg	0.5-4 hours			1.10 - 2.15
Oral tab (retard) 20-40mg	0.5-10 hours			9.52 - 18.95
	NB: tolerance			
Pentaeritritol tetranitrate				
Oral tab 30 mg	1-5 hours			4.45
Isosorbide mononitrate				
Oral tab 10-40mg	0.5-4 hours			5.70 - 13.30
Oral tab/caps (retard)	1-10 hours			25.00 - 40.82
	NB: tolerance			

* Indicative prices only, based on prices given in the British National Formulary of March 1994

After comparing the three groups you may conclude that nitrates are the group of first choice because, with acceptable efficacy and equal safety, they offer the advantages of an immediate effect and easy handling by the patient, at no extra cost.

Step v: Choose a P-drug

Choose an active substance and a dosage form

Not all nitrates can be used in acute attacks, as some are meant for prophylactic treatment. In general, three active substances are available for the treatment of an acute attack: glyceryl trinitrate (nitroglycerin), isosorbide mononitrate and isosorbide dinitrate (Table 4). All three are available in sublingual tablets with a rapid effect. In some countries an oromucosal spray of glyceryl trinitrate is available as well. The advantage of such sprays is that they can be kept longer; but they are more expensive than tablets.

There is no evidence of a difference in efficacy and safety between the three active substances in this group. With regard to suitability, the three substances hardly differ in contraindications and possible interactions. This means that the ultimate choice depends on cost. Cost may be expressed as cost per unit, cost per day, or cost per total treatment. As can be seen from Table 4, costs may vary considerably. Since tablets are cheapest in most countries, these might well be your first choice. In this case the active substance for your P-drug of choice for an attack of angina pectoris would be: sublingual tablets of glyceryl trinitrate 1 mg.

Choose a standard dosage schedule

As the drug is to be taken during an acute attack, there is no strict dosage schedule. The drug should be removed from the mouth as soon as the pain is gone. If the pain persists, a second tablet can be taken after 5-10 minutes. If it continues even after a second tablet, the patient should be told to contact a doctor immediately.

Choose a standard duration of the treatment

There is no way to predict how long the patient will suffer from the attacks, so the duration of the treatment should be determined by the need for follow-up. In general only a small supply of glyceryl trinitrate tablets should be prescribed as the active substance is rather volatile and the tablet may become ineffective after some time.

If you agree with this choice, glyceryl trinitrate sublingual tablets would be the first P-drug of your personal formulary. If not, you should have enough information to choose another drug instead.

Summary

Example of selecting a P-drug: angina pectoris

i. Define the diagnosis	Stable angina pectoris, caused by a partial occlusion of coronary artery

Reduce myocardial oxygen need by decreasing preload, contractility, heart rate or afterload

iii. Make inventory of effective groups
   Nitrates
   ß-blockers
   Calcium channel blockers

iv. Choose a group according

to criteria	efficacy	safety	suitability	cost
Nitrates (tablet)	+	±	++	+
Beta-blockers (injection)	+	±	-	-
Calcium channel blockers (injection)	+	±	-	-

v. Choose a P-drug

	efficacy	safety	suitability	cost
Glyceryl trinitrate (tablet)	+	±	+	+
(spray)	+	±	(+)	-
Isosorbide dinitrate (tablet)	+	±	+	±
Isosorbide mononitrate (tablet)	+	±	+	±

Conclusion

Active substance, dosage form:	glyceryl trinitrate, sublingual tablet 1 mg
Dosage schedule:	1 tablet as needed; second tablet if pain persists
Duration:	length of monitoring interval

C hapter 4

Guidelines for selecting P-drugs

Cartoon 2

The previous chapter gave an example of choosing a P-drug for the treatment of acute angina pectoris, on the basis of efficacy, safety, suitability and cost. This chapter presents more general information on each of the five steps.

Step i: Define the diagnosis

When selecting a P-drug, it is important to remember that you are choosing a drug of first choice for a common condition. You are <u>not</u> choosing a drug for an individual patient (when actually treating a patient you will verify whether your P-drug is suitable for that particular case - see Chapter 8).

To be able to select the best drug for a given condition, you should study the pathophysiology of the disease. The more you know about this, the easier it is to choose a P-drug. Sometimes the physiology of the disease is unknown, while treatment is possible and necessary. Treating symptoms without really treating the underlying disease is called symptomatic treatment.

When treating an individual patient you should start by carefully defining the patient's problem (see Chapter 6). When selecting a P-drug you only have to choose a common problem to start the process.

Step ii: Specify the therapeutic objective

It is very useful to define exactly what you want to achieve with a drug, for example, to decrease the diastolic blood pressure to a certain level, to cure an

infectious disease, or to suppress feelings of anxiety. Always remember that the (patho)physiology determines the possible site of action of your drug and the maximum therapeutic effect that you can achieve. The better you define your therapeutic objective, the easier it is to select your P-drug.

Step iii: Make an inventory of effective groups of drugs

In this step you link the therapeutic objective to various drugs. Drugs that are not effective are not worth examining any further, so **efficacy** is the first criterion for selection. Initially, you should look at groups of drugs rather than individual drugs. There are tens of thousands of different drugs, but only about 70 pharmacological groups! All drugs with the same working mechanism (dynamics) and a similar molecular structure belong to one group. As the active substances in a drug group have the same working mechanism, their effects, side effects, contraindications and interactions are also similar. The benzodiazepines, beta-blockers and penicillins are examples of drug groups. Most active substances in a group share a common stem in their generic name, such as dia*zepam*, lora*zepam* and tema*zepam* for benzodiazepines, and propran*olol* and aten*olol* for beta-blockers.

There are two ways to identify effective groups of drugs. The first is to look at formularies or guidelines that exist in your hospital or health system, or at international guidelines, such as the WHO treatment guidelines for certain common disease groups, or the WHO Model List of Essential Drugs. Another way is to check the index of a good pharmacology reference book and determine which groups are listed for your diagnosis or therapeutic objective. In most cases you will find only 2-4 groups of drugs which are effective. In Annex 2 various sources of information on drugs and therapeutics are listed.

> **Exercise**
> **Look at a number of advertisements for new drugs. You will be surprised at how very few of these 'new' drugs are real innovations and belong to a drug group that is not already known.**

Step iv: Choose an effective group according to criteria

To compare groups of effective drugs, you need information on **efficacy**, **safety**, **suitability** and **cost** (Tables 3 and 4). Such tables can also be used when you study other diagnoses, or when looking for alternative P-drugs. For example, beta-blockers are used in hypertension, angina pectoris, migraine, glaucoma and arrhythmia. Benzodiazepines are used as hypnotic, anxiolytic and antiepileptic drugs.

Although there are many different settings in which drugs are selected, the criteria for selection are more or less universal. The WHO criteria for the selection of essential drugs are summarized in Box 2.

Efficacy

This column in Table 3 (Chapter 3) shows data on pharmacodynamics and pharmacokinetics. In order to be effective, the drug has to reach a minimum plasma concentration and the kinetic profile of the drug must allow for this with an easy dosage schedule. Kinetic data on the drug group as a whole may not be available as they are related to dosage form and product formulation, but in most cases general features can be listed. Kinetics should be compared on the grounds of **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion (ADME factors, see Annex 1).

Box 2:   Criteria for the selection of essential drugs (WHO)

Priority should be given to drugs of proven efficacy and safety, in order to meet the needs of the majority of the people. Unnecessary duplication of drugs and dosage forms should be avoided.

Only those drugs for which adequate scientific data are available from controlled clinical trials and/or epidemiological studies and for which evidence of performance in general use in a variety of settings has been obtained, should be selected. Newly released products should only be included if they have distinct advantages over products currently in use.

Each drug must meet adequate standards of quality, including when necessary bioavailability, and stability under the anticipated conditions of storage and use.

The international nonproprietary name (INN, generic name) of the drug should be used. This is the shortened scientific name based on the active ingredient. WHO has the responsibility for assigning and publishing INNs in English, French, Latin, Russian and Spanish.

The cost of treatment, and especially the cost/benefit ratio of a drug or a dosage form, is a major selection criterion.

Where two or more drugs appear to be similar, preference should be given to (1) drugs which have been most thoroughly investigated; (2) drugs with the most favourable pharmacokinetic properties; and (3) drugs for which reliable local manufacturing facilities exist.

Most essential drugs should be formulated as single compounds. Fixed-ratio combination products are only acceptable when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, compliance or cost.

Safety

This column summarizes possible side effects and toxic effects. If possible, the incidence of frequent side effects and the safety margins should be listed. Almost all side effects are directly linked to the working mechanism of the drug, with the exception of allergic reactions.

Suitability

Although the final check will only be made with the individual patient, some general aspects of suitability can be considered when selecting your P-drugs. Contraindications are related to patient conditions, such as other illnesses which make it impossible to use a P-drug that is otherwise effective and safe. A change in the physiology of your patient may influence the dynamics or kinetics of your P-drug: the required plasma levels may not be reached, or toxic side effects may occur at normal plasma concentrations. In pregnancy or lactation, the well-being of the child has to be considered. Interactions with food or other drugs can also strengthen or diminish the effect of a drug. A convenient dosage form or dosage schedule can have a strong impact on patient adherence to the treatment.

All these aspects should be taken into account when choosing a P-drug. For example, in the elderly and children drugs should be in convenient dosage forms, such as tablets or liquid formulations that are easy to handle. For urinary tract infections, some of your patients will be pregnant women in whom sulfonamides - a possible P-drug - are contraindicated in the third trimester. Anticipate this by choosing a second P-drug for urinary tract infections in this group of patients.

Cost of treatment

The cost of the treatment is always an important criterion, in both developed and developing countries, and whether it is covered by the state, an insurance company or directly by the patient. Cost is sometimes difficult to determine for a group of drugs, but you should always keep it in mind. Certain groups are definitely more expensive than others. Always look at the total cost of treatment rather than the cost per unit. The cost arguments really start counting when you choose between individual drugs.

The final choice between drug groups is your own. It needs practice, but making this choice on the basis of efficacy, safety, suitability and cost of treatment makes it easier. Sometimes you will not be able to select only one group, and will have to take two or three groups on to the next step.

Box 3:   Efficacy, safety and cost

Efficacy: Most prescribers choose drugs on the grounds of efficacy, while side effects are only taken into consideration after they have been encountered. This means that too many patients are treated with a drug that is stronger or more sophisticated than necessary (e.g. the use of wide spectrum antibiotics for simple infections). Another problem is that your P-drug may score favourably on an aspect that is of little clinical relevance. Sometimes kinetic characteristics which are clinically of little importance are stressed to promote an expensive drug while many cheaper alternatives are available.

Safety: Each drug has side effects, even your P-drugs. Side effects are a major hazard in the industrialized world. It is estimated that up to 10% of hospital admissions are due to adverse drug reactions. Not all drug induced injury can be prevented, but much of it is caused by

inappropriate selection or dosage of drugs, and you can prevent that. For many side effects, high risk groups can be distinguished. Often these are exactly the groups of patients you should always be very careful with: the elderly, children, pregnant women and those with kidney or liver disease.

Cost: Your ideal choice in terms of efficacy and safety may also be the most expensive drug, and in case of limited resources this may not be possible. Sometimes you will have to choose between treating a small number of patients with a very expensive drug, and treating a much larger number of patients with a drug which is less ideal but still acceptable. This is not an easy choice to make, but it is one which most prescribers will face. The conditions of health insurance and reimbursement schemes may also have to be considered. The best drug in terms of efficacy and safety may not (or only partially) be reimbursed; patients may request you to prescribe the reimbursed drug, rather than the best one. Where free distribution or reimbursement schemes do not exist, the patient will have to purchase the drug in a private pharmacy. When too many drugs are prescribed the patient may only buy some of them, or insufficient quantities. In these circumstances you should make sure that you only prescribe drugs that are really necessary, available and affordable. You, the prescriber, should decide which drugs are the most important, not the patient or the pharmacist.

Step v: Choose a P-drug

There are several steps to the process of choosing a P-drug. Sometimes short-cuts are possible. Don't hesitate to look for them, but do not forget to collect and consider all essential information, including existing treatment guidelines.

Choose an active substance and a dosage form

Choosing an active substance is like choosing a drug group, and the information can be listed in a similar way. In practice it is almost impossible to choose an active substance without considering the dosage form as well; so consider them together. First, the active substance and its dosage form have to be effective. This is mostly a matter of kinetics.

Although active substances within one drug group share the same working mechanism, differences may exist in safety and suitability because of differences in kinetics. Large differences may exist in convenience to the patient and these will have a strong influence on adherence to treatment. Different dosage forms will usually lead to different dosage schedules, and this should be taken into account when choosing your P-drug. Last, but not least, cost of treatment should always be considered. Price lists may be available from the hospital pharmacy or from a national formulary (see Table 4, Chapter 3 for an example).

Keep in mind that drugs sold under generic (nonproprietary) name are usually cheaper than patented brand-name products. If two drugs from the same group appear equal you could consider which drug has been longest on the market (indicating wide experience and probably safety), or which drug is manufactured in your country. When two drugs from two different groups appear equal you can choose both. This will give you an alternative if one is not suitable for a particular patient. As a final check you should always compare

your selection with existing treatment guidelines, the national list of essential drugs, and with the WHO Model List of Essential Drugs, which is reviewed every two years.

Choose a standard dosage schedule

A recommended dosage schedule is based on clinical investigations in a group of patients. However, this statistical average is not necessarily the optimal schedule for your individual patient. If age, metabolism, absorption and excretion in your patient are all average, and if no other diseases or other drugs are involved, the average dosage is probably adequate. The more your patient varies from this average, the more likely the need for an individualized dosage schedule.

Recommended dosage schedules for all P-drugs can be found in formularies, desk references or pharmacology textbooks. In most of these references you will find rather vague statements such as '2-4 times 30-90 mg per day'. What will you choose in practice?

The best solution is to copy the different dosage schedules into your own formulary. This will indicate the minimum and maximum limits of the dosage. When dealing with an individual patient you can make your definitive choice. Some drugs need an initial loading dose to quickly reach steady state plasma concentration. Others require a slowly rising dosage schedule, usually to let the patient adapt to the side effects. Practical aspects of dosage schedules are further discussed in Chapter 8.

Box 4:   General characteristics of dosage forms

Systemic dosage forms
   oral (mixture, syrup, tablet (coated, slow-release), powder, capsule)
   sublingual (tablet, aerosol)
   rectal (suppository, rectiol)
   inhalation (gasses, vapour)
   injections (subcutaneous, intramuscular, intravenous, infusion)

Local dosage forms
   skin (ointment, cream, lotion, paste)
   sense organ (eye drops/ointment, ear drops, nose drops)
   oral/local (tablets, mixture)
   rectal/local (suppository, enema)
   vaginal (tablet, ovule, cream)
   inhalation/local (aerosol, powder)

Oral forms
   efficacy: (-) uncertain absorption and first-pass metabolism, (+) gradual effect
   safety: (-) low peak values, uncertain absorption, gastric irritation
   convenience: (-)? handling (children, elderly)
Sublingual tablets and aerosols
   efficacy: (+) act rapidly, no first-pass metabolism
   safety: (-) easy overdose
   convenience: (-) aerosol difficult to handle, (+) tablets easy to use
Rectal preparations
   efficacy: (-) uncertain absorption, (+) no first-pass metabolism, rectiol fast effect
   safety: (-) local irritation
   convenience: (+) in case of nausea, vomiting and problems with swallowing
Inhalation gasses and vapours
   efficacy: (+) fast effect
   safety: (-) local irritation
   convenience: (-) need handling by trained staff
Injections
   efficacy: (+) fast effect, no first-pass metabolism, accurate dosage possible
   safety: (-) overdose possible, sterility often a problem
   convenience: (-) painful, need trained staff, more costly than oral forms
Topical preparations
   efficacy: (+) high concentrations possible, limited systemic penetration
   safety: (-) sensitization in case of antibiotics, (+) few side effects
   convenience: (-) some vaginal forms difficult to handle

Choose a standard duration of treatment

When you prescribe your P-drug to a patient you need to decide the duration of
the treatment. By knowing the pathophysiology and the prognosis of the disease
you will usually have a good idea of how long the treatment should be

continued. Some diseases require life-long treatment (e.g. diabetes mellitus, congestive cardiac failure, Parkinson's disease).

The total amount of a drug to be prescribed depends on the dosage schedule and the duration of the treatment. It can easily be calculated. For example, in a patient with bronchitis you may prescribe penicillin for seven days. You will only need to see the patient again if there is no improvement and so you can prescribe the total amount at once.

If the duration of treatment is not known, the monitoring interval becomes important. For example, you may request a patient with newly diagnosed hypertension to come back in two weeks so that you can monitor blood pressure and any side effects of the treatment. In this case you would only prescribe for the two week period. As you get to know the patient better you could extend the monitoring interval, say, to one month. Three months should be about the maximum monitoring interval for drug treatment of a chronic disease.

Summary

How to select a P-drug

i **Define the diagnosis (pathophysiology)**

ii **Specify the therapeutic objective**

iii **Make an inventory of effective groups**

iv **Choose a group according to criteria**

	efficacy	safety	suitability	cost
Group 1				
Group 2				
Group 3				

v **Choose a P-drug**

	efficacy	safety	suitability	cost
Drug 1				
Drug 2				
Drug 3				

Conclusion: Active substance, dosage form:
Standard dosage schedule:
Standard duration:

C hapter 5

P-drug and P-treatment

Not all health problems need treatment with drugs. As explained in Chapter l, the treatment can consist of advice and information, non-drug therapy, drug treatments, referral for treatment, or combinations of these. Making an inventory of effective treatment alternatives is especially important in order not to forget that non-drug treatment is often possible and desirable. Never jump to the conclusion that your P-drug *should* be prescribed! As with selecting your P-drugs, the criteria of efficacy, safety, suitability and cost should be used when comparing treatment alternatives. The examples illustrate how this works in practice.

> **Exercise**
> **Make a list of possible effective and safe treatments for the following common patient problems: constipation, acute diarrhoea with mild dehydration in a child, and a superficial open wound. Then choose your P-treatment for each. The answers are discussed below.**

Constipation

Constipation is usually defined as a failure to pass stools for at least a week. The list of possible effective treatments is as follows.

Advice and information:	Drink a lot of fluids, eat fruit and high fibre food. Only go to the toilet when the need is felt. Do not try to pass stools by force. Reassure patient that nothing points to serious disease.
Non-drug treatment:	Physical exercise.
Drug treatment:	Laxative (your P-drug).
Referral for treatment:	Not indicated.

In many cases advice and non-drug treatment will solve the problem. Because of tolerance, laxatives are only effective for a short period and may then lead to abuse and eventually even to electrolyte disturbances. The first treatment plan, your P-treatment, should therefore be advice; not drugs! If the constipation is severe (and temporary) your P-drug could be prescribed, e.g. senna tablets for a few days. If it persists, further examination is needed to exclude other diseases, e.g. a colon carcinoma.

Acute watery diarrhoea with mild dehydration in a child

In acute diarrhoea with mild dehydration in a child, the main objective of the treatment is to prevent further dehydration and to rehydrate; the goal is not to cure the infection! The inventory of possible effective treatments is therefore:

Advice and information:	Continue breast feeding and other regular feeding; careful observation.
Non-drug treatment:	Additional fluids (rice water, fruit juice, homemade sugar/salt solution).
Drug treatment:	Oral rehydration solution (ORS), oral or by nasogastric tube.
Referral for treatment:	Not necessary.

Your advice will prevent further dehydration, but will not cure it, and extra fluids and ORS will be needed to correct the loss of water and electrolytes. Metronidazole and antibiotics, such as cotrimoxazole or ampicillin, are not listed in the inventory because these are not effective in treating watery diarrhoea. Antibiotics are only indicated for persistent bloody and/or slimy diarrhoea, which is much less common than watery diarrhoea; metronidazole is mainly used for proven amoebiasis. Antidiarrhoeal drugs, such as loperamide and diphenoxylate, are not indicated, especially for children, as they mask the continuing loss of body fluids into the intestines and may give the false impression that 'something is being done'.

Your P-treatment is therefore: advice to continue feeding and to give extra fluids (including home made solutions or ORS, depending on the national treatment guidelines), and to observe the child carefully.

Superficial open wound

The therapeutic objective in the treatment of an open wound is to promote healing and to prevent infection. The inventory of possible treatments is:

Advice and information:	Regularly inspect the wound; return in case of wound infection or fever.
Non-drug treatment:	Clean and dress the wound.
Drug treatment:	Antitetanus prophylaxis. Antibiotics (local, systemic).
Referral for treatment:	Not necessary.

The wound should be cleaned and dressed, and tetanus prophylaxis should probably be given. All patients with an open wound should be warned about possible signs of infection, and to return immediately if these occur. Local antibiotics are never indicated in wound infections because of their low penetration and the risk of sensibilization. Systemic antibiotics are rarely indicated for prophylactic purposes, except in some defined cases such as intestinal surgery. They will not prevent infection, as permeability into the

wound tissue is low, but they can have serious side effects (allergy, diarrhoea) and may cause resistance.

Your P-treatment for a superficial open wound is therefore to clean and dress the wound, give antitetanus prophylaxis, and advice on regular wound inspection. No drugs!

Conclusion

These three examples show that for common complaints the treatment of first choice often does not include any drugs. Advice and information are often sufficient, as in the case of constipation. Advice, fluids and rehydration are essential in the treatment of acute watery diarrhoea, rather than antidiarrhoeals or antibiotics. Dressing and advice are essential in the case of open wounds, not antibiotics.

In more serious cases, e.g. persistent constipation, serious dehydration in a small child or a deep open wound, referral may be the treatment of choice, and not 'stronger' drugs. Referral can therefore also be your P-treatment, e.g. when no facilities exist for further examination or treatment.

Part 3: Treating your patients

This part of the book shows you how to treat a patient with your P-drugs. Each step of the process is described in separate chapters. Practical examples illustrate how to select, prescribe and monitor the treatment, and how to communicate effectively with your patients. When you have gone through this material you are ready to put into practice what you have learned.

Chapter 11

C hapter 6

STEP 1: Define the patient's problem

A patient usually presents with a complaint or a problem. It is obvious that making the right diagnosis is a crucial step in starting the correct treatment.

Making the right diagnosis is based on integrating many pieces of information: the complaint as described by the patient; a detailed history; physical examination; laboratory tests; X-rays and other investigations. A discussion on each of these components is outside the scope of this manual. In the next sections on (drug) treatment we shall therefore assume that the diagnosis has been made correctly.

Patients' complaints are mostly linked to symptoms. A symptom is not a diagnosis, although it will usually lead to it. The following five patients all have the same complaint, a sore throat. But do they all have the same diagnosis? Let's look at them in more detail.

Exercise: patients 3-7
Define the problem for each of the following patients. The cases are discussed below.

Patient 3:
> *Man, 54 years. Complains of a severe sore throat. No general symptoms, no fever, slight redness in the throat; no other findings.*

Patient 4:
> *Woman, 23 years. Complains of a sore throat but is also very tired and has enlarged lymph nodes in her neck. Slight fever. She has come for the results of last week's laboratory tests.*

Patient 5:
> *Woman student, 19 years. Complains of a sore throat. Slight redness of the throat; but no fever and no other findings. She is a little shy and has never consulted you before for such a minor complaint.*

Patient 6:
> *Man 43 years. Complains of a sore throat. Slight redness of the throat; no fever and no other findings. Medical record mentions that he suffers from chronic diarrhoea.*

Patient 7:
> *Woman, 32 years. Very sore throat, caused by a severe bacterial infection, despite penicillin prescribed last week.*

Patient 3 (sore throat)

The sore throat of patient 3 probably results from a minor viral infection. Perhaps he is afraid of a more serious disease (throat cancer?). He needs reassurance and advice, not drugs. He does not need antibiotics, because they will not cure a viral infection.

Patient 4 (sore throat)

Her blood test confirms your clinical diagnosis of AIDS. Her problem is completely different from the previous case, as the sore throat is a symptom of underlying disease.

Patient 5 (sore throat)

You noticed that she was rather shy and remembered that she had never consulted you before for such a minor complaint. You ask her gently what the real trouble is, and after some hesitation she tells you that she is 3 months overdue. Her real concern had nothing to do with her throat.

Patient 6 (sore throat)

In this case, information from the patient's medical record is essential for a correct understanding of the problem. His sore throat is probably caused by the loperamide he takes for his chronic diarrhoea. This drug may produce reduced salivation and dry mouth as a side effect. Routine treatment of a sore throat would not have solved his problem. You may have to investigate the reason for his chronic diarrhoea, and consider AIDS.

Patient 7 (sore throat)

A careful history of patient 7, whose bacterial infection persists despite the penicillin, reveals that she stopped taking the drugs after three days because she felt much better. She should, of course, have completed the course. Her problem has come back because of inadequate treatment.

These examples illustrate that one complaint may be related to many different problems: a need for reassurance; a sign of underlying disease; a hidden request for assistance in solving another problem; a side effect of drug treatment; and non-adherence to treatment. So the lesson is: don't jump to therapeutic conclusions!

Example: patient 8

> *Man, 67 years. He comes for his medication for the next two months. He says that he is doing very well and has no complaints. He only wants a prescription for digoxin 0.25 mg (60 tablets), isosorbide dinitrate 5 mg (180 tablets), furosemide 40 mg (60 tablets), salbutamol 4 mg (180 tablets), cimetidine 200 mg (120 tablets), prednisolone 5 mg (120 tablets), and amoxicillin 500 mg (180 tablets).*

This patient states that he has no complaints. But is there really no problem? He may suffer from a heart condition, from asthma and from his stomach, but he definitely has one other problem: **polypharmacy**! It is unlikely that he needs all these drugs. Some may even have been prescribed to cure the side effects of another. In fact it is a miracle that he feels well. Think of all the possible side effects and interactions between so many different drugs: hypokalemia by furosemide leading to digoxin intoxication is only one example.

Careful analysis and monitoring will reveal whether the patient really needs all these drugs. The digoxin is probably needed for his heart condition. Isosorbide dinitrate should be changed to sublingual glyceryl trinitrate tablets, only to be used when needed. You can probably stop the furosemide (which is rarely indicated for maintenance treatment), or change it to a milder diuretic such as hydrochloro-thiazide. Salbutamol tablets could be changed to an inhaler, to reduce the side effects associated with continuous use. Cimetidine may have been prescribed for suspected stomach ulcer, whereas the stomach ache was probably caused by the prednisolone, for which the dose can probably be reduced anyway. It can also be changed to an aerosol. So you first have to diagnose whether he has an ulcer or not, and if not, stop the cimetidine. And finally, the large quantity of amoxicillin has probably been prescribed as a prevention against respiratory tract infections. However, most micro-organisms in his body will now be resistant to it and it should be stopped. If his respiratory problems become acute, a short course of antibiotics should be sufficient.

Box 5:   Patient demand

A patient may demand a treatment, or even a specific drug, and this can give you a hard time. Some patients are difficult to convince that a disease is self-limiting or may not be willing to put up with even minor physical discomfort. There may be a 'hidden' psycho-social problem, e.g. long-term use and dependence on benzodiazepine. In some cases it may be difficult to stop the treatment because psychological or physical dependence on the drugs has been created. Patient demand for specific drugs occurs most frequently with pain killers, sleeping pills and other psychotropic drugs, antibiotics, nasal decongestants, cough and cold preparations, and eye/ear medicines.

The personal characteristics and attitudes of your patients play a very important role. Patients' expectations are often influenced by the past (the previous doctor always gave a drug), by the family (the drug that helped Aunt Sally so much), by advertisements to the public, and many other factors. Although patients do sometimes demand a drug, physicians often assume such a demand even when it doesn't exist. So a prescription is written because the physician thinks that the patient thinks... This also applies to the use of injections, or 'strong drugs' in general.

Patient demand for a drug may have several symbolic functions. A prescription legitimizes a patient's complaint as an illness. It may also fulfill the need that something be done, and

symbolize the care of the physician. It is important to realize that the demand for a drug is much more than a demand for a chemical substance.

There are no absolute rules about how to deal with patient demand, with the exception of one: ensure that there is a real dialogue with the patient and give a careful explanation. You need good communication skills to be a good physician. Find out why the patient thinks as (s)he does. Make sure you have understood the patient's arguments, and that the patient has understood you. Never forget that patients are partners in therapy; always take their point of view seriously and discuss the rationale of your treatment choice. Valid arguments are usually convincing, provided they are described in understandable terms.

Your enemy when dealing with patient demand is time, i.e. the lack of it. Dialogue and explanation take time and you often will feel pressed for it. However, in the long run the investment is worthwhile.

Conclusion

Patients may come to you with a request, a complaint or a question. All may be related to different problems: a need for reassurance; a sign of underlying disease; a hidden request for assistance in solving another problem; a side effect of drug treatment; non-adherence to treatment; or (psychological) dependence on drugs. Through careful observation, structured history taking, physical examination and other examinations, you should try to define the patient's real problem. Your definition (your working diagnosis) may differ from how the patient perceives the problem. Choosing the appropriate treatment will depend upon this critical step. In many cases you will not need to prescribe a drug at all.

Summary

STEP 1: Define the patient's problem

- Disease or disorder
- Sign of underlying disease
- Psychological or social problems, anxiety
- Side effect of drugs
- Refill request (polypharmacy)
- Non-adherence to treatment
- Request for preventive treatment
- Combinations of the above

C hapter 7

STEP 2: Specify the therapeutic objective

Before choosing a treatment it is essential to specify your therapeutic objective. What do you want to achieve with the treatment? The following exercises enable you to practice this crucial step.

Exercise: patients 9-12
For each of these patients try to define the therapeutic objective. The cases are discussed below.

Patient 9:

> *Girl, 4 years, slightly undernourished. Watery diarrhoea without vomiting for three days. She has not urinated for 24 hours. On examination she has no fever (36.8ºC), but a rapid pulse and low elasticity of the skin.*

Patient 10:

> *Woman student, 19 years. Complains of a sore throat. Slight redness of the throat, no other findings. After some hesitation she tells you that she is three months overdue. On examination, she is three months pregnant.*

Patient 11:

> *Man, 44 years. Sleeplessness during six months, and comes for a refill of diazepam tablets, 5 mg, 1 tablet before sleeping. He wants 60 tablets.*

Patient 12:

> *Woman, 24 years. Consulted you 3 weeks ago, complaining of constant tiredness after delivery of her second child. Slightly pale sclerae, but normal Hb. You had already advised her to avoid strenuous exercise. She has now returned because the tiredness persists and a friend told her that a vitamin injection would do her good. This is what she wants.*

Patient 9 (diarrhoea)

In this patient the diarrhoea is probably caused by a viral infection, as it is watery (not slimy or bloody) and there is no fever. She has signs of dehydration (listlessness, little urine and decreased skin turgor). This dehydration is the most worrying problem, as she is already slightly undernourished. The therapeutic objective in this case is therefore (1) to prevent further dehydration and (2) to rehydrate. Not: to cure the infection! Antibiotics would be ineffective anyway.

Patient 10 (pregnancy)

In Patient 10 you will have recognized Patient 5 who complained of a sore throat while her real problem was the suspected pregnancy. You will not solve her problem by prescribing something for her throat. The therapeutic objective depends on her attitude towards the pregnancy and she will probably need counselling more than anything else. The therapeutic objective is then to assist her to plan for the future. This will probably not involve drug treatment for her sore throat. Moreover, the fact that she is in early pregnancy should stop you from prescribing any drug at all, unless it is absolutely essential.

Patient 11 (sleeplessness)

In Patient 11 the problem is not which drugs to prescribe, but how to stop prescribing them. Diazepam is not indicated for long term treatment of sleeplessness as tolerance quickly develops. It should only be used for short periods, when strictly necessary. The therapeutic objective in this case is not to treat the patient's sleeplessness but to avoid a possible dependence on diazepam. This could be achieved through a gradual and carefully monitored lowering of the dose to diminish withdrawal symptoms, coupled with more appropriate behavioural techniques for insomnia, which should lead to eventual cessation of the drug.

Patient 12 (tiredness)

In Patient 12 there is no clear cause for the tiredness and it is therefore difficult to make a rational treatment plan. Having excluded anaemia you may guess that as a young mother with small children and perhaps a job outside the home, she is chronically overworked. The therapeutic objective is therefore to help her reduce physical and emotional overload. To achieve this it may be necessary to involve other members of the family. This is a good example of the need for non-drug therapy. Vitamins will not help, and would only act as a placebo. In fact, they would probably act as a placebo for yourself as well, creating the false impression that something is being done.

Conclusion

As you can see, in some cases the therapeutic objective will be straightforward: the treatment of an infection or a condition. Sometimes the picture will be less clear, as in the patient with unexplained tiredness. It may even be misleading, as in the student with the sore throat. You will have noticed that specifying the therapeutic objective is a good way to structure your thinking. It forces you to concentrate on the real problem, which limits the number of treatment possibilities and so makes your final choice much easier.

Specifying your therapeutic objective will prevent a lot of unnecessary drug use. It should stop you from treating two diseases at the same time if you cannot choose between them, like prescribing antimalarial drugs and antibiotics in case

of fever, or antifungal and corticosteroid skin ointment when you can not choose between a fungus and eczema.

Specifying your therapeutic objective will also help you avoid unnecessary prophylactic prescribing, for example, the use of antibiotics to prevent wound infection, which is a very common cause of irrational drug use.

It is a good idea to discuss your therapeutic objective with the patient before you start the treatment. This may reveal that (s)he has quite different views about illness causation, diagnosis and treatment. It also makes the patient an informed partner in the therapy and improves adherence to treatment.

C hapter 8

STEP 3:   Verify the suitability of your P-drug

After defining your therapeutic objective you should now verify whether your P-drug is suitable for the individual patient. You will remember that you have chosen your P-drugs for an imaginary, standard patient with a certain condition, using the criteria of efficacy, safety, convenience and cost. However, you cannot assume that this 'first-choice' treatment will always be suitable for everyone. 'Cookbook' medicine does not make for good clinical practice! You should therefore always verify whether your P-drug is suitable for *this* individual patient. The same applies when you practice within the limits of national treatment guidelines, a hospital formulary or departmental prescribing policies.

Chapter 5 explained the relationship between P-drug and P-treatment. In fact, you should define P-*treatments* for the most common problems you will encounter in practice; such P-treatments will frequently include non-drug treatment. However, as this manual is primarily concerned with the development of prescribing skills, from now on the focus will be on drug treatment, based on the use of P-*drugs*. Always keep in mind that many patients do not need drugs at all!

The starting point for this step is to look up your P-drugs (described in Part 2), or the treatment guideline that is available to you. In all cases you will need to check three aspects: (1) are the active substance and the dosage form suitable for this patient? (2) is the standard dosage schedule suitable? and (3) is the standard duration of treatment suitable? For each aspect, you have to check whether the proposed treatment is **effective** and **safe**. A check on effectiveness includes a review of the drug indication and the convenience of the dosage form. Safety relates to contraindications and possible interactions. Be careful with certain high risk groups.

Verify the suitability of your P-drug

A Active substance and dosage form
B Standard dosage schedule
C Standard duration of treatment

> **Effectiveness** (indication, convenience)
> **Safety** (contraindications, interactions, high risk groups)

Step 3A: Are the active substance and dosage form suitable for this patient?

Effectiveness

We assume that all your P-drugs have already been selected on the basis of efficacy. However, you should now verify that the drug will also be **effective** in this individual patient. For this purpose you have to review whether the active substance is likely to achieve the therapeutic objective, and whether the dosage form is convenient for the patient. **Convenience** contributes to patient adherence to the treatment, and therefore to effectiveness. Complicated dosage forms or packages and special storage requirements can be major obstacles for some patients.

Safety

Table 5:
High risk factors/
groups

Pregnancy
Lactation
Children
Elderly
Renal failure
Hepatic failure
History of drug
  allergy
Other diseases
Other medication

The safety of a drug for the individual patient depends on contraindications and interactions; these may occur more frequently in certain high risk groups. **Contraindications** are determined by the mechanism of action of the drug and the characteristics of the individual patient. Drugs in the same group usually have the same contraindications. Some patients will fall into certain high risk groups (see Table 5) and any other illnesses should also be considered. Some side effects are serious for categories of patients only, such as drowsiness for drivers. **Interactions** can occur between the drug and nearly every other substance taken by the patient. Best known are interactions with other prescribed drugs, but you must also think of over-the-counter drugs the patient might be taking. Interactions may also occur with food or drinks (especially alcohol). Some drugs interact chemically with other substances and become ineffective (e.g. tetracycline and milk). Fortunately, in practice only a few interactions are clinically relevant.

Exercise: patients 13-16
Verify in each of these cases whether the active substance and dosage form of your P-drug is suitable (effective, safe) for this patient. Examples are discussed below.

Patient 13:
Man, 45 years. Suffers from asthma. Uses salbutamol inhaler. A few weeks ago you diagnosed essential hypertension (145/100 on various occasions). You advised a low-salt diet, but blood pressure remains high. You decide to add a drug to your treatment. Your P-drug for hypertension in patients under 50 is atenolol tablets, 50 mg a day.

Patient 14:

> *Girl, 3 years. Brought in with a severe acute asthmatic attack, probably precipitated by a viral infection. She has great difficulty in breathing (expiratory wheeze, no viscid sputum), little coughing and a slight temperature (38.2^{o}C). Further history and physical examination reveal nothing. Apart from minor childhood infections she has never been ill before and she takes no drugs. Your P-drug for such a case is a salbutamol inhaler.*

Patient 15:

> *Woman, 22 years, 2 months pregnant. Large abscess on her right forearm. You conclude that she will need surgery fast, but in the meantime you want to relieve the pain. Your P-drug for common pain is acetylsalicylic acid (aspirin) tablets.*

Patient 16:

> *Boy, 4 years. Cough and fever of 39.5^{o}C. Diagnosis: pneumonia. One of your P-drugs for pneumonia is tetracycline tablets.*

Patient 13 (hypertension)

Atenolol is a good P-drug for the treatment of essential hypertension in patients below 50 years of age, and it is very convenient. However, like all beta-blockers, it is relatively contraindicated in asthma. Despite the fact that it is a selective beta-blocker, it can induce asthmatic problems, especially in higher doses because selectivity then diminishes. If the asthma is not very severe, atenolol can be prescribed in a low dose. In severe asthma you should probably switch to diuretics; almost any thiazide is a good choice.

Patient 14 (child with acute asthma)

In this child a fast effect is needed, and tablets work too slowly for that. Inhalers only work when the patient knows how to use them and can still breathe enough to inhale. In the case of a severe asthma attack this is usually not possible; moreover, some children below the age of five may experience difficulties with an inhaler. Intravenous injection in young children can be very difficult. If an inhaler cannot be used, the best alternative is to give salbutamol by subcutaneous or intramuscular injection, which is easy and only briefly painful.

Patient 15 (abscess)

This patient is pregnant and will soon be operated on. In this case acetylsalicylic acid is contraindicated as it affects the blood clotting mechanism and also passes the placenta. You should switch to another drug that does not interfere with clotting. Paracetamol is a good choice and there is no evidence that it has any effect on the fetus when it is given for a short time.

Patient 16 (pneumonia)

Tetracycline is not a good drug for children below 12 years of age, because it can cause discolouration of the teeth. The drug may interact with milk and the child may have problems swallowing the large tablets. The drug and, if possible, the dosage form, will therefore have to be changed. Good alternatives are

cotrimoxazole and amoxicillin. Tablets or parts of tablets could be crushed and dissolved in water, which is cost-effective if you can clearly explain the procedure to the parents.[3] You could also prescribe a more convenient dosage form, such as a syrup, although this is more expensive.

In all these patients your P-drug was not suitable, and in each case you had to change either the active substance or the dosage form, or both. Atenolol was contraindicated because of another disease (asthma); an inhaler was not suitable because the child was too young to handle it; acetylsalicylic acid was contraindicated because it affects the blood clotting mechanism and because the patient is pregnant; and tetracycline tablets were contraindicated because of serious side effects in young children, possible interactions with milk, and inconvenience as a dosage form.

Step 3B: Is the standard dosage schedule suitable for this patient?

The aim of a dosage schedule is to maintain the plasma level of the drug within the therapeutic window. As in the previous step, the dosage schedule should be **effective** and **safe** for the individual patient. There are two main reasons why a standard dosage schedule may have to be adapted. The window and/or plasma curve may have changed, or the dosage schedule is inconvenient to the patient. If you are not familiar with the concept of the therapeutic window and the plasma concentration-time curve, read Annex 1.

> **Exercise: patients 17-20**
> **Review for each of the following cases whether the dosage schedule is suitable (effective, safe) for the patient. Adapt the schedule where necessary. The cases are discussed below.**
>
> **Patient 17:**
> *Woman, 43 years. History of insulin dependent diabetes for 26 years. Stable on treatment with two daily doses of neutral insulin, 20 IU and 30 IU. Recently mild hypertension was diagnosed, and diet and general advice have not been sufficiently effective. You would like to treat this condition with a beta-blocker. Your P-drug is atenolol 50 mg once daily.*
>
> **Patient 18:**
> *Man, 45 years. Terminal lung cancer. He has lost 3 kg during the last week. You have been treating his pain successfully with your P-drug, oral morphine solution, 10 mg twice daily. Now he complains that the pain is getting worse.*
>
> **Patient 19:**
> *Woman, 50 years. Chronic rheumatic disease, treated with your P-drug, indometacin, 3 times 50 mg daily plus a 50 mg suppository at night. She complains of pain early in the morning.*

---

[3] This is a cheap and convenient way of giving a drug to a small child. However, it should not be done with capsules nor with special tablets such as sugarcoated or slow-release preparations.

Patient 18 again, after one week:

He has lost another 6 kg, and looks very ill. He was on oral morphine solution, 15 mg twice daily, to which he had responded well. However, he has become very drowsy and has to be woken up to hear what you say. He has no pain.
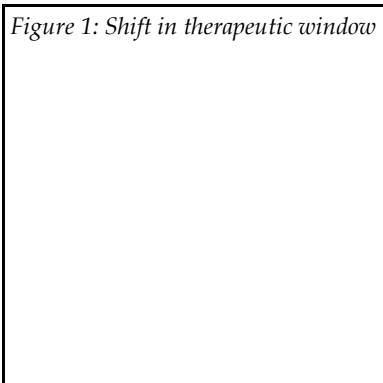
Patient 20:

Man, 73 years. Has suffered from depression for two years, after the death of his wife. You want to prescribe an antidepressant drug. Your P-drug is amitriptyline, 25 mg daily initially, followed by a slowly rising dose till the drug is effective (with a maximum of 150 mg per day).

Changes in therapeutic window

Figure 1: Shift in therapeutic window

For a variety of reasons (e.g. age, pregnancy, disturbed organ functions) individual patients may differ from the standard. These differences may influence the pharmaco-dynamics or pharmacokinetics of your P-drug. A change in pharmacodynamics may affect the level (position) or width of the therapeutic window (Figure 1; see also Annex 1). The therapeutic window reflects the sensitivity of the patient to the action of the drug. Changes in the therapeutic window are sometimes expressed as the patient being 'resistant' or 'hyper-sensitive'. The only way to determine the therapeutic window in the individual patient is by trial, careful monitoring and logical thinking.

In **Patient 17 (diabetes)** it is important to note that β-blockers counteract the effect of insulin. This means that higher concentrations of insulin are needed for the same effect: the therapeutic window for insulin shifts upwards. The plasma curve no longer matches the window, and the daily dose of insulin must be raised. β-blockers may also mask any signs of hypoglycemia. For these two reasons you may decide to change to another drug group that does not affect glucose tolerance, e.g. calcium channel blockers.

Patient 18 (lung cancer) has probably become tolerant to morphine, as he responded well to the drug before. Tolerance to effect and also to side effects, is common in opiates. The therapeutic window is shifted upwards and the dose has to be raised, for example to 15 mg twice daily. In terminal patients drug absorption and metabolism may be so disturbed that even larger dosages (e.g. 10 times the normal dose) may be necessary.

Changes in plasma concentration-time curve
The plasma concentration-time curve may be lowered or raised, or the concentration may fluctuate outside the therapeutic window. This effect depends on the pharmacokinetics of the drug in that patient.

Figure 2: Slow fall in plasma concentration late at night in patient 19
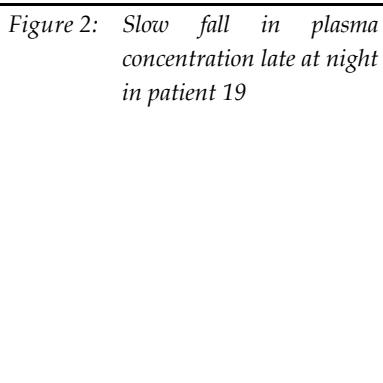
In **Patient 19 (pain at night)** the plasma concentration of indometacin probably falls below the therapeutic window early in the morning (see Figure 2). Any change in medication should therefore aim at increasing the plasma level in that period. You could advise her to take the evening dose later, or to set the alarm in the night to take an extra tablet. You could also increase the strength of the evening suppository to 100 mg, while decreasing her first morning tablet to 25 mg.

Figure 3: Plasma concentration rising above therapeutic window in patient 18

Table 6:
Relation between ADME factors and plasma concentration

Plasma concentration curve will drop if:
    Absorption is low
    Distribution is high
    Metabolism is high
    Excretion is high

Plasma concentration curve will rise if:
    Absorption is high
    Distribution is low
    Metabolism is low
    Excretion is low

Figure 4: Downward shifted window and upward shifted curve in patient 20

The second visit of **Patient 18 (lung cancer)** presents a complicated problem. He has probably been overdosed, because his metabolism is impaired by the terminal cancer, decreasing the elimination of the drug and therefore lengthening its half-life. In addition, the distribution volume of his body is reduced because of emaciation. The curve therefore probably lies above the window, implying that the daily dose should be reduced. Remember that it takes about four half-lives to lower the plasma concentration to a new steady state. If you want to speed up this process you can stop the morphine for one day, after which you can start with the new dose. This is the reverse process of a loading dose.

Four factors determine the course of the concentration curve, usually called ADME-factors: Absorption, Distribution, Metabolism and Excretion. You always have to check whether ADME-factors in your patient are different compared to average patients. If so, you have to determine what this will do to the plasma curve. Any change in ADME-factors influences plasma concentration (see Table 6).

How can you define the position of the plasma curve in an individual patient? The plasma concentration can be measured by laboratory investigations, but in many settings this is not possible and it may be expensive. More important, each measurement represents only one point of the curve and is difficult to interpret without special training and experience. More measurements are expensive and may be stressful to the patient, especially in an outpatient setting. It is simpler to look for clinical signs of toxic effects. These are often easy to detect by history taking and clinical investigation.

Changes in window and curve

Changes in both window and curve are also possible, as illustrated in **Patient 20 (depression)** (see Figure 4). Elderly people are one of several categories of high-risk patients. Dosage schedules for antidepressant drugs in the elderly usually recommend that the dose be reduced to half the adult dose, for two reasons. First, in the elderly the therapeutic window of antidepressant drugs shifts downwards (a lower plasma concentration will suffice). At a full adult dose the plasma curve may rise above the therapeutic window, leading to side effects, especially

anticholinergic and cardiac effects. Secondly, metabolism and renal clearance of the drug and its active metabolites may be reduced in the elderly, also increasing the plasma curve. Thus, in prescribing the normal adult dosage your patient will be exposed to unnecessary and possibly harmful side effects.

Convenience

A dosage schedule should be convenient. The more complex the schedule, the less convenient it is. For example, two tablets once daily are much more convenient than half a tablet four times daily. Complex dosage schedules decrease patient adherence to treatment, especially when more than one drug is used, and thus decrease effectiveness. Try to adjust a dosage schedule to other schedules of the patient.

In patients 17-20 the standard dosage schedule of your P-drug was not suitable. If you had not adapted the schedule, the P-drug treatment would have been less effective, or unsafe. You can prevent this by carefully checking the suitability of the standard dosage schedule before writing the prescription. You may have to modify the schedule, or change to a completely different P-drug.

How to adapt a dosage schedule

Figure 5:   *Relation between frequency and fluctuations in plasma concentration*
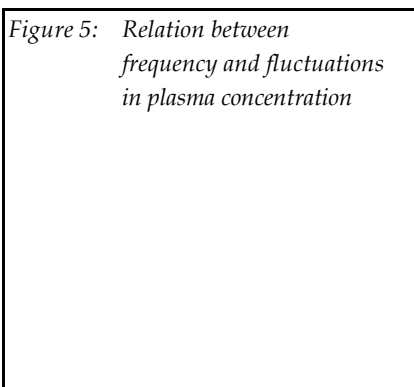
There are three ways to restore the mismatch between curve and window: change the dose, change the frequency of administration, or both. Changing dose or frequency have different effects. The daily dose determines the mean plasma concentration, while the frequency of administration defines the fluctuations in the plasma curve. For example, twice daily 200 mg will give the same mean plasma concentration as four times daily 100 mg, but with more fluctuations in plasma level. The minimum fluctuation would be obtained by delivering 400 mg in 24 hours by means of a continuous infusion (Figure 5).

Decreasing the daily dose is usually easy. You can reduce the number of tablets, or divide them into halves. Beware of antibiotics, because some may need high peaks in plasma concentration to be effective. In that case you should reduce the frequency, not the dose.

Increasing the daily dose is a little more complicated. Doubling the dose while maintaining the same frequency not only doubles the mean plasma level, but also increases the fluctuations on both sides of the curve. In drugs with a narrow safety margin the curve may now fluctuate outside the therapeutic window. The safest way to prevent this is to raise the frequency of dosage. However, few patients like taking drugs 12 times a day and a compromise has to be found to maintain adherence to treatment. After changing the daily dose it takes four times the half-life of the drug to reach the new steady state. Table 7 lists those

drugs for which it is advisable to start treatment with a slowly rising dosage schedule.

Table 7:   Drugs in which slowly raising the dose is advisable

- ♦   Tricyclic antidepressants (anticholinergic effects)
- ♦   Some anti-epileptics (carbamazepine, valproic acid)
- ♦   Dopa-based anti-Parkinson drugs
- ♦   ACE-inhibitors in patients using diuretics
- ♦   Alpha-receptor blocking agents in hypertension (orthostasis)
- ♦   Some hormonal drug therapies (corticosteroids, levothyroxin)
- ♦   Gold salts in rheumatism
- ♦   Mixtures for desensitization
- ♦   Opiates in cancer

Step 3C: Is the standard duration of treatment suitable for this patient?

Many doctors not only prescribe too much of a drug for too long, but also frequently too little of a drug for too short a period. In one study about 10% of patients on benzodiazepines received them for a year or longer. Another study showed that 16% of outpatients with cancer still suffered from pain because doctors were afraid to prescribe morphine for a long period. They mistook tolerance for addiction. The duration of the treatment and the quantity of drugs prescribed should also be effective and safe for the individual patient.

Overprescribing leads to many undesired effects. The patient receives unnecessary treatment, or drugs may lose some of their potency. Unnecessary side effects may occur. The quantity available may enable the patient to overdose. Drug dependence and addiction may occur. Some reconstituted drugs, such as eye drops and antibiotic syrups, may become contaminated. It may be very inconvenient for the patient to take so many drugs. Last, but not least, valuable and often scarce resources are wasted.

Underprescribing is also serious. The treatment is not effective, and more aggressive or expensive treatment may be needed later. Prophylaxis may be ineffective, resulting in serious disease, e.g. malaria. Most patients will find it inconvenient to return for further treatment. Money spent on ineffective treatment is money wasted.

Exercise: patients 21-28
For each of the following cases verify whether the duration of treatment and total quantity of the drugs are suitable (effective, safe). In all cases you may assume that the drugs are your P-drugs.

Patient 21:
> *Woman, 56 years. Newly diagnosed depression. R/amitriptyline 25 mg, one tablet daily at night, give 30 tablets.*

Patient 22:

Child, 6 years. Giardiasis with persistent diarrhoea. R/metronidazole 200 mg/5 ml oral suspension, 5 ml three times daily, give 105 ml.

Patient 23:

Man, 18 years. Dry cough after a cold. R/codeine 30 mg, 1 tablet three times daily, give 60 tablets.

Patient 24:

Woman, 62 years. Angina pectoris, waiting for referral to a specialist. R/glyceryl trinitrate 5 mg, as necessary 1 tablet sublingual, give 60 tablets.

Patient 25:

Man, 44 years. Sleeplessness. Comes for a refill, R/diazepam 5 mg, 1 tablet before sleeping, give 60 tablets.

Patient 26:

Girl, 15 years. Needs malaria prophylaxis for a two week trip to Ghana. R/mefloquine 250 mg, 1 tablet weekly, give 7 tablets; start one week before departure and continue four weeks after return.

Patient 27:

Boy, 14 years. Acute conjunctivitis. R/tetracycline 0.5% eye drops, first 3 days every hour 1 drop, then 2 drops every six hours, give 10 ml.

Patient 28:

Woman, 24 years. Feels weak and looks a bit anaemic. No Hb result available. R/ferrous sulfate 60 mg tablets, 1 tablet three times daily, give 30 tablets.

Patient 21 (depression)

A dose of 25 mg per day is probably insufficient to treat her depression. Although she can start with such a low dose for a few days or a week, mainly to get used to side effects of the drug, she may finally need 100-150 mg per day. With 30 tablets the quantity is sufficient for one month, if the dosage is not changed before that time. But is it safe? At the beginning of the treatment the effect and side effects cannot be foreseen. And if the treatment has to be stopped, the remaining drugs are wasted. The risk of suicide also has to be considered: depressive patients are more liable to commit suicide in the initial stages of treatment when they become more active because of the drug, but still feel depressed. For these reasons 30 tablets are not suitable. It would be better to start with 10 tablets, for the first week or so. If she reacts well you should increase the dose.

Patient 22 (giardiasis)

With most infections time is needed to kill the microbes, and short treatments may not be effective. However, after prolonged treatment the micro-organisms may develop resistance and more side effects will occur. In this patient the treatment is both effective and safe. Giardiasis with persistent diarrhoea needs to be treated for one week, and 105 ml is exactly enough for that period. Maybe it is

even too exact. Most pharmacists do not want to dispense quantities such as 105 ml or 49 tablets. They prefer rounded figures, such as 100 ml or 50 tablets, because calculating is easier and drugs are usually stocked or packed in such quantities.

Patient 23 (dry cough)

The quantity of tablets is much too high for this patient. The persistent dry cough prevents healing of the irritated bronchial tissue. Since tissue can regenerate within three days the cough needs to be suppressed for five days at most, so 10-15 tablets will be sufficient. Although a larger quantity will not harm the patient, it is unnecessary, inconvenient and needlessly expensive. Many prescribers would argue that no drug is needed at all (see p.8).

Patient 24 (angina)

For this patient the quantity is excessive. She will not use 60 tablets before her appointment with the specialist. And did you remember that the drug is volatile? After some time the remaining tablets will no longer be effective.

Patient 25 (sleeplessness)

The diazepam refill for patient 25 is worrying. You suddenly remember that he came for a similar refill recently and check the medical record. It was two weeks ago! Looking more closely you find that he has used diazepam four times daily for the last three years. This treatment has been expensive, probably ineffective and has resulted in a severe dependency. You should talk to the patient at the next visit and discuss with him how he can gradually come off the drug.

Box 6:   Repeat prescriptions in practice

In long-term treatment, patient adherence to treatment can be a problem. Often the patient stops taking the drug when the symptoms have disappeared or if side effects occur. For patients with chronic conditions repeat prescriptions are often prepared by the receptionist or assistant and just signed by the physician. This may be convenient for doctor and patient but it has certain risks, as the process of renewal becomes a routine, rather than a conscious act. Automatic refills are one of the main reasons for overprescribing in industrialized countries, especially in chronic conditions. When patients live far away, convenience may lead to prescriptions for longer periods. This may also result in over prescribing. You should see your patients on long-term treatment at least four times per year.

Patient 26 (malaria prophylaxis)

There is nothing wrong with this prescription which follows the WHO guidelines on malaria prophylaxis for travellers to Ghana. The dosage schedule is correct, and she received enough tablets for the trip plus four weeks afterwards. Apart from a small risk of drug resistance this drug treatment is effective and safe.

Patient 27 (acute conjunctivitis)

The prescription of 10 ml eyedrops seems adequate, at first sight. In fact, eyedrops are usually prescribed in bottles of 10 ml. But did you ever check how many drops there are in a bottle of 10 ml? One ml is about 20 drops, so 10 ml is about 200 drops. One drop every hour for the first three days means 3 x 24 = 72 drops. That leaves about 128 drops in the bottle. Two drops four times per day for the remaining period is 8 drops a day. That is for another 130/8 = 16 days. The total treatment therefore covers 3 + 16 = 19 days! Yet, seven days treatment at most should be enough for bacterial conjunctivitis. After some arithmetic (72 + (4 x 8) = 104 drops = 104 x 0.05 = 5.2 ml) you conclude that 5 ml will be enough in future. This will also prevent any leftovers from being used again without a proper diagnosis. Even more important, eyedrops become contaminated after a few weeks, especially if they are not kept cool, and can cause severe eye infections.

Patient 28 (weakness)

Did you notice that this is a typical example of a prescription without a clear therapeutic objective? If the diagnosis is uncertain, the Hb should be measured. If the patient is really anaemic she will need much more iron than the ten days given here. She will probably need treatment for several weeks or months, with regular Hb measurements in between.

Conclusion

Verifying whether your P-drug is also suitable for the individual patient in front of you is probably the most important step in the process of rational prescribing. It also applies if you are working in an environment in which essential drugs lists, formularies and treatment guidelines exist. In daily practice, adapting the dosage schedule to the individual patient is probably the most common change that you will make.

Summary

STEP 3:   Verify that your P-drug is suitable for this patient

3A   Are the active substance and dosage form suitable?
Effective: Indication (drug really needed)?
Convenience (easy to handle, cost)?
Safe: Contraindications (high risk groups, other diseases)?
Interactions (drugs, food, alcohol)?

3B   Is the dosage schedule suitable?
Effective: Adequate dosage (curve within window)?

Safe: Contraindications (high risk groups, other diseases)?
Interactions (drugs, food, alcohol)?

3C   **Is the duration suitable?**
Effective: Adequate duration (infections, prophylaxis, lead time)?
Convenience (easy to store, cost)?
Safe: Contraindications (side effects, dependence, suicide)?
Quantity too large (loss of quality, use of leftovers)?

If necessary, change the dosage form, the dosage schedule or the duration of treatment.

In some cases it is better to change to another P-drug.

C hapter 9

STEP 4: Write a prescription

Cartoon 3

A prescription is an instruction from a prescriber to a dispenser. The prescriber is not always a doctor but can also be a paramedical worker, such as a medical assistant, a midwife or a nurse. The dispenser is not always a pharmacist, but can be a pharmacy technician, an assistant or a nurse. Every country has its own standards for the minimum information required for a prescription, and its own laws and regulations to define which drugs require a prescription and who is entitled to write it. Many countries have separate regulations for opiate prescriptions.

Information on a prescription

There is no global standard for prescriptions and every country has its own regulations. Do you know the legal requirements in your own country? The most important requirement is that the prescription be clear. It should be legible and indicate precisely what should be given. Few prescriptions are still written in Latin; the local language is preferred. If you include the following information, not much can go wrong.

Name and address of the prescriber, with telephone number (if possible)

This is usually pre-printed on the form. If the pharmacist has any questions about the prescription (s)he can easily contact the prescriber.

Date of the prescription

In many countries the validity of a prescription has no time limit, but in some countries pharmacists do not give out drugs on prescriptions older than three to six months. You should check the rules in your own country.

Name and strength of the drug

R/ (not Rx) is derived from *Recipe* (Latin for 'take'). After R/ you should write the name of the drug and the strength. It is strongly recommended to use the generic (nonproprietary) name. This facilitates education and information. It means that you do not express an opinion about a particular brand of the drug, which may be unnecessarily expensive for the patient. It also enables the pharmacist to maintain a more limited stock of drugs, or dispense the cheapest drug. However, if there is a particular reason to prescribe a special brand, the trade name can be added. Some countries allow generic substitution by the pharmacist and require the addition '*Do not substitute*' or '*Dispense as written*' if that brand, and no other, is to be dispensed.

The strength of the drug indicates how many milligrams each tablet, suppository, or milliliter of fluid should contain. Internationally accepted abbreviations should be used: g for gram, ml for milliliter. Try to avoid decimals and, where necessary, write words in full to avoid misunderstanding. For example, write levothyroxin 50 micrograms, not 0.050 milligrams or 50 ug. Badly handwritten prescriptions can lead to mistakes, and it is the legal duty of the doctor to write legibly (Box 7). In prescriptions for controlled drugs or those with a potential for abuse it is safer to write the strength and total amount in words, to prevent tampering. Instructions for use must be clear and the maximum daily dose mentioned. Use indelible ink.

Box 7:   Legal obligation to write clearly

Doctors are legally obliged to write clearly, as emphasized in the UK Court of Appeal ruling in the following case. A doctor had written a prescription for Amoxil tablets (amoxicillin). The pharmacist misread this and dispensed Daonil (glibenclamide) instead. The patient was not a diabetic and suffered permanent brain damage as a result of taking the drug.

The court indicated that a doctor owed a duty of care to a patient to write a prescription clearly and with sufficient legibility to allow for possible mistakes by a busy pharmacist. The court concluded that the word Amoxil on the prescription could have been read as Daonil. It found that the doctor had been in breach of his duty to write clearly and had been negligent. The court concluded that the doctor's negligence had contributed to the negligence of the pharmacist, although the greater proportion of the responsibility (75%) lay with the pharmacist.

On appeal the doctor argued that the word on the prescription standing on its own could reasonably have been read incorrectly but that various other aspects of the prescription should have alerted the pharmacist. The strength prescribed was appropriate for Amoxil but not for Daonil; the prescription was for Amoxil to be taken three times a day while Daonil was usually taken once a day; the prescription was for only seven days' treatment, which was unlikely for Daonil; and finally, all prescriptions of drugs for diabetes were free under the National Health Service but the patient did not claim free treatment for the drug. All of these factors should have raised doubts in the mind of the pharmacist and as a result he should have contacted the doctor. Therefore, the chain of causation from the doctor's bad handwriting to the eventual injury was broken.

This argument was rejected in the Court of Appeal. The implications of this ruling are that doctors are under a legal duty of care to write clearly, that is with sufficient legibility to allow for mistakes by others. When illegible handwriting results in a breach of that duty, causing personal injury, then the courts will be prepared to punish the careless by awarding sufficient ~~damages. Liability does not end when the prescription leaves the doctor's consulting room. It~~

Source: J R Coll Gen Pract, 1989: 347-8

Dosage form and total amount

Only use standard abbreviations that will be known to the pharmacist.

Information for the package label

S stands for *Signa* (Latin for 'write'). All information following the S or the word 'Label' should be copied by the pharmacist onto the label of the package. This includes how much of the drug is to be taken, how often, and any specific instructions and warnings. These should be given in lay language. Do not use abbreviations or statements like 'as before' or 'as directed'. When stating 'as required', the maximum dose and minimum dose interval should be indicated. Certain instructions for the pharmacist, such as 'Add 5 ml measuring spoon' are written here, but of course are not copied onto the label.

Prescriber's initials or signature

Name and address of the patient; age (for children and elderly)

Box 8:   Incomplete labels

The label on the drug package is very important for the patient as a reminder of the instructions for use. In many cases, however, labels are incomplete. An analysis of 1533 (=100%) labels showed:

No label or illegible	1 %
Quantity not recorded	50 %
No directions, or only 'as before'/'as directed'	26 %
No date	14 %

The data listed above are the core of every prescription. Additional information may be added, such as the type of health insurance the patient has. The layout of the prescription form and the period of validity may vary between countries. The number of drugs per prescription may be restricted. Some countries require prescriptions for opiates on a separate sheet. Hospitals often have their own standard prescription forms. As you can check for yourself, all prescriptions in this chapter include the basic information given above.

Exercise: Patients 29-32
Write a prescription for each of the following patients. Prescriptions are discussed below.

Patient 29:

Boy, 5 years. Pneumonia with greenish sputum. Your P-drug is amoxicillin syrup.

Patient 30:

Woman, 70 years. Moderate congestive cardiac failure. For several years on digoxin 0.25 mg 1 tablet daily. She phones to ask for a repeat prescription. As you have not seen her for some time you ask her to call. During the visit she complains of slight nausea and loss of appetite. No vomiting or diarrhoea. You suspect side effects of digoxin, and call her cardiologist. As she has an appointment with him next week, and he is very busy, he advises you to halve the dose until then.

Patient 31:

Woman, 22 years. New patient. Migraine with increasingly frequent vomiting. Paracetamol no longer effective during attacks. You explain to her that the paracetamol does not work because she vomits the drug before it is absorbed. You prescribe paracetamol plus an anti-emetic suppository, metoclopramide, which she should take first, and wait 20-30 minutes before taking the paracetamol.

Patient 32:

Man, 53 years. Terminal stage of pancreatic cancer, confined to bed at home. You visit him once a week. Today his wife calls and asks you to come earlier because he is in considerable pain. You go immediately. He has slept badly over the weekend and regular painkillers are not working. Together you decide to try morphine for a week. Making sure not to underdose him, you start with 10 mg every six hours, with 20 mg at night. He also has non-insulin dependent diabetes, so you add a refill for his tolbutamide.

There is nothing wrong with any of the four prescriptions (Figures 6, 7, 8 and 9). However, a few remarks can be made. Repeat prescriptions, such as the one for patient 30, are permitted. Many prescriptions are like that. But they also need your full attention. Do not write a repeat prescription automatically! Check how many times it has been repeated. Is it still effective? It is still safe? Does it still meet the original needs?

For the opiate for patient 32, the strength and the total amount have been written in words so they cannot easily be altered. The instructions are detailed and the maximum daily dose is mentioned. In some countries it is mandatory to write an opiate prescription on a separate prescription sheet.

Summary

```
Dr B. Who
Farmstreet 12
Kirkville
tel. 3876
R/                        date




Ms/Mr
address:
age:
```

```
Dr B. Who
Farmstreet 12
Kirkville
tel. 3876
R/                        date




Ms/Mr
address:
```

A prescription should include:

* Name, address, telephone of prescriber
* Date
* Generic name of the drug, strength
* Dosage form, total amount
* Label: instructions, warnings
* Name, address, age of patient
* Signature or initials of prescriber

Figure 6: Prescription for patient 29

Figure 7: Prescription for patient 30

Figure 8: Prescription for patient 31

Figure 9: Prescription for patient 32

Dr B. Who
Farmstreet 12
Kirkville
tel. 3876
R/ date

Ms/Mr
address:

Dr B. Who
Farmstreet 12
Kirkville
tel. 3876
R/ date

Ms/Mr
address:

Chapter 10

STEP 5: Give information, instructions and warnings

Cartoon 4

<u>**Example: patient 33**</u>
Woman, 59 years. She is taking drugs for congestive heart failure and hypertension. She also has a newly diagnosed gastric ulcer, for which she has been prescribed another drug. As the doctor is explaining why she needs the new drug and how she should take it, her thoughts are drifting away. The doctor's voice sinks into the background as she starts worrying about the new illness, afraid of the consequences and how she will remember to take all these drugs. The doctor doesn't notice the loss of attention, doesn't encourage a dialogue but just keeps on talking and talking. In the pharmacy her thoughts are still wandering off even when the pharmacist is explaining how to take the drug. When she gets home she finds her daughter waiting to hear the results of her visit to the doctor. Without telling her the diagnosis she talks about her worry: how to cope with all these different drugs. Finally her daughter reassures her and says that she will help her to take the drugs correctly.

On average, 50% of patients do not take prescribed drugs correctly, take them irregularly, or not at all. The most common reasons are that symptoms have ceased, side effects have occurred, the drug is not perceived as effective, or the dosage schedule is complicated for patients, particularly the elderly. Non adherence to treatment may have no serious consequences. For example, irregular doses of a thiazide still give the same result, as the drug has a long half-life and a flat dose-response curve. But drugs with a short half-life (e.g. fenytoin) or a narrow therapeutic margin (e.g. theophylline) may become ineffective or toxic if taken irregularly.

Patient adherence to treatment can be improved in three ways: prescribe a well chosen drug treatment; create a good doctor-patient relationship; take time to give the necessary information, instructions and warnings. A number of patient

aids are discussed in Box 9. A well chosen drug treatment consists of as few drugs as possible (preferably only one), with rapid action, with as few side effects as possible, in an appropriate dosage form, with a simple dosage schedule (one or two times daily), and for the shortest possible duration.

How to improve patient adherence to treatment

        * Prescribe a well-chosen treatment
        * Create a good doctor-patient relationship
        * Take the time to give information, instructions and warnings

---

A good doctor-patient relationship is established through respect for the patient's feelings and viewpoint, understanding, and willingness to enter into a dialogue which empowers the patient as a partner in therapy. Patients need information, instructions and warnings to provide them with the knowledge to accept and follow the treatment and to acquire the necessary skills to take the drugs appropriately. In some studies less than 60% of patients had understood how to take the drugs they had received. Information should be given in clear, common language and it is helpful to ask patients to repeat in their own words some of the core information, to be sure that it has been understood. A functional name, such as a 'heart pill' is often easier to remember and clearer in terms of indication.

Box 9:   Aids to improving patient adherence to treatment

Patient leaflets
Patient leaflets reinforce the information given by the prescriber and pharmacist. The text should be in clear, common language and in easily legible print.

Pictorials and short descriptions
If the patient cannot read, try pictorials. If they are not available, make pictorials or short descriptions for your own P-drugs, and photocopy them.

Day calendar
A day calendar indicates which drug should be taken at different times of the day. It can use words or pictorials: a low sun on the left for morning, a high sun for midday, a sinking sun for the end of the day and a moon for the night.

Drug passport
A small book or leaflet with an overview of the different drugs that the patient is using, including recommended dosages.

Dosage box

The dosage box is becoming popular in industrialized countries. It is especially helpful when many different drugs are used at different times during the day. The box has compartments for the different times per day (usually four), spread over seven days. It can then be refilled each week. If cost is a problem, the box can be made locally from cardboard. In tropical countries a

Even if the patient aids described here don't exist in your country, with creativity you can often find your own solutions. The important thing is to give your patients the information and tools they need to use drugs appropriately.

The six points listed below summarize the **minimum** information that should be given to the patient.

1. **Effects of the drug**
   Why the drug is needed
   Which symptoms will disappear, and which will not
   When the effect is expected to start
   What will happen if the drug is taken incorrectly or not at all

2. **Side effects**
   Which side effects may occur
   How to recognize them
   How long they will continue
   How serious they are
   What action to take

3. **Instructions**
   How the drug should be taken
   When it should be taken
   How long the treatment should continue
   How the drug should be stored
   What to do with left-over drugs

4. **Warnings**
   When the drug should not be taken
   What is the maximum dose
   Why the full treatment course should be taken

5. **Future consultations**
   When to come back (or not)
   In what circumstances to come earlier
   What information the doctor will need at the next appointment

6. **Everything clear?**
   Ask the patient whether everything is understood
   Ask the patient to repeat the most important information
   Ask whether the patient has any more questions

This may seem a long list to go through with each patient. You may think that there is not enough time; that the patient can read the package insert with the medicine; that the pharmacist or dispenser should give this information; or that too much information on side effects could even decrease adherence to treatment. Yet it is the prime responsibility of the doctor to ensure that the treatment is understood by the patient, and this responsibility cannot be shifted to the pharmacist or a package insert. Maybe not all side effects have to be mentioned, but you should at least warn your patients of the most dangerous or inconvenient side effects. Having too many patients is never accepted by a court of law as a valid excuse for not informing and instructing a patient correctly.

Exercise: Patients 34-38
Review the following prescriptions and list the most important instructions and warnings that should be given to the patient. You may consult your pharmacology books. Cases are discussed below.

Patient 34:
> *Man, 56 years. Newly diagnosed depression. R/amitriptyline 25 mg, 1 tablet daily at night for one week.*

Patient 35:
> *Woman, 28 years. Vaginal trichomonas infection. R/metronidazole 500 mg, 1 vaginal tablet daily for 10 days.*

Patient 36:
> *Man, 45 years. Newly diagnosed essential hypertension. R/atenolol 50 mg, 1 tablet daily.*

Patient 37:
> *Boy, 5 years. Pneumonia. R/amoxicillin syrup, 5 ml (= 250 mg) three times daily.*

Patient 38:
> *Woman, 22 years. Migraine. R/paracetamol 500 mg, 2 tablets 20 min. after R/metoclopramide 10 mg 1 suppository, at the onset of an attack.*

Patient 34 (depression)
It will take approximately two to three weeks before the patient starts to feel better, but side effects, such as dry mouth, blurred vision, difficulty in urinating and sedation, may occur quickly. Because of this many patients think that the treatment is worse than the disease and stop taking the drug. If they are not told that this may happen and that these effects disappear after some time, adherence to treatment will be poor. For this reason a slowly rising dosage schedule is usually chosen, with the tablets taken before bedtime. This should be explained carefully to the patient. Older people, especially, may not remember difficult dosage schedules. Write them down, or give a medication box. You can also ask

the pharmacist to explain it again (write this on the prescription). Instructions are to follow the dosage schedule, to take the drug at bedtime and not to stop the treatment. Warnings are that the drug may slow reactions, especially in combination with alcohol.

Patient 35 (vaginal trichomonas)
As in any infection the patient should be told why the course has to be finished completely, even when the symptoms disappear after two days. The patient should also be informed that treatment is useless if the partner is not treated as well. Careful and clear instructions are needed for vaginal tablets. If possible, pictures or leaflets should be used to show the procedure (see Annex 3). Side effects of metronidazole are a metal taste, diarrhoea or vomiting, especially with alcohol, and dark urine. Give a clear warning against the use of alcohol.

Patient 36 (essential hypertension)
The problem with the treatment of hypertension is that patients rarely experience any positive effect of the drugs, yet they have to take them for a long time. Adherence to treatment may be very poor if they are not told why they should take the drug, and if treatment is not monitored regularly. The patient should be told that the drug prevents complications of high blood pressure (angina, heart attack, cerebral problems). You can also say that you will try to decrease the dosage after three months, or even stop the drug entirely. Remember to check whether the patient has a history of asthma.

Patient 37 (boy with pneumonia)
The patient's mother should be told that the penicillin will need some time to kill the bacteria. If the course of treatment is stopped too soon, the stronger ones will survive, and cause a second, possibly more serious infection. In this way she will understand why it is necessary to finish the course. Knowing that any side effects will disappear soon will increase the likelihood of adherence to treatment. She should also be told to contact you immediately if a rash, itching or rising fever occur.

Patient 38 (migraine)
In addition to other information the important instruction here is that the drug (preferably a suppository) should be taken 20 minutes before the analgesic, to prevent vomiting. Because of possible sedation and loss of coordination she should be warned not to drive a car or handle dangerous machinery.

Sample page of a personal formulary

Tablet 50, 100 mg	Beta blocker	**ATENOLOL**

* DOSAGE
Hypertension: start with 50 mg in the morning. Average: 50-100 mg per day.

Angina pectoris: **100 mg per day in 1-2 doses** as low as possible. Raise the dose after 2 weeks, if needed.

Adjust to each patient individually, start as low as possible. Raise the dose after 2 weeks, if needed.

* WHAT TO TELL THE PATIENT

Information

Hypertension: drug decreases blood pressure, patient will usually not notice any effect. Drug will prevent complications of high blood pressure (angina, heart attack, cerebrovascular accident).

Angina pectoris: decreases blood pressure, prevents the heart from working too hard, preventing chest pain.

Side effects: hardly any, sometimes slight sedation.

Instructions

Take the drug .. times per day, for .. days

Warnings

Angina pectoris: do not suddenly stop taking the drug.

Next appointment

Hypertension: one week.

Angina pectoris: within one month, earlier if attacks occur more frequently, or become more severe.

* FOLLOW-UP

Hypertension: during first few months pulse and blood pressure should be checked weekly. Try to decrease dosage after three months. Higher dosages do not increase therapeutic effect, but may increase side effects. Try to stop treatment from time to time.

Angina pectoris: in case frequency or severity of the attacks increase, more diagnostic tests or other treatment are needed. Try to stop drug treatment from time to time.

Your personal formulary

During your medical studies you should continue to expand your list of common complaints and diseases, with your P-drugs and P-treatments. However, very soon you will notice that many drugs are used for more than one indication. Examples are analgesics, certain antibiotics, and even more specific drugs like beta-blockers (used for hypertension and angina pectoris). You can, of course, repeat the necessary drug information with each disease or complaint, but it may be easier to make a separate section in your personal formulary where you collect the necessary information for each of your P-drugs. This way you write down or update the drug information only once. You can also find the information more easily when you need it.

It is good advice to note the essential instructions and warnings with each P-drug in your personal formulary. If you do this for every new drug you learn to use, the formulary will be reasonably complete and ready for use by the time you finish your medical studies. An example of the contents of such a personal formulary is given on the previous page. Please note that this is not a published text, but should be your personal (handwritten?) summary of important information.

Summary

STEP 5: Give information, instruction and warnings

1. **Effects of the drug**
   Which symptoms will disappear; and when; how important is it to take the drug; what happens if it is not taken;

2. **Side effects**
   Which side effects may occur; how to recognize them; how long will they remain; how serious they are; what to do if they occur;

3. **Instructions**
   When to take; how to take; how to store; how long to continue the treatment; what to do in case of problems;

4. **Warnings**
   What not to do (driving, machinery); maximum dose (toxic drugs); need to continue treatment (antibiotics);

5. **Next appointment**
   When to come back (or not); when to come earlier; what to do with left-over drugs; what information will be needed;

6. **Everything clear?**
   Everything understood; repeat the information; any more questions.

C hapter 11

STEP 6: Monitor (and stop?) the treatment

You have now learned how to choose a rational drug treatment, how to write the prescription and what to tell your patient. Yet even a well chosen treatment may not always help the patient. Monitoring the treatment enables you to determine whether it has been successful or whether additional action is needed. To do this you need to keep in touch with your patient, and this can be done in two ways.

Passive monitoring means that you explain to the patient what to do if the treatment is not effective, is inconvenient or if too many side effects occur. In this case monitoring is done by the patient.

Active monitoring means that you make an appointment to determine yourself whether the treatment has been effective. You will need to determine a monitoring interval, which depends on the type of illness, the duration of treatment, and the maximum quantity of drugs to prescribe. At the start of treatment the interval is usually short; it may gradually become longer, if needed. Three months should be the maximum for any patient on long-term drug therapy. Even with active monitoring the patient will still need the information discussed in Chapter 10.

The purpose of monitoring is to check whether the treatment has solved the patient's problem. You chose the treatment on the basis of efficacy, safety, suitability and cost. You should use the same criteria for monitoring the effect, but in practice they can be condensed into two questions: is the treatment effective? Are there any side effects?

History taking, physical examination and laboratory tests will usually provide the information you need to determine the effectiveness of treatment. In some cases more investigations may be needed.

Treatment is effective

If the disease is cured, the treatment can be stopped.[4] If the disease is not yet cured or chronic, and the treatment is effective and without side effects, it can be continued. If serious side effects have occurred you should reconsider your selected drug and dosage schedule, and check whether the patient was correctly

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[4] Except in cases in which a standard duration of treatment is crucial, such as with most antibiotics.

Table 8: Some examples of drugs in which a slow reduction in dose should be considered
Amphetamines Antiepileptics Antidepressants Antipsychotics Cardiovascular drugs   clonidine   methyldopa   beta-blockers   vasodilators Corticosteroids Hypnotics/sedatives   benzodiazepines   barbiturates Opiates

instructed. Many side effects are dose dependent, so you may try to lower the dose before changing to another drug.

Treatment is not effective

If the treatment is not effective, with or without side effects, you should reconsider the diagnosis, the treatment which was prescribed, whether the dose was too low, whether the patient was correctly instructed, whether the patient actually took the drug, and whether your monitoring is correct. When you have determined the reason for the treatment failure you should look for solutions. So the best advice is to go again through the process of diagnosis, definition of therapeutic objective, verification of the suitability of the P-drug for this patient, instructions and warnings, and monitoring. Sometimes you will find that there is no real alternative to a treatment that has not been effective or has serious side effects. You should discuss this with the patient. When you cannot determine why the treatment was not effective you should seriously consider stopping it.

If you decide to stop drug treatment you should remember that not all drugs can be stopped at once. Some drugs (Table 8) have to be tailed off, with a decreasing dosage schedule.

    <u>Exercise: patients 39-42</u>
    In the following cases, try to decide whether the treatment can be stopped or not. Cases are discussed below.

    Patient 39:
        Man, 40 years. Review visit after pneumonia, treated with oral ampicillin (2 grams daily) for one week. No symptoms remain, only slight unproductive cough. Examination normal.

    Patient 40:
        Man, 55 years. Severe myalgia and undefined arthritis for many years. Has been on prednisolone (50 mg daily) and indometacin (10 mg daily) for a long time. Epigastric pain and pyrosis over several months, for which he takes aluminum hydroxide tablets from time to time. During the consultation he complains that the epigastric pain and pyrosis have not disappeared; in fact they have become worse.

Patient 41:

> *Woman, 52 years. Mild hypertension for the past two years. Responded well to a thiazide diuretic (25 mg daily). The maintenance dose has already been decreased twice because her blood pressure had dropped to around normal. She regularly forgets to take the drug.*

Patient 42:

> *Man, 75 years. Had been prescribed temazepam for one week, (10 mg daily) because of sleeplessness after his wife died six months ago. He asks for more, because he is afraid he will still not be able to sleep.*

Patient 39 (pneumonia)

The course of treatment was defined in advance. It was effective and without side effects. The ampicillin can be stopped.

Patient 40 (epigastric pain)

In this case the treatment has not been effective because the epigastric pain is a side effect of the drugs used for myalgia. The treatment that really needs monitoring is the anti-inflammatory drugs, not the aluminium hydroxide. The problem can be solved by finding out whether the pain occurs at certain times, rather than being continuous. In this case the dosage schedule could be adjusted to reach peak plasma concentrations at those times, and the total daily dose could be lowered. The lesson to be learned from this patient is that it is better to reconsider the original therapy rather than to 'treat' its side effects with another drug.

Patient 41 (mild hypertension)

This treatment seems effective and without side effects. The patient is no longer hypertensive and may not need continued therapy, especially since she regularly forgets to take the drug. You can stop the treatment for assessment but you must continue to monitor the patient.

Patient 42 (insomnia)

As the patient wants to continue the treatment it was obviously effective. However, benzodiazepines can produce psychological and physical dependence when taken regularly for more than a few weeks. In addition, tolerance develops quickly and this can lead patients to take more than the recommended dose. You should explain this to the patient and also tell him that the nature of the sleep induced by such drugs is not the same as normal sleep, but the result of suppressed brain activity. Encourage him to try to return to natural sleep patterns; possibly a warm bath or a hot milk drink will help to promote relaxation before bedtime. It may also help to encourage him to express his feelings about his loss; acting as a sympathetic listener is probably your major therapeutic role in this case, rather than prescribing more drugs. In this case the

drug can be stopped at once because it was only used for one week. This cannot be done when patients have taken benzodiazepines for longer periods of time.

Summary

STEP 6:   Monitor (and stop?) the treatment

Was the treatment effective?

a. Yes, and disease cured: Stop the treatment

b. Yes, but not yet completed: Any serious side effects?
                                     •No: treatment can be continued
                                     •Yes: reconsider dosage or drug choice

c. No, disease not cured: Verify all steps:
                                     •Diagnosis correct?
                                     •Therapeutic objective correct?
                                     •P-drug suitable for this patient?
                                     •Drug prescribed correctly?
                                     •Patient instructed correctly?
                                     •Effect monitored correctly?

Part 4: Keeping up-to-date

In this section various sources of drug and therapeutic information are discussed, together with their relative advantages and disadvantages. It also includes practical advice on how to read scientific papers in general, and clinical trials in particular.

Chapter 12

C hapter 12

How to keep up-to-date about drugs

Knowledge and ideas about drugs are constantly changing. New drugs come on the market and experience with existing drugs expands. Side effects become better known and new indications or ways of using existing drugs are developed. In general a physician is expected to know about developments in drug therapy. For example, if a drug-induced illness occurs which the physician could have known and prevented, courts in many countries would hold the doctor liable. Lack of knowledge is not an excuse.

How can you keep up-to-date? This problem can be solved in the usual way: make an inventory of available types of information; compare their advantages and disadvantages; and choose your own source(s) of information.

Make an inventory of available sources of information

There are numerous sources of drug information, ranging from international data bases, journals and reference books, to national or regional drug information centres, and locally produced formularies and bulletins. Annex 2 provides a list of essential references. Some sources are commercial and independent, others are non-commercial. Information is available verbally or in written form, on tape or video, 'on-line' (interactive connection with a central computer data base) or on CD-ROM (Compact Disk Read-Only Memory, a compact disk with information, read by personal computer).

Reference books

Reference books can cover general or clinical pharmacology, or specialize in a particular aspect. Examples of general pharmacological reference books in English are Goodman and Gilman's *The Pharmacological Basis of Therpautics* and Laurence and Bennett's *Clinical Pharmacology* (see Annex 2). Good equivalents exist in other languages. An important criterion in choosing reference books is the frequency of new editions. Only publications that are revised every two to five years can provide up-to-date knowledge.

Martindale's *The Extra Pharmacopoeia* is an excellent reference book with detailed drug information on most active substances and chemicals. However, it does not distinghuish between essential and non-essential drugs and does not contain comparative therapeutic information. Avery's *Drug Treatment* is a more

specialized book, appropriate for prescribers with a special interest in clinical pharmacology.

Another example of a specialized textbook is Meyler's *Side Effects of Drugs*, which provides an annually updated assessment of side effects of drugs reported worldwide. It is, however, expensive. Other specialized books address such areas as psychotropic drugs, or specific risk groups such as drugs in lactation, drugs for children, or drugs for the elderly.

Drug compendia

In many countries there are publications that list the drugs available on the market. These compendia vary in type and scope but usually include generic and brand names; chemical composition; clinical indications and contraindications; warnings, precautions and interactions; side effects; administration and dosage recommendations. Some are based on the official labelling information for the product as approved by the national regulatory authority. An example is the annual *Physician's Desk Reference,* which is available free of charge to physicians in the United States.

Commercially sponsored drug compendia may have additional limitations. For example, the drug listing may be incomplete, and comparative assessments are usually lacking. An example is the *Monthly Index of Medical Specialities (MIMS)* which is published in different parts of the world.

However, comprehensive and objective compendia are available which do include comparative assessments and/or provide criteria for choice within well-defined therapeutic drug categories. Examples are the *United States Pharmacopeia Dispensing Information (USP DI)*, which is not available free of charge, and the *British National Formulary (BNF)*, which is free to all UK prescribers. The latter includes information on cost, which is not often included in other compendia. The frequent revisions of both publications contribute to their value. In fact, they are issued so frequently that old copies, which may be available at very low cost or free of charge, remain useful for quite some time.

National lists of essential drugs and treatment guidelines

In many developing countries a national list of essential drugs exists. It usually indicates the essential drugs chosen for each level of care (dispensary, health centre, district hospital, referral hospital). It is based on a consensus on the treatment of choice for the most common diseases and complaints, and defines the range of drugs that is available to prescribers. If no national list of essential drugs exists, you may consult the WHO model list (see Annex 2). Very often national treatment guidelines, which include the most important clinical information for the prescriber (treatment of choice, recommended dosage schedule, side effects, contraindications, alternative drugs, etc.) are available.

You should verify whether such guidelines exist in your country. Try to obtain the most recent edition.

Drug formularies

Formularies contain a list of pharmaceutical products, together with information on each drug. They can be national, regional or institutional. They are usually developed by therapeutic committees and they list the drugs that are approved for use in that country, region, district or hospital. In many countries drug formularies are also developed for health insurance programmes, listing the products that are reimbursed. Drug formularies are usually drug-centred. Their value is enhanced if they contain comparisons between drugs, evaluations and cost information, but that is often not the case. The excellent *BNF* has already been mentioned. Try to get your own copy, even if it is not the most recent one. It fits well in your pocket.

Drug bulletins

These periodicals promote rational drug therapy and appear at frequent intervals, ranging from weekly to quarterly. Independent drug bulletins, i.e. non-industry sponsored, provide impartial assessments of drugs and practical recommend-ations, based on a comparison between treatment alternatives.

Drug bulletins can be a critical source of information in helping prescribers to determine the relative merits of new drugs and in keeping up-to-date. Drug bulletins can have a variety of sponsors, such as government agencies, professional bodies, university departments, philanthropic foundations and consumer organizations. They are published in many countries, are often free of charge, and are highly respected because of their unbiased information. Examples in English are: *Drug and Therapeutics Bulletin* (UK), *Medical Letter* (USA) and *Australian Prescriber* (Australia). A good independent drug bulletin in French is *Prescrire*; it is not free of charge.

National drug bulletins are appearing in an increasing number of developing countries, which include Bolivia, Cameroon, Malawi, the Philippines and Zimbabwe. The main advantages of national drug bulletins are that they can select topics of national relevance and use the national language.

Medical journals

Some medical journals are general, such as *The Lancet*, the *New England Journal of Medicine* or the *British Medical Journal*; others are more specialized. Most countries have their own national equivalents. Both types contain much information of relevance to prescribers. The general journals regularly publish review articles on treatment. The specialized journals include more detailed information on drug therapy for specific diseases.

Good medical journals are 'peer reviewed', that is, all articles are sent for independent expert review prior to publication. You can usually check whether journals meet this important criterion by reading the published instructions for submission of articles.

Some journals are not independent. They are usually glossy and often present information in an easily digestible format. They can be characterized as: free of charge, carrying more advertisements than text, not published by professional bodies, not publishing original work, variably subject to peer review, and deficient in critical editorials and correspondence. In the industrialized world they are promoted to the physician as a 'way to save time'. In fact reading them is a loss of time, which is why they are commonly referred to as 'throwaways'. Also be careful with journal supplements. They sometimes report on commercially sponsored conferences; in fact, the whole supplement may be sponsored.

So don't assume that because a review article or research study appears in print that it is necessarily good science. Thousands of 'medical' journals are published and they vary enormously in quality. Only a relatively small proportion publish scientifically validated, peer reviewed articles. If in doubt about the scientific value of a journal, verify its sponsors, consult senior colleagues, and check whether it is included in the *Index Medicus*, which covers all major reputable journals.

Verbal information

Another way to keep up-to-date is by drawing on the knowledge of specialists, colleagues, pharmacists or pharmacologists, informally or in a more structured way through postgraduate training courses or participation in therapeutic committees. Community based committees typically consist of general practitioners and one or more pharmacists. In a hospital setting they may include several specialists, a clinical pharmacologist and/or a clinical pharmacist. Such committees meet regularly to discuss aspects of drug treatment. In some cases they establish local formularies and follow up on their use. Using a clinical specialist as the first source of information may not be ideal when you are a primary health care physician. In many instances the knowledge of specialists may not really be applicable to your patients. Some of the diagnostic tools or more sophisticated drugs may not be available, or needed, at that level of care.

Drug information centres

Some countries have drug information centres, often linked to poison information centres. Health workers, and sometimes the general public, can call and get help with questions concerning drug use, intoxications, etc. Modern informatics, such as on-line computers and CD-ROM, have dramatically improved access to large volumes of data. Many major reference data bases, such as *Martindale* and *Meylers Side Effects of Drugs*, are now directly accessible

Cartoon 5

through international electronic networks. When drug information centres are run by the pharmaceutical department of the ministry of health, the information is usually drug focused. Centres located in teaching hospitals or universities may be more drug problem or clinically oriented.

Computerized information

Computerized drug information systems that maintain medication profiles for every patient have been developed. Some of these systems are quite sophisticated and include modules to identify drug interactions or contraindications. Some systems include a formulary for every diagnosis, presenting the prescriber with a number of indicated drugs from which to choose, including dosage schedule and quantity. Prescribers can also store their own formulary in the computer. If this is done, regular updating is needed using the sources of information described here. In many parts of the world access to the hardware and software needed for this technology will remain beyond the reach of individual prescribers. In countries where such technology is easily accessible it can make a useful contribution to prescribing practice. However, such systems cannot replace informed prescriber choice, tailored to meet the needs of individual patients.

Pharmaceutical industry sources of information

Information from the pharmaceutical industry is usually readily available through all channels of communication: verbal, written and computerized. Industry promotion budgets are large and the information produced is invariably attractive and easy to digest. However, commercial sources of information often emphasize only the positive aspects of products and overlook or give little coverage to the negative aspects. This should be no surprise, as the primary goal of the information is to promote a particular product. Commercial information is often tailored to the prescriber's specific situation: information on an anti-nauseant given to a gynaecologist in a university hospital may differ from that given to a general practitioner in rural practice.

Usually the pharmaceutical industry uses a 'multi-track' approach. This means that the information is provided through a number of media: medical representatives (detail men/women), stands at professional meetings, advertising in journals and direct mailing.

From industry's point of view, medical representatives are usually very effective in promoting drug products, and much more effective than mailings alone. Often over 50% of the promotional budget of pharmaceutical companies in industrialized countries is spent on representatives. Studies from a number of countries have shown that over 90% of physicians see representatives, and a substantial percentage rely heavily on them as sources of information about therapeutics. However, the literature also shows that the more reliant doctors are on commercial sources of information only, the less adequate they are as prescribers.

In deciding whether or not to use the services of drug representatives to update your knowledge on drugs, you should compare the potential benefits with those of spending the same time reading objective comparative information.

If you do decide to see representatives, there are ways to optimize the time you spend with them. Take control of the discussion at the outset so that you get the information you need about the drug, including its cost. If your country has a health insurance scheme, check whether the drug is included in the list of reimbursable products. Early on in the discussion ask the representative to give you a copy of the officially registered drug information (data sheet) on the product under discussion, and during the presentation compare the verbal statements with those in the official text. In particular look at side effects and contraindications. This approach will also help you to memorize key information about the drug.

Always ask for copies of the published references on efficacy and safety. Even before reading these, the quality of the journals in which they appear will be a strong indication of the likely quality of the study. You should know that the majority of newly marketed drugs do not represent true therapeutic advances but are what is known as 'me too' products. In other words, they are very similar in chemical composition and action to other products on the market. The difference is usually in price; the most recently marketed drug is usually the most expensive! Seeing medical representatives can be useful to learn what is new, but the information should always be verified and compared with impartial, comparative sources.

Drug information from commercial sources is also issued as news reports, and as scientific articles in professional journals. Industry is also a major sponsor of scientific conferences and symposia. The line between objective and promotional information is not always clear. A number of countries and professional associations are tightening regulations controlling drug promotion to tackle this problem. Some journals now require that any sponsorship from the pharmaceutical industry should be mentioned in the article.

As mentioned above and as studies show, it is not good practice to use only commercial information to keep up-to-date. Although it may seem an easy way

to gather information, this source is often biased towards certain products and is likely to result in irrational prescribing. This is particularly true for countries without an effective regulatory agency, because more drugs of sometimes doubtful efficacy may be available and there may be little control on the contents of data-sheets and advertisements.

WHO has issued *Ethical Criteria for Medicinal Drug Promotion* which contain global guidelines for promotional activities. The International Federation of Pharmaceutical Manufacturers' Associations also has a code of pharmaceutical marketing practices. In several countries national guidelines exist as well. Most guidelines specify that the promotional information should be accurate, complete and in good taste. It is a very good exercise to compare a number of drug advertisements with the national or global criteria. Most guidelines also cover the use of samples and gifts, participation in promotional conferences and clinical trials, etc.

If you do use commercial information follow these ground rules. First, look for more information than advertisements contain. Second, look or ask for references, and check their quality. Only references in well established peer reviewed journals should be taken seriously. Then check the quality of the research methodology on which the conclusions are based. Third, check what your colleagues, and preferably a specialist in the field, know about the drug. Finally, always collect data from unbiased sources before actually using the drug. Do **not** start by using free samples on a few patients or family members, and do **not** base your conclusions on the treatment of a few patients!

Yet commercial information is sometimes helpful in a general sense, especially to know of new developments. However, comparative information from drug bulletins or therapeutic reviews is absolutely essential to help you evaluate the new drug in relation to existing treatments, and to decide whether you wish to include it in your personal formulary.

Choose between sources of information

The advantages and disadvantages of various drug information sources have been outlined. Possible information sources will vary according to country and your own personal situation. Your job is now to decide how best to keep up-to-date, by making a list of all the possible resources to which you have access. Try to find at least one each of the following: (1) medical journals; (2) drug bulletins; (3) pharmacology or clinical reference books; (4) therapeutic committees or consultants or a postgraduate training course.

Although your primary source of prescribing information in your daily clinical work should be your personal formulary, you will sometimes face a difficult problem, which calls for an additional source of information. This could be a

pharmacology or clinical reference book, a drug bulletin, consultants (pharmacist, specialist, colleagues), a drug compendium or a formulary.

The limitations of commercial information have been clearly described. If you decide, nevertheless, that it has a role to play, follow the ground rules already outlined. But do not use commercial information in isolation from other more objective sources.

Efficient reading

Articles

Many prescribers have a problem in reading everything they would like. The reasons are lack of time and - in industrialized countries - the sheer volume of materials mailed to them. It's wise to adopt a strategy to use your time as efficiently as possible.

You can save time when reading clinical journals by identifying at an early stage articles which are worth reading, through the steps listed below.

1. Look at the **title** to determine if it appears interesting or useful to you. If not, move on to the next article.

2. Review the **authors**. The experienced reader will know of many authors whether they generally provide valuable information or not. If not, reject the article. If the authors are unknown, give them the benefit of the doubt.

3. Read the **abstract**. The main point here is to decide whether the conclusion is important to you. If not, reject the article.

4. Consider the site to see if it is sufficiently similar to your own situation, and decide whether the conclusion may be **applicable** to your work. For example, a conclusion from research in a hospital may not be relevant for primary care. If the site differs too much from your own situation, reject the article.

5. Check the **'materials and methods'** section. Only by knowing and accepting the research method can you decide whether the conclusion is valid.

6. Check the **references**. If you know the subject you will probably be able to judge whether the authors have included the key references in that field. If these are missing, be careful.

Clinical trials

It is beyond the scope of this book to go into the details of how reports on clinical trials should be assessed, but a few general principles are given here. Generally, only randomized, double-blind clinical trials give valid information about the effectiveness of a treatment. Conclusions drawn from studies of other design may be biased.

Second, a complete description of a clinical trial should include (1) the patients in the trial, with number, age, sex, criteria for inclusion and exclusion; (2) administration of the drug(s): dose, route, frequency, checks on non-adherence to treatment, duration; (3) methods of data collection and assessment of therapeutic effects; and (4) a description of statistical tests and measures to control for bias.

Finally you should look at the clinical relevance of the conclusion, not only its statistical significance. Many statistical differences are too small to be clinically relevant.

Sometimes conflicting evidence is presented by different sources. If in doubt, first check on the methodology, because different methods may give different results. Then look at the population studied to see which one is more relevant to your situation. If doubts remain, it is better to wait and to postpone a decision on your P-drug choice until more evidence has emerged.

Conclusion

Keeping up-to-date should not be too difficult for prescribers in developed countries; it can be far from easy in some parts of the world where access to independent sources of drug information is very limited. But wherever you live and work it is important to develop a strategy to maximize your access to the key information you need for optimal benefit of the drugs you prescribe. Be aware of the limitations of some types of information, and spend your time on information that is worth it.

A nnexes

A nnex 1

Essentials of pharmacology in daily practice

Contents

Introduction

Pharmacology describes the interaction between drugs and organisms. In this interaction two features are especially important. **Pharmacodynamics** deals with the effects of a drug on the body; how a drug acts and its side effects, in which tissues, at which receptor sites, at which concentration, etc. The effects of drugs may be altered by other drugs or disease states. Antagonism, synergism, addition and other phenomena are also described by pharmacodynamics. **Pharmacokinetics** deals with the effects of the body on the drug, through Absorption, Distribution, Metabolism and Excretion (ADME).

The dynamics and kinetics of a drug determine its therapeutic usefulness. The **pharmacodynamics** of a drug determine its effectiveness and which side effects may occur, and at what concentration. The prescriber has very little influence on this. The **pharmacokinetics** of a drug determine how often, in what quantity and dosage form and for how long the drug should be given to reach and

maintain the required plasma concentration. As the prescriber can actively influence the process, the following section concentrates on this aspect.

Pharmacodynamics

Figure 10: Dose-response curve

The effects of a drug are usually presented in a **dose-response curve**. The effect of the drug is plotted on the Y-axis and the dose on the X-axis (Figure 10). The dose is usually plotted on a logarithmic scale. The higher the dose the stronger the effect, until the effect levels off to a maximum. The effect is usually expressed as a percentage of the maximum. The maximum effect of one drug may be more than that of another. Desired and side effects can both be plotted in dose-response curves.

The dose is usually expressed per kilogram body weight or per m^2 body surface area. However, the most accurate way is to use the plasma concentration, because it excludes differences in absorption and elimination of the drug. In the following text the plasma concentration-response curve (Cp/response curve) is used.

The Cp/response curve

The shape of the Cp/response curve is determined by pharmacodynamic factors. Cp/response curves reflect the result in a number of individuals, referred to as a 'population'. If the plasma concentration is lower than where the curve begins, 0% of the population will experience an effect. An effect of 50% means that the average effect in the total population is 50% of the maximum (and not a 50% effect in one individual) (Figure 10).

Unfortunately, most drugs have a Cp/response curve for side effects as well. This curve should be interpreted in the same way as Cp/response curves. The two curves together define the minimum and maximum plasma concentrations. The concentration that gives the minimum useful effect is the **therapeutic threshold**, while the plasma concentration at which the maximum tolerated side effects occur is called the **therapeutic ceiling**. Remember that Cp/response curves represent the dynamics in a group of patients, and can only offer a guideline when thinking in terms of an individual patient.
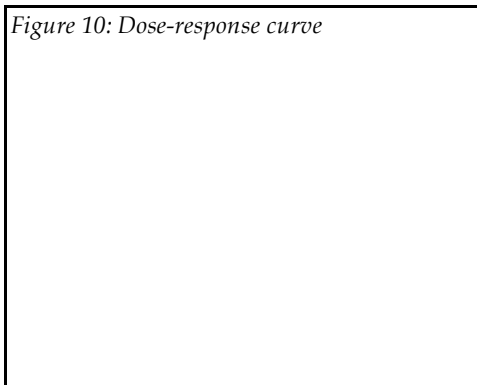
Pharmacokinetics

A dose is usually repeated over a certain period. The plasma concentration in one or more patients during a certain period is depicted in a so called **plasma concentration/time curve** (Cp/time curve). Figure 11 shows the Cp/time curve of the first 7 days after starting treatment.

Figure 11: Cp/time curve
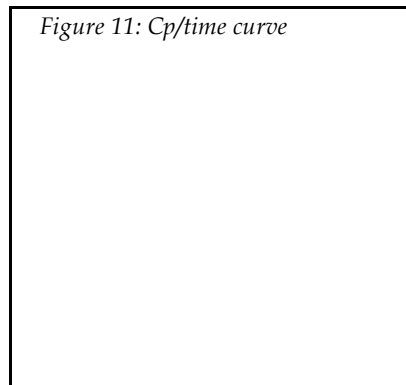
The shape of the Cp/time curves is defined by pharmacokinetic factors. The relationship between dose and plasma concentration is linear. This implies that if the dose is doubled, the steady state plasma concentration is also doubled (Figure 12).

Figure 12: Cp/time curve, dose doubled

The Cp/time curve with a therapeutic window

Two horizontal lines can be placed over the Cp/time curve, indicating therapeutic threshold and ceiling. The space between these two lines is called the **therapeutic window** (Figure 13). Drug treatment aims at plasma concentrations within this therapeutic window. The possible variables to be considered are therefore (1) the position and the width of the window, and (2) the profile of the curve.

Figure 13: Cp/time curve and therapeutic window

Therapeutic window

The position and the width of the window are determined by pharmacodynamic factors (Figure 14). The position of the window may shift upwards in case of resistance by the patient or competitive antagonism by another drug: a higher plasma concentration is needed to exert the same effect. The window can shift downwards in case of hypersensitization or synergism by another drug: a lower plasma concentration is needed.

Figure 14: Place and width of therapeutic window

The width of the window may also vary. It may become narrower in case of a decreased safety-margin. For example, the therapeutic window of theophylline is narrower in small children than in adults. A broader window usually has no consequences.

Curve

The profile of the curve is determined by four factors: *A*bsorption, *D*istribution, *M*etabolism and *E*xcretion. These are usually referred to as ADME factors. Although most treatments consist of more than one dose of a drug, some pharmacokinetic parameters can best be explained by looking at the effect of one dose only.

One of the most important parameters is the **half-life** of a drug (Figure 15). Most drugs are eliminated by means of a **first-order process**. This means that per unit of time the *same percentage* of drug is eliminated, for example 6% per hour. The half-life of a drug is the time it takes to decrease the plasma concentration to half of its initial value. With 6% per hour the half-life is about 11 hours (if no more of the drug is given in the meantime). After 2 half-lives

Figure 15: Half-life of a drug

(22 hours) it will be 25%; after 3 half-lives 12.5%; and after 4 half-lives 6.25%. If the original plasma concentration falls within the therapeutic window, a decline to 6.25% will usually be far below the therapeutic threshold. For this reason it is usually said that drugs no longer have a pharmacological effect 4 half-lives after the last dose.
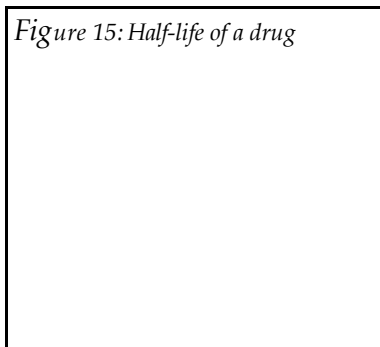
Drug treatment

The total Cp/time curve is influenced by three actions by the prescriber: starting the drug-treatment; steady state treatment; stopping the treatment. All have a distinct effect on the curve.

Starting drug treatment

The most important issue in starting treatment is the speed at which the curve reaches steady state, within the therapeutic window. If you give a fixed dose per unit of time, this speed is only determined by the half-life of the drug. On a fixed dosage schedule, steady state is reached after about 4 half-lives (Figure 16). In case of a long half-life it may therefore take some time for the drug to reach a therapeutic concentration. If you want to reach the window quicker, you can use a loading dose (see below).

Figure 16: Steady state is reached after 4 half-lives
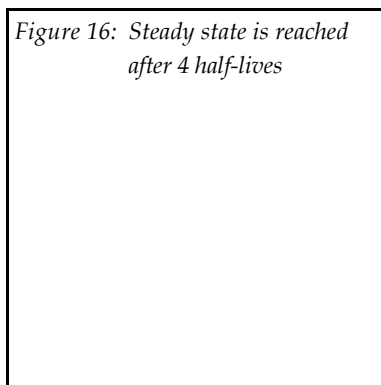
Steady state drug treatment

In steady state drug treatment two aspects are important. First, the mean plasma concentration is determined by the dose per day. The relation between dose and plasma concentration is linear: at double dose the mean plasma concentration also doubles.

Figure 17: Dose dependent fluctuations in the Cp/time curve

Second, fluctuations in the curve are determined by the frequency of administration. With the same total dose per day, a higher frequency of administration gives fewer fluctuations in the curve (Figure 17). With a continuous infusion there are no fluctuations at all.

If you decide to raise the dose it will again take about 4 half-lives before you reach the new steady state. The same applies when you decrease it by giving a lower dose.

Stopping drug treatment

For drugs with **first-order elimination** kinetics the plasma concentration decreases by 50% each half-life period, if no more of the drug is taken (Figure 18). The effect of the drug stops when the concentration falls below the therapeutic threshold. For example, if the initial plasma concentration is 300 ug/ml, the therapeutic threshold 75 ug/ml and the half-life 8 hours, this will take 16 hours (2 half-lives). This principle applies equally to drugs taken in overdose.

Figure 18: Stopping drug treatment

Some drugs are eliminated by **zero-order elimination** process. This means that the *same amount* of drug is eliminated per period of time. For example, 100 mg is eliminated per day, regardless of whether the total amount in the body is 600 mg or 20 grams. Such drugs do not have a half-life. This also means that the Cp/time curve never levels off to a certain maximum: the plasma concentration can rise forever if more of the drug is administered than the body can eliminate. To maintain a steady state you will have to administer exactly the amount that the body eliminates. The dosage of drugs in this category requires great care because of the increased risk of accumulation. Fortunately only a few such drugs exist. Examples are phenytoin, dicoumarol and probenicid. Acetylsalicylic acid in high dosage (grams per day) also behaves like this. And so does alcohol!

Special features of the curve

In commonly used dosage schedules with identical doses taken at regular intervals, the required steady state is reached after 4 half-lives, and plasma concentration drops to zero when the treatment is stopped.

Loading dose

There may be reasons to use another schedule. In steady state the total amount of drug in the body remains constant. If you want to reach this state quickly you can administer at once the total amount of drug which is present in the body in steady state (Figure 19). What quantity is then needed? Theoretically you will need the mean plasma concentration, multiplied by the distribution volume. In the majority of cases these figures can be found in pharmacology books, or may be obtained from the pharmacist or the manufacturer. For several drugs fixed schedules exist, e.g. for digoxin.

Figure 19: Loading dose
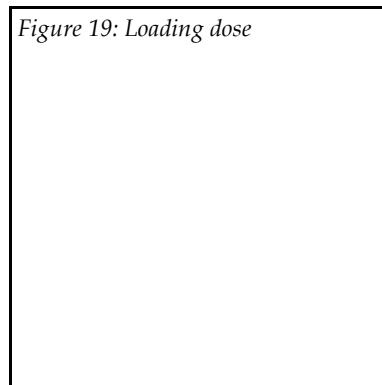
Slowly raising initial dose

Some drugs cannot be used in full dosage at once. There are three possible reasons for this. The first reason is when a drug has a narrow therapeutic window or a large variation in location of the therapeutic window in individuals. The aim is to get slowly within the window, without an overshoot. This is called **dose-finding**. A second reason is variation in kinetics among different patients. A third is to induce tolerance of side effects. The rule is 'go low, go slow'.

As mentioned earlier, it takes about 4 half-lives to reach a steady state. This means that you should not raise the dose before this time has elapsed and you have verified that no unwanted effects have occurred. Table 7 in Chapter 8 lists drugs in which slowly raising the dose is usually recommended.

Tapering the dose

Sometimes the human body gets used to the presence of a certain drug and physiological systems are adjusted to its presence. To prevent rebound symptoms the treatment cannot be abruptly stopped but must be tailed off to enable the body to readjust. To do this the dose should be lowered in small steps each time a new steady state is reached. Table 8 in Chapter 11 lists the most important drugs for which the dosage should be decreased slowly.

A nnex 2

Essential references

Practical low-cost books on drugs and prescribing

National essential drugs list, national formulary, hospital formulary, institutional and national treatment guidelines. These are essential tools in your prescribing, as they indicate which drugs are recommended and available in the health system. If these references do not exist:

WHO Model List of Essential Drugs. See: **The use of essential drugs** (containing the latest model list) under WHO publications on p.86. In the absence of a national list, the WHO model list offers a good indication of effective, safe and relatively cheap essential drugs within each therapeutic category.

WHO treatment guidelines for common diseases, such as acute respiratory tract infections, diarrhoeal diseases, malaria and other parasitic diseases, sexually transmitted diseases, tuberculosis, leprosy and others. These are very useful references, based on international expert consensus. In many cases they are used by countries when developing their national treatment guidelines.

British National Formulary. London: British Medical Association & The Pharmaceutical Society of Great Britain. This is a highly respected reference work containing essential information on a selection of drugs available on the UK market, with price indication. There are short evaluative statements for each therapeutic group. Although revised every six months, old issues remain a valuable source of information and may be available to you at no or very low cost.

Clinical Guidelines - Diagnostic and Treatment Manual. Paris: Médecins sans Frontières. Editions Hatier, 1990. This is a very practical book, which is largely based on WHO treatment guidelines for common diseases.

Major reference works

Avery GS. **Drug Treatment**. 2nd ed. Sydney: ADIS Press, 1987.

Laurence DR, Bennett PN. **Clinical Pharmacology**. 7th ed. Edinburgh: Churchill Livingstone, 1992.

Goodman & Gilman. **The Pharmacological Basis of Therapeutics**. 8th ed. New York: McMillan Publications Co, 1992.

Martindale. **The Extra Pharmacopoeia**. 30th Ed. London: Pharmaceutical Press, 1993

USP DI, Vol. 1.: **Drug Information for the Health Care Provider**, Vol. 2.: **Information for the Patient**. Under authority of the United States Pharmacopeial Convention Inc., 12601 Twinbrook Parkway, Rockville, Maryland 20832, USA.

Drug bulletins

Drug and Therapeutics Bulletin, Consumers' Association, 14 Buckingham Street, London WC2N 6DS, UK. Published fortnightly; offers comparative assessments of therapeutic value of different drugs and treatments.

Prescrire International, Association Mieux Prescrire, BP 459, 75527 Paris Cedex ll, France. Published quarterly; provides English translations of selected articles on clinical pharmacology, ethical and legal aspects of drugs, which have appeared in La Revue Prescrire.

The Medical Letter, The Medical Letter Inc. 56 Harrison Street, New Rochelle, NY 10801, USA. Published fortnightly; provides comparative drug profiles and advice on the choice of drugs for specific problems.

If you want to check whether an independent drug bulletin is published in your country contact: **The International Society of Drug Bulletins**, l03 Hertford Road, London N2 9BX, UK, or the WHO Action Programme on Essential Drugs.

WHO publications

The Use of Essential Drugs (including the 8th Model List of Essential Drugs). Geneva: World Health Organization, 1995. Technical Report Series 850. This booklet also contains the criteria for the selection of essential drugs and information on applications of the model list. The book is updated every two years.

WHO Model Prescribing Information. Geneva: World Health Organization. A series of authoritative booklets with unbiased drug information for the prescriber, including most drugs on the WHO Model List of Essential Drugs. Each module deals with one therapeutic group. The series is not yet complete.

WHO Ethical Criteria for Medicinal Drug Promotion. Geneva: World Health Organization, 1988. This is the text of a WHO statement adopted by the World Health Assembly of 1988, setting out general principles which could be adapted by governments to national circumstances. Reprinted in Essential Drugs Monitor 17.

WHO Drug Information. Geneva: World Health Organization. A quarterly journal that provides an overview of topics relating to drug development and regulation. It seeks to relate regulatory activity to therapeutic practice.

International Nonproprietary Names (INN) for Pharmaceutical Substances. Geneva: World Health Organization, 1992. This book contains an updated cumulative list of officially approved generic names in Latin, English, French, Russian and Spanish.

Essential Drugs Monitor, Geneva: World Health Organization, Action Programme on Essential Drugs. Free of charge and published three times per year; contains regular features on issues related to the rational use of drugs, including drug policy, research, education and training, and a review of new publications.

A nnex 3

How to explain the use of some dosage forms

Information, in simple language, on how to administer eye drops to a child or how to use an aerosol inhaler is not always easily available. This annex contains step by step guidance on how to administer different dosage forms. This information is included because, as a doctor, you are ultimately responsible for your patient's treatment, even if that treatment is actually administered by a colleague, such as a nurse, or by patients themselves. You will often need to explain to patients how to administer a treatment correctly. You may also need to teach other health workers.

The instructions have been presented in such a way that they can be used as a self-standing information sheet for patients. If you have access to a photocopy machine you might consider making copies of them as they are. You might also wish to adapt them to your own situation or translate them into a national language.

Table of contents page

CHECKLIST 1

Eye drops

1. Wash your hands.
2. Do not touch the dropper opening.
3. Look upward.
4. Pull the lower eyelid down to make a 'gutter'.
5. Bring the dropper as close to the `gutter' as possible without touching it or the eye.
6. Apply the prescribed amount of drops in the 'gutter'.
7. Close the eye for about two minutes. Do not shut the eye too tight.
8. Excess fluid can be removed with a tissue.
9. If more than one kind of eye-drop is used wait at least five minutes before applying the next drops.
10. Eye-drops may cause a burning feeling but this should not last for more than a few minutes. If it does last longer consult a doctor or pharmacist.
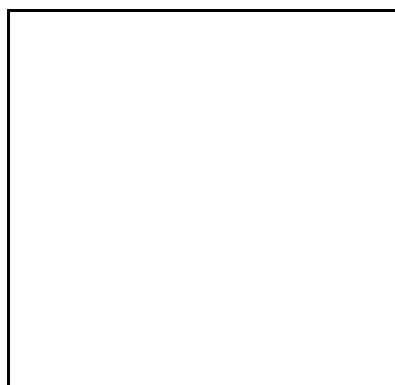
Steps 4 and 5

When giving eye-drops to children:

1. Let the child lie back with head straight.
2. The child's eyes should be closed.
3. Drip the amount of drops prescribed into the corner of the eye.
4. Keep the head straight.

5.   Remove excess fluid.

CHECKLIST 2

Eye ointment

1. Wash your hands.
2. Do not touch anything with the tip of the tube.
3. Tilt the head backwards a little.
4. Take the tube in one hand, and pull down the lower eyelid with the other hand, to make a 'gutter'.
5. Bring the tip of the tube as close to the 'gutter' as possible.
6. Apply the amount of ointment prescribed.
7. Close the eye for two minutes.
8. Remove excess ointment with a tissue.
9. Clean the tip of the tube with another tissue.
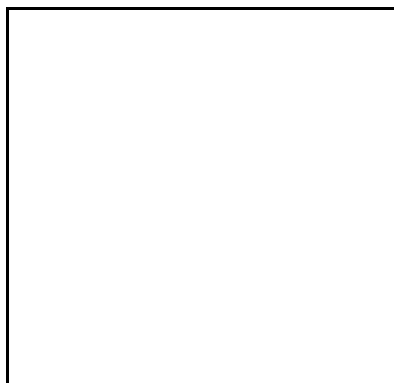
Steps 4 and 5

CHECKLIST 3

Ear drops

1. Warm the ear-drops by keeping them in the hand or the armpit for several minutes. Do not use hot water tap, no temperature control!
2. Tilt head sideways or lie on one side with the ear upward.
3. Gently pull the lobe to expose the ear canal.
4. Apply the amount of drops prescribed.
5. Wait five minutes before turning to the other ear.
6. Use cotton wool to close the ear canal after applying the drops ONLY if the manufacturer explicitly recommends this.
7. Ear-drops should not burn or sting longer than a few minutes.
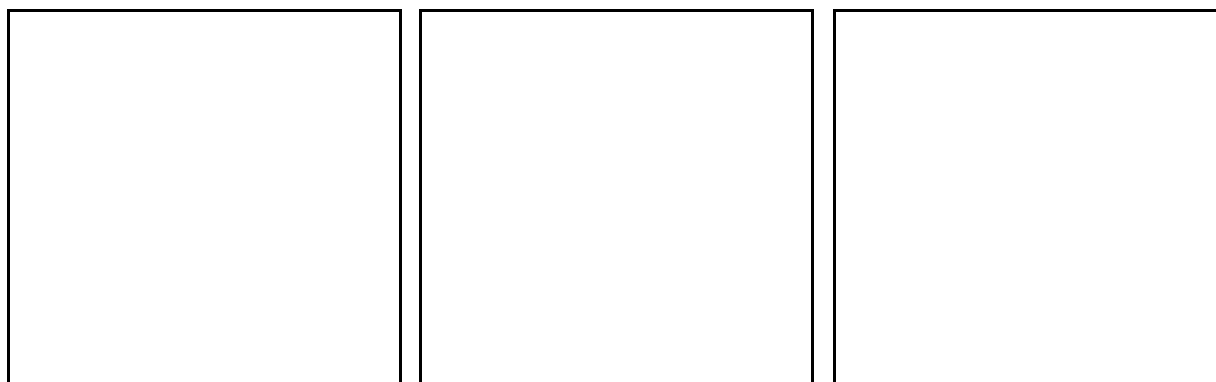
Step 1   **Steps 2 and 3**   **Step 6**

CHECKLIST 4

Nasal drops

1. Blow the nose.
2. Sit down and tilt head backward strongly or lie down with a pillow under the shoulders; keep head straight.
3. Insert the dropper one centimeter into the nostril.
4. Apply the amount of drops prescribed.
5. Immediately afterward tilt head forward strongly (head between knees).
6. Sit up after a few seconds, the drops will then drip into the pharynx.
7. Repeat the procedure for the other nostril, if necessary.
8. Rinse the dropper with boiled water.
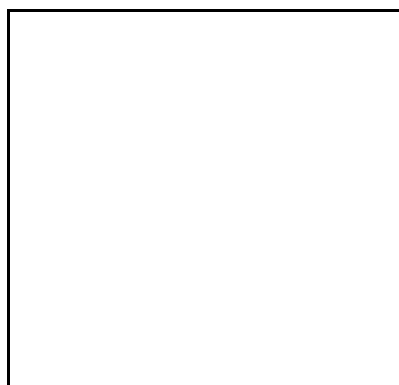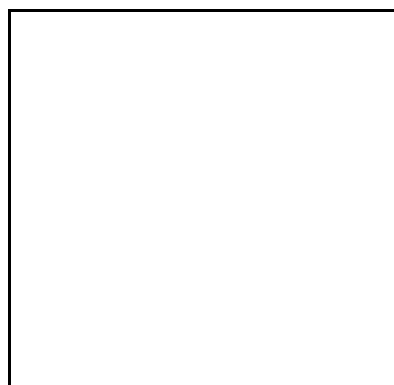
Steps 2 and 3   **Step 5**

CHECKLIST 5

Nasal spray

1. Blow the nose.
2. Sit with the head slightly tilted forward.
3. Shake the spray.
4. Insert the tip in one nostril.
5. Close the other nostril and mouth.
6. Spray by squeezing the vial (flask, container) and sniff slowly.
7. Remove the tip from the nose and bend the head forward strongly (head between the knees).
8. Sit up after a few seconds; the spray will drip down the pharynx.
9. Breathe through the mouth.
10. Repeat the procedure for the other nostril, if necessary.
11. Rinse the tip with boiled water.
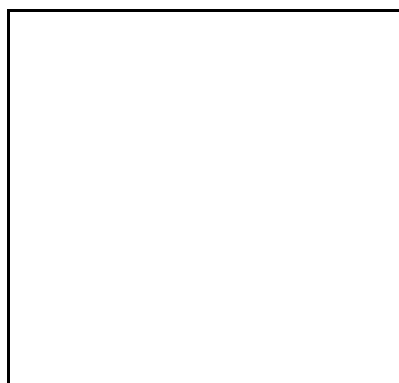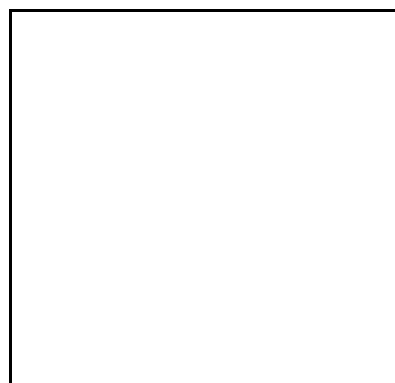
Steps 4 and 5 **Step 7**

CHECKLIST 6

Transdermal patch

1. For patch site see instructions included with the drug or check with your pharmacist.
2. Do not apply over bruised or damaged skin.
3. Do not wear over skin folds or under tight clothing and change spots regularly.
4. Apply with clean, dry hands.
6. Clean and dry the area of application completely.
7. Remove patch from package, do not touch 'drug' side.
8. Place on skin and press firmly. Rub the edges to seal.
9. Remove and replace according to instructions.
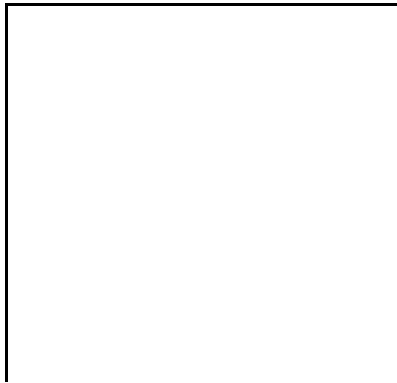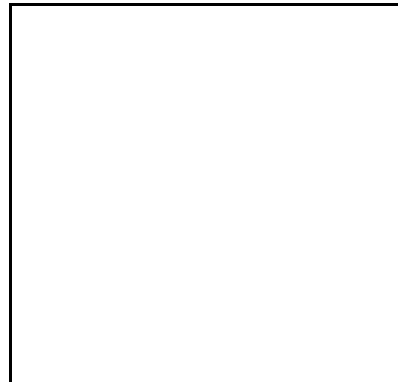
Step 7   **Step 8**

CHECKLIST 7

Aerosol

1. Cough up as much sputum as possible.
2. Shake the aerosol before use.
3. Hold the aerosol as indicated in the manufacturer's instructions (this is usually upside down).
4. Place the lips tightly around the mouthpiece.
5. Tilt the head backward slightly.
6. Breathe out slowly, emptying the lungs of as much air as possible.
8. Breathe in deeply and activate the aerosol, keeping the tongue down.
9. Hold the breath for ten to fifteen seconds.
10. Breathe out through the nose.
11. Rinse the mouth with warm water.
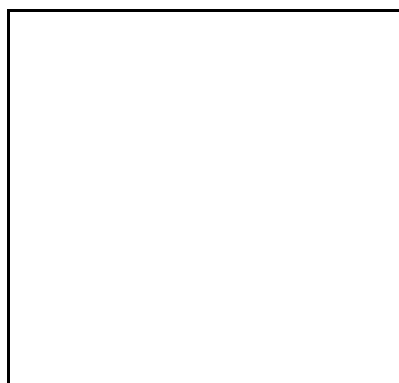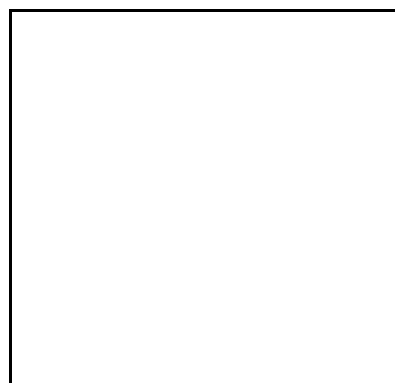
Steps 4 and 5   **Step 8**

CHECKLIST 8

Inhaler with capsules

1. Cough up as much sputum as possible.
2. Place the capsule(s) in the inhaler according to manufacturer's instructions.
3. Breathe out slowly and empty lungs of as much air as possible.
4. Place lips tightly around the mouthpiece.
5. Tilt head backward slightly.
6. Take a deep breath through the inhaler.
7. Hold the breath for ten to fifteen seconds.
8. Breathe out through the nose.
9. Rinse the mouth with warm water.
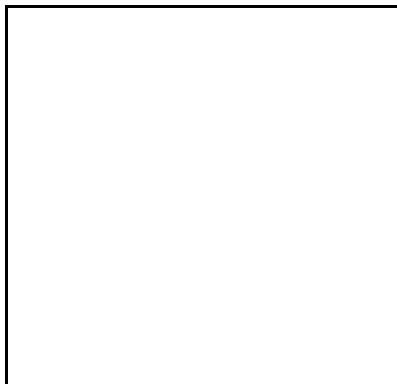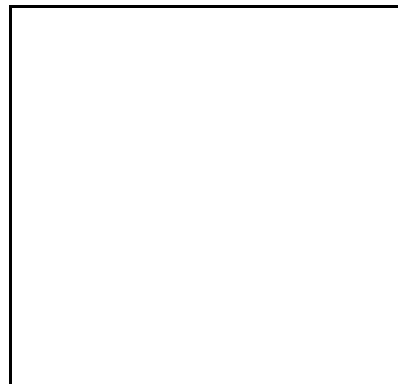
Step 4   **Step 5**

CHECKLIST 9

Suppository

1.   Wash your hands.
2.   Remove the covering (unless too soft).
3.   If the suppository is too soft let it harden first by cooling it (fridge or hold under cold running water, still packed!) then remove covering.
4.   Remove possible sharp rims by warming in the hand.
5.   Moisten the suppository with cold water.
6.   Lie on your side and pull up your knees.
7.   Gently insert the suppository, rounded end first, into the back passage.
8.   Remain lying down for several minutes.
9.   Wash your hands.
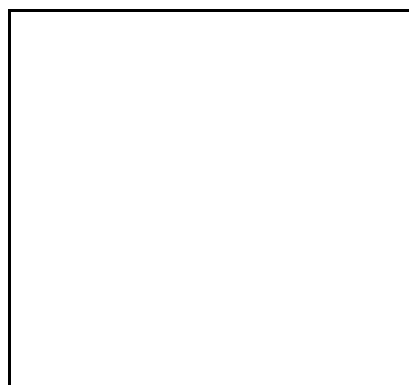
10. Try not to have a bowel movement during the first hour.

Step 6

CHECKLIST 10

Vaginal tablet with applicator

1. Wash your hands.
2 Remove the wrapper from the tablet.
3. Place the tablet into the open end of the applicator.
4. Lie on your back, draw your knees up a little and spread them apart.
5. Gently insert the applicator with the tablet in front into the vagina as far as possible, do NOT use force!
6. Depress the plunger so that the tablet is released.
7. Withdraw the applicator.
8. Discard the applicator (if disposable).
9. Clean both parts of the applicator thoroughly with soap and boiled, lukewarm water (if not disposable).
10. Wash your hands.
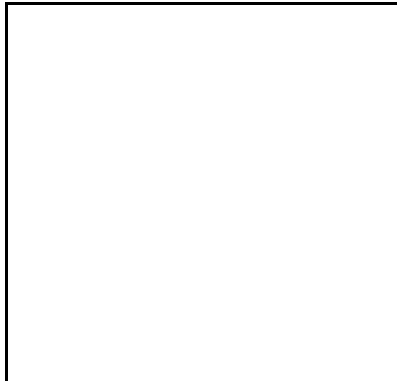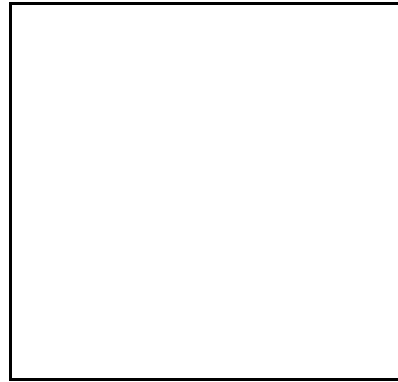
Steps 4 and 5   **Step 6**

CHECKLIST 11

Vaginal tablet without applicator

1. Wash your hands.
2. Remove the wrapper from the tablet.
3. Dip the tablet in lukewarm water just to moisten it.
4. Lie on your back, draw your knees up and spread them apart.
5. Gently insert the tablet into the vagina as high as possible, do NOT use force!
6. Wash your hands.
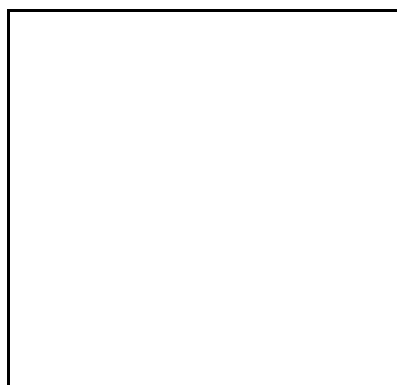
Steps 4 and 5

CHECKLIST 12

Applying vaginal creams, ointments and gels
(most of these drugs come with an applicator)

1. Wash your hands.
2. Remove the cap from the tube containing the drug.
3. Screw the applicator to the tube.
4. Squeeze the tube until the required amount is in the applicator.
5. Remove the applicator from the tube (hold the cylinder).
6. Apply a small amount of cream to the outside of the applicator.
7. Lie on your back, draw your knees up and spread them apart.
8. Gently insert the applicator into the vagina as far as possible, do NOT use force.
9. Hold the cylinder and with the other hand push the plunger down thus inserting the drug into the vagina.
10. Withdraw the applicator from the vagina.
11. Discard the applicator if disposable or clean thoroughly (boiled water) if not.
12. Wash your hands.
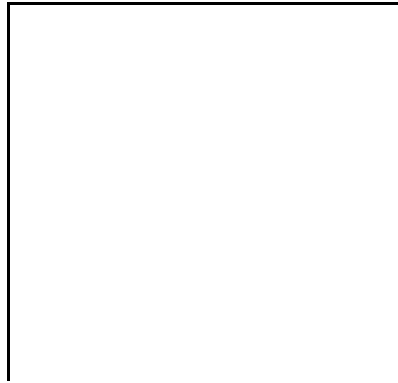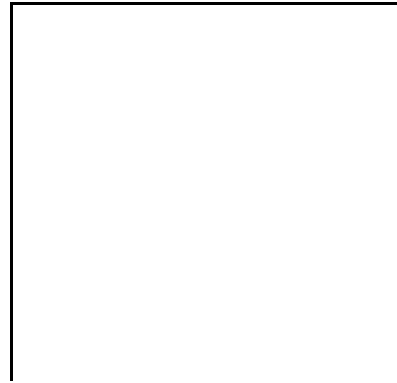
Steps 4 and 5   **Steps 7 and 8**

A nnex 4

The use of injections

There are two main reasons to prescribe an injection. The first is because a fast effect is needed, and the second is because the injection is the only dosage form available that has the required effect. A prescriber should know how to give injections, not only for emergency and other situations where it might be necessary, but also because it will sometimes be necessary to instruct other health workers (e.g. a nurse) or the patients themselves.

Many injections are prescribed which are unnecessarily dangerous and inconvenient. Nearly always they are much more expensive than tablets, capsules and other dosage forms. For every injection the prescriber should strike a balance between the medical need on the one hand and the risk of side effects, inconvenience and cost on the other.

When a drug is injected certain effects are expected, and also some side effects. The person giving the injection must know what these effects are, and must also know how to react if something goes wrong. This means that if you do not give the injection yourself you must make sure that it is done by someone who is qualified.

A prescriber is also responsible for how waste is disposed of after the injection. The needle and sometimes the syringe are contaminated waste and special measures are needed for their disposal. A patient who injects at home must also be aware of this problem.

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General practical aspects of injecting

Apart from the specific technique of injecting, there are a few general rules that you should keep in mind.

1. **Expiry dates**
   Check the expiry dates of each item including the drug.
   If you make housecalls, check the drugs in your medical bag regularly to make sure that they have not passed the expiry date.

2. **Drug**
   Make sure that the vial or ampoule contains the right drug in the right strength.

3. **Sterility**
   During the whole preparation procedure, material should be kept sterile.
   Wash your hands before starting to prepare the injection.
   Disinfect the skin over the injection site.

4. **No bubbles**
   Make sure that there are no air bubbles left in the syringe.
   This is more important in intravenous injections.

5. **Prudence**
   Once the protective cover of the needle is removed extra care is needed.
   Do not touch anything with the unprotected needle.
   Once the injection has been given take care not to prick yourself or somebody else.

6. **Waste**
   Make sure that contaminated waste is disposed of safely.
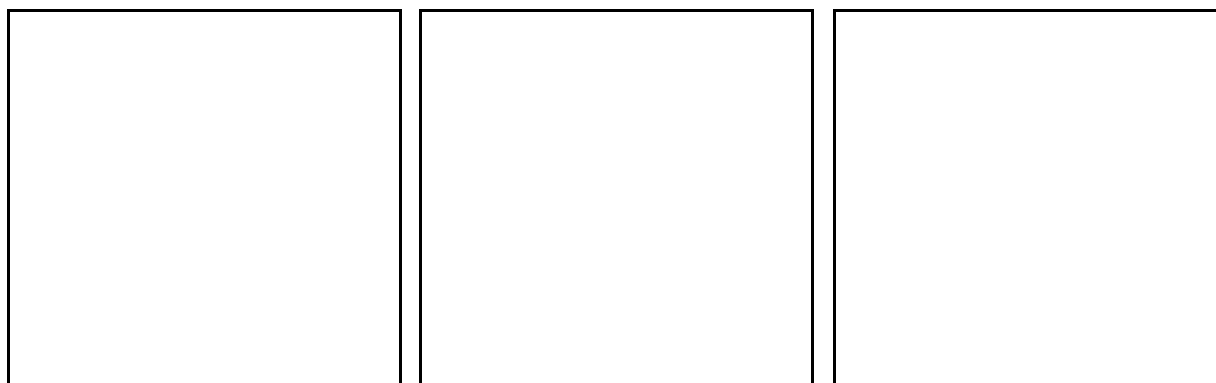
CHECKLIST 1

Aspirating from ampoules
(glass, plastic)

Materials needed
Syringe of appropriate size, needle of required size, ampoule with required drug or solution, gauze.

Technique
1. Wash your hands.
2. Put the needle on the syringe.
3. Remove the liquid from the neck of the ampoule by flicking it or swinging it fast in a downward spiralling movement.
4. File around the neck of the ampoule.
5. Protect your fingers with gauze if ampoule is made of glass.
6. Carefully break off the top of the ampoule (for a plastic ampoule twist the top).
7. Aspirate the fluid from the ampoule.
8. Remove any air from the syringe.

9. Clean up; dispose of working needle safely; wash your hands.

Step 4   **Step 5**   **Step 6**

CHECKLIST 2

Aspirating from a vial

Materials needed

Vial with required drug or solution, syringe of the appropriate size, needle of right size (im, sc, or iv) on syringe, disinfectant, gauze.

Technique
1.   Wash your hands.
2.   Disinfect the top of the vial.
3.   Use a syringe with a volume of twice the required amount of drug or solution and add the needle.
4.   Suck up as much air as the amount of solution needed to aspirate.
5.   Insert needle into (top of) vial and turn upside-down.
6.   Pump air into vial (creating pressure).
7.   Aspirate the required amount of solution and 0.1 ml extra. Make sure the tip of the needle is below the fluid surface.
8.   Pull the needle out of the vial.
9.   Remove possible air from the syringe.
10. Clean up; dispose of waste safely; wash your hands.
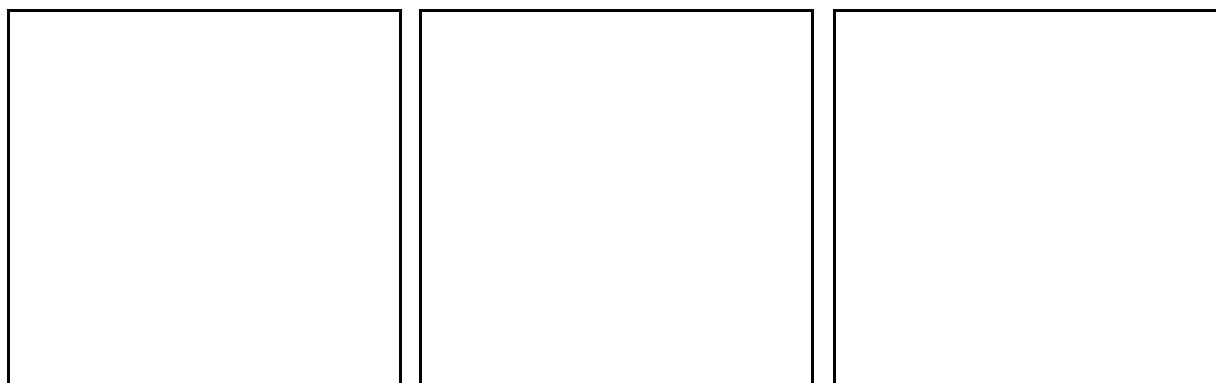
**Step 4**   **Step 6**   **Step 7**

CHECKLIST 3

Dissolving dry medicine

Materials needed
Vial with dry medicine to be dissolved, syringe with the right amount of solvent, needle of right size (iv, sc or iv) on syringe, disinfectant, injection needle, gauze.

Technique
1. Wash hands.
2. Disinfect the rubber cap (top) of the vial containing the dry medicine.
3. Insert the needle into the vial, hold the whole upright.
4. Suck up as much air as the amount of solvent already in the syringe.
5. Inject only the fluid into the vial, not the air!
6. Shake.
7. Turn the vial upside-down.
8. Inject the air into the vial (creating pressure).
9. Aspirate the total amount of solution (no air).
10. Remove any air from the syringe.
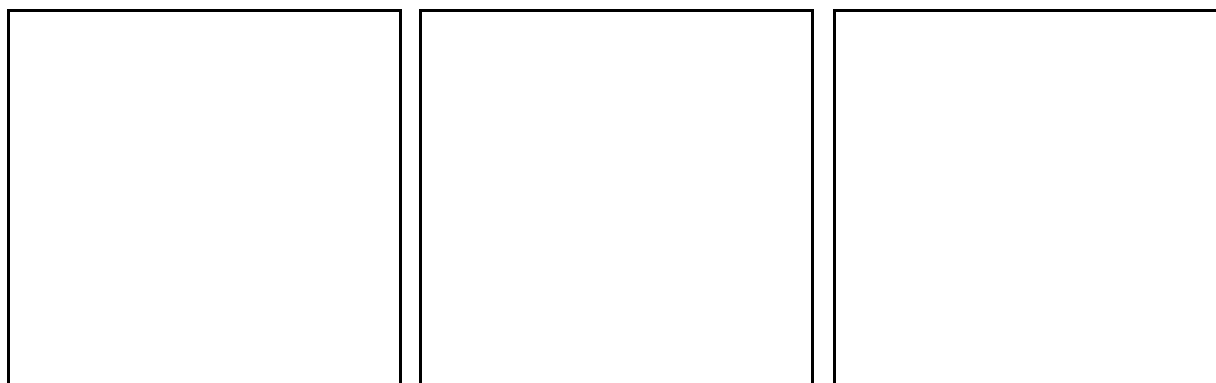
11. Clean up; dispose of waste safely; wash hands.
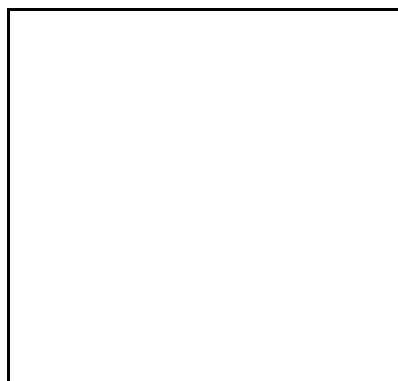
Step 4 **Step 5** **Step 8**

CHECKLIST 4
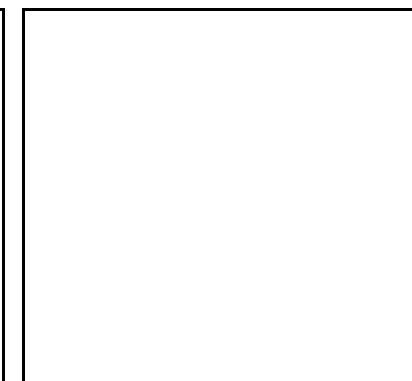
Subcutaneous injection

Materials needed
Syringe with the drug to be administered (without air), needle (Gauss 25, short and thin; on syringe), liquid disinfectant, cotton wool, adhesive tape.
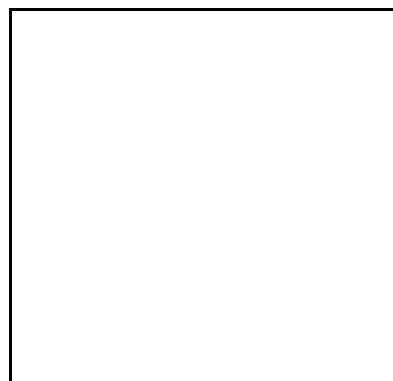
Technique
1. Wash hands.
2. Reassure the patient and explain the procedure.
3. Uncover the area to be injected (upper arm, upper leg, abdomen).
4. Disinfect skin.
5. 'Pinch' fold of the skin.
6. Insert needle in the base of the skin-fold at an angle of 20 to 30 degrees.
7. Release skin.
8. Aspirate briefly; if blood appears: withdraw needle, replace it with a new one, if possible, and start again from point 4.
9. Inject slowly (0.5 - 2 minutes!).
10. Withdraw needle quickly.
11. Press sterile cotton wool onto the opening. Fix with adhesive tape.
12. Check the patient's reaction and give additional reassurance, if necessary.
13. Clean up; dispose of waste safely; wash hands.
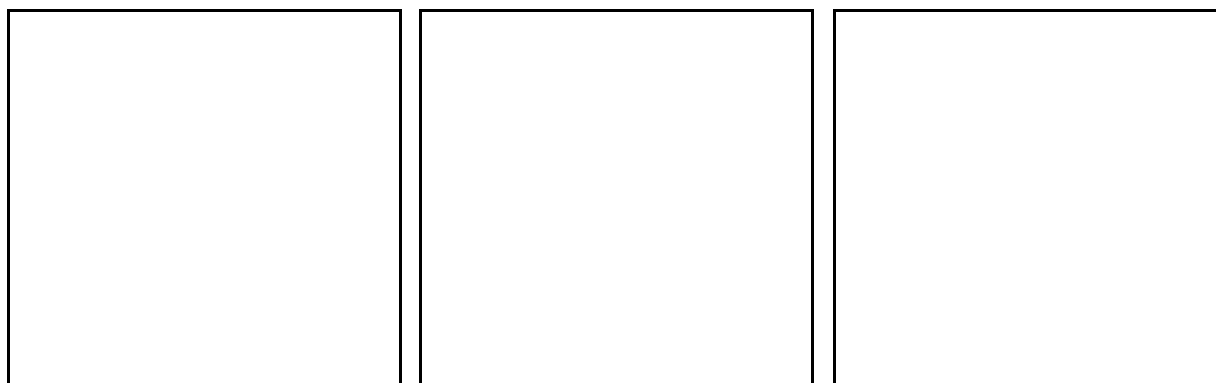
Step 3   **Step 5**   **Step 6**

CHECKLIST 5

Intramuscular injection

Materials needed
Syringe with the drug to be administered (without air), needle (Gauss 22, long and medium thickness; on syringe), liquid disinfectant, cotton wool, adhesive tape.

Technique
1. Wash hands.
2. Reassure the patient and explain the procedure.
3. Uncover the area to be injected (lateral upper quadrant major gluteal muscle, lateral side of upper leg, deltoid muscle).
4. Disinfect the skin.
5. Tell the patient to relax the muscle.
6. Insert the needle swiftly at an angle of 90 degrees (watch depth!).
7. Aspirate briefly; if blood appears, withdraw needle. Replace it with a new one, if possible, and start again from point 4.
8. Inject slowly (less painful).
9. Withdraw needle swiftly.
10. Press sterile cotton wool onto the opening. Fix with adhesive tape.

11. Check the patient's reaction and give additional reassurance, if necessary.
12. Clean up; dispose of waste safely; wash your hands.

Step 4   **Step 5**   **Step 6**
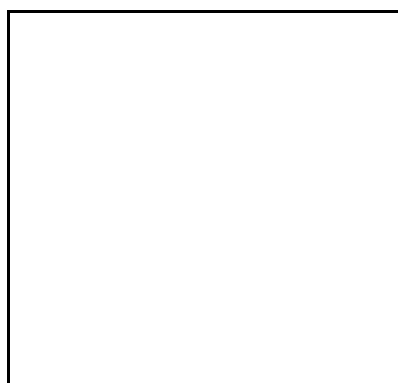
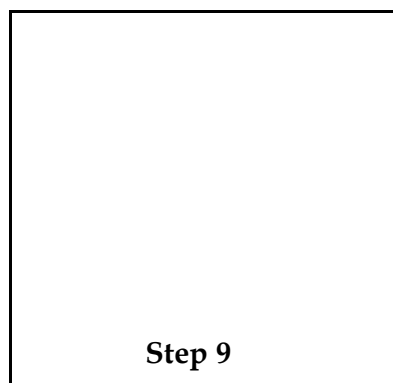# CHECKLIST 6

Intravenous injection

Materials needed
Syringe with the drug to be administered (without air), needle (Gauss 20, long and medium thickness; on syringe), liquid disinfectant, cotton wool, adhesive tape, tourniquet.

Technique
1. Wash your hands.
2. Reassure the patient and explain the procedure.
3. Uncover arm completely.
4. Have the patient relax and support his arm below the vein to be used.
5. Apply tourniquet and look for a suitable vein.
6. Wait for the vein to swell.
7. Disinfect skin.
8. Stabilize the vein by pulling the skin taut in the longitudinal direction of the vein. Do this with the hand you are not going to use for inserting the needle.
9. Insert the needle at an angle of around 35 degrees.
10. Puncture the skin and move the needle slightly into the vein (3-5 mm).
11. Hold the syringe and needle steady.
12. Aspirate. If blood appears hold the syringe steady, you are in the vein. If it does not come, try again.
13. Loosen tourniquet.
14. Inject (very) slowly. Check for pain, swelling, hematoma; if in doubt whether you are still in the vein aspirate again!
15. Withdraw needle swiftly. Press sterile cotton wool onto the opening. Secure with adhesive tape.
16. Check the patient's reactions and give additional reassurance, if necessary.
17. Clean up; dispose of waste safely; wash your hands.

Step 8

Step 9

St