MEDICAL PRACTICE

For Debate . . .

Minimum information needed by prescribers

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Summary

The prescriber needs adequate and concise information about each product that he uses, to allow him to obtain optimal effects while minimising harm. Neither the present UK data sheets nor their equivalents in other countries have succeeded in providing such information clearly or completely. This paper develops the proposals on the arrangement of drug information made in the WHO report "The selection of essential drugs." Three sets of minimum information (on tetracycline, propranolol, and aspirin) which illustrate this approach were compared with the manufacturers' data sheets: the latter were incomplete. The information content of our proposals was worked out with a group of clinical pharmacologists, general practitioners, and specialists, and we suggest that this approach should be extended to other drugs.

Introduction

It is now universally recognised that prescribers need accurate objective information about the drugs they use, but a satisfactory way of providing it has not been found. The longest established sources of such information are the pharmacopoeias, but these do not contain enough for prescribers' needs and they do contain much that is not relevant to them. Formularies such as the *BNF* are more compact and easier to use, but still lack some important information about the drugs they list. In the UK manufacturers now have to publish a data sheet about each of their advertised products, giving information under headings specified in guidelines from the licensing authority. The manufacturer may, however, include what information he wishes, provided that it does not conflict with the terms of his product licence. This means that in practice some data sheets emphasise points of promotional value or draw insufficient attention to possible disadvantages.

In the USA the contents of the manufacturer's standard information are strictly controlled by the Food and Drug Administration (FDA), so that the balance is more impartial, but no clear distinction is made between important points and relatively minor detail, so that the information is sometimes overwhelming and needlessly difficult to use. The manufacturers favour "full disclosure," partly to protect the patient and the prescriber, and partly to protect themselves from the possible legal consequences of failure to give adequate warnings. Nevertheless, in most countries the prescriber gets his information about drugs directly from the manufacturer, who naturally wishes his drug to be used as widely as possible. The recent WHO report on *The Selection of Essential Drugs*[1] emphasises that the prescriber needs adequate and concise information about each product to allow him to obtain optimal effects while minimising harm. The aim should be to provide information of practical importance clearly and briefly.

Organisations which are handicapped by commercial or legal obligations cannot easily produce such information. Nevertheless, in some hospitals[2] drug information cards have been produced which largely meet prescribers' needs; unfortunately, their distribution has been limited, and it has proved difficult to deal with a large range of drugs and keep the cards up to date.

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Arrangement of information

Appropriate arrangements of the information have been discussed by Hollister[3] and Herxheimer[4]; a further development is proposed in the WHO report.[1] It is logical to give the information in the order in which the user needs it, as follows.

The non-proprietary (generic) name and important synonyms appear at the head. The brand names appropriate to the country of use should be added since many prescribers are more familiar with them. For combination products that have no generic name the non-proprietary names of the active ingredients should be given.

The therapeutic class of the drug, its *pharmacological effects*, the *mechanisms of action*, where known, and the clinically important *pharmacokinetic properties*—for example, absorption, fate, duration of action. Major differences between the drug and others in the same chemical category should be noted.

Clinical information is conveniently set out under several subheadings:

Uses, defined as specifically as possible. Clearly validated uses should be distinguished from any for which evidence of efficacy is conflicting or scanty. The word "use" seems clearer than the word "indication."

Contraindications should include all categories of patients who must avoid the drug and all those in whom it is relatively undesirable.

Precautions are acts (or avoidance of acts) which precede or accompany the administration of a medicine that are intended to ensure its efficacy or to prevent or reduce an adverse effect. They thus differ from *warnings*, which are statements made about a drug to the user concerning possible undesirable consequences of using it. *Adverse effects* should be summarised, with clear indications of their seriouness and estimated frequency (where possible) and any special points about their management. *Drug interactions* of clinical importance also belong in this section.

The dosage regimen should state the usual dose and the dose ranges for adults and children, the dosage interval, the usual duration of treatment, and any adjustments required for patients in special circumstances (for example, renal or hepatic failure, etc). Where the dosage differs for different uses or groups of uses, details should be given.

Overdosage. The effects of overdose and its treatment should be briefly described.

Pharmaceutical information should be as follows:

The recommended dosage forms: their strengths, and any excipients which may be of clinical importance (for example, starch, which should be avoided by people with coeliac disease). Available dosage forms that are not considered important may be omitted.

Storage conditions and shelf life.

Package sizes that are locally available.

Description of the products, (size, colour, marking of tablets, etc) that are locally available, since this may help to identify the preparation.

Legal category (for example, prescription-only medicine).

Some kinds of information are common to several drugs in a therapeutic class. To avoid repetition it may be convenient to give this in an introductory chapter preceding the minimum information for the drugs in that class.

Information content: some examples

We have used the suggested arrangement to compile draft "minimum information" for three important and widely prescribed drugs, tetracycline, propranolol, and aspirin. We present our suggestions for one of these—tetracycline—in the appendix; those for the other two will be supplied by us on request. Initial versions were sent to several general practitioners, clinical pharmacologists, and other specialists, as well as the major manufacturers of these drugs in Britain. The comments of those who replied contributed greatly to the drafts we present.

TETRACYCLINE

It is instructive to compare the information content with that of the manufacturers' current data sheets,[5] in the case of tetracycline with those for Achromycin (Lederle), Steclin (Squibb), Tetrachel (Berk), and Tetrex (Bristol). Effects and mechanism of action are either not mentioned or inadequately dealt with. Information on pharmacokinetics is also variable: for one product it mainly concerns drug interactions (Achromycin); for another it highlights special features of the formulation (Tetrex). The information on uses varies greatly for the three brands, and is quite inadequate for Tetrex and Tetrachel. None of the data sheets distinguishes between conditions in which tetracycline is the first choice, and those in which the drug is useful only when the first choice drug is not tolerated or the infecting organisms are resistant to it. Only one of the data sheets (Steclin) mentions which organisms are sensitive to the drug.

The data sheets mention that the drug is contraindicated in renal failure, pregnant women, children, and people hypersensitive to tetracycline. Nevertheless, these contraindications are not explicitly identified as such and some are wrongly presented as precautions. None of the data sheets mentions systemic lupus erythematosus as a contraindication. Of course, this is rare, but it seems none the less desirable to protect patients with this disorder. Precautions listed in the data sheets mainly concern the avoidance of interactions with milk, antacids, and iron preparations, but for Tetrex the message is obscure, and for Tetrachel incomplete.

Adverse effects and warnings show similar inconsistencies. The data sheet for Tetrex gives no hint that the drug may cause gastrointestinal symptoms, which are common. Three manufacturers do not mention intracranial hypertension, and two omit photosensitivity reactions. Interactions with drugs that affect absorption have already been discussed; but only one data sheet (Achromycin) mentions that tetracycline can potentiate oral anticoagulants. The dosage recommendations for adults with an infection are the same for all four preparations, but those for children vary considerably. One data sheet (Achromycin) mentions its use in acne, but does not recommend a dosage for this condition. Directions for storage vary in detail, where they are given.

PROPRANOLOL

It is simpler to compare our minimum information on propranolol with that given in the data sheet, since only one brand is available, Inderal. The data sheet says little on effects and pharmacokinetics. The information on uses is not detailed enough, but fairly complete. Prophylactic use in migraine and use in Fallot's tetralogy are not included, though the latter is mentioned under dosage. The contraindications and precautions in the data sheet contain all the items listed in the minimum information. The warnings about adverse reactions do not specifically mention Raynaud's phenomenon, intermittent claudication, or vivid dreams—any of which may be important. They are not adequately covered by the terms "cold extremities" and "insomnia." The dosage recommendations and pharmaceutical information are detailed and complete.

ASPIRIN

Branded aspirin preparations for prescription are all special formulations intended to minimise the effects of the drug on the stomach. The five data sheets in the *Compendium* for aspirin-only preparations give insufficient detail about pharmacokinetics. Indications are fairly clearly described, but contraindications are adequately stated only for one brand (Breoprin). The only contraindication included in all five data sheets is hypersensitivity to salicylates. Information on adverse effects is almost completely lacking in the data sheets for Levius and Claradin, and another merely states "The unwanted effects of Solprin are those associated with soluble aspirin." Drug interactions are mentioned for Breoprin and Nuseals, but not for other products. The pharmaceutical information is satisfactory for all the products.

Problems in producing minimum information packages

Obviously the information selected must be both relevant and reliable. Use of the headings and subheadings ensures that only relevant material is included. The required information is then obtained from standard sources, such as Martindale's *Extra Pharmacopoeia*, *AMA Drug Evaluations*, *Side Effects of Drugs*, and, of course, the manufacturers. But before this information is used it needs to be critically evaluated.

Many formulations vary from one country to another, and the description must therefore refer to a particular country. For example, tablets of metronidazole contain 250 mg in the USA and 200 mg in Britain; in many European countries most aspirin tablets contain 500 mg, while the British ones contain

300 mg. Such differences cause needless problems, especially in drug-importing countries, and an international agreement is needed to eliminate them. There is also variation and sometimes lack of good information about children's doses. Most paediatricians prefer them to be expressed in terms of body weight or surface area, but in many instances the dose is still given in terms of age. Clarity and uniformity in this respect are essential for effective and safe prescribing.

The example given at the end of this paper suggests that it might be difficult to fit information about 200 or more drugs into a slim pocket-sized book. It may be more realistic to assemble the information in a book for the prescriber's desk.

Who should be responsible for providing minimum information?

Until now the manufacturers have had the responsibility for providing full information on the use of medicines, but the constraints already mentioned have prevented them from meeting the needs of prescribers. Professional bodies such as the Joint Formulary Committee of the BMA and Pharmaceutical Society, and the American Medical Association, have published very useful books, but with different intent—not that of giving prescribers the minimum information they need. We believe that minimum information packages should be put together by a small professional group consisting of clinical pharmacologists and clinicians, able to get advice from a wide range of specialists, general practitioners, and pharmacists.

The group would need whole-hearted support and co-operation from manufacturers and drug regulatory authorities. Ideally, sets of minimum information should be put together by an international group, since the drugs and the information needed to use them well are much the same everywhere. The work of such a group would save an enormous amount of duplicative effort in individual countries, and would also stimulate the world-wide use of the information. Countries that could not undertake to produce their own minimum information could easily adapt it to their needs. It could quickly provide a counterbalance to one-sided promotional information. The last World Health Assembly's discussion on drug information for less developed countries,[6] and the recommendations of the WHO Expert Committee on the selection of essential drugs[1] will no doubt assure the support of WHO for such activities.

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References

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[2] Golightly, P, and Banks, D, personal communication, 1978.
[3] Hollister, L E, *Drugs*, 1974, **7**, 414.
[4] Herxheimer, A, *Drugs*, 1974, **8**, 321.
[5] ABPI, *Data Sheet Compendium*. London, Pharmind, 1978.
[6] Thirty-first World Health Assembly, Technical Discussions, groups 1 and 2, 1978.

Appendix

DRAFT: MINIMUM INFORMATION ON TETRACYCLINE

(We will supply similar proposals for propranolol and aspirin on request.)

NAME

Tetracycline (brands include Achromycin, Steclin, Tetrachel, Tetrex).

PHARMACOLOGY

Effects and mechanism of action

It is a broad-spectrum antibiotic effective against many Gram-positive and Gram-negative bacteria, the spirochaetes, the rickettsiae, mycoplasma, chlamydia, and some protozoa. The different tetracyclines have essentially the same spectrum of antibacterial activity. Several of the strains of common Gram-positive and Gram-negative bacteria originally sensitive to tetracycline have acquired resistance, particularly streptococci, staphylococci, *Escherichia coli*, Klebsiella-Enterobacter group. Cross-resistance between the different tetracyclines is usually complete, except in the case of minocycline. Tetracyclines interfere with bacterial protein synthesis and are bacteriostatic.

Pharmacokinetics

Tetracycline is incompletely absorbed from the gut. More is absorbed when it is taken on an empty stomach than when it is taken with food. The drug is largely excreted unchanged in urine and to some extent in the bile.

CLINICAL INFORMATION

Uses

(*a*) It is the drug of first choice in infections caused by *Francisella tularensis* (tularaemia), Vibrio species (cholera), *Pseudomonas pseudomallei* (melioidosis), rickettsiae (scrub typhus, Q fever, Rocky mountain spotted fever), *Borrellia spp* (relapsing fever), *Chlamydia spp* (psittacosis, ornithosis, lymphogranuloma venereum, trachoma, inclusion conjunctivitis), *Calymmatobacterium granulomatis* (granuloma inguinale), *Mycoplasma pneumoniae*, and non-specific urethritis.

It is also the drug of first choice in infections due to *Brucella suis* or *Br melitensis* (brucellosis) and *Yersinia pestis* (plague). In severely ill patients with brucellosis or plague it is sometimes given in combination with streptomycin.

(*b*) It is not the drug of first choice but may be useful in several conditions where the drug of first choice is not tolerated or the infecting organisms are resistant to it, but tetracycline is best avoided unless the organism is sensitive to it in vitro. Examples are *Diplococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* (though tetracycline resistance is common among these), anaerobic streptococci, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Treponema pallidum*. The clinical effectiveness of the different tetracyclines in these conditions is similar.

(*c*) In acne vulgaris, and rosacea with inflammatory lesions not responding adequately to local treatment tetracycline is very effective and the first choice.

Contraindications

Tetracycline should be avoided by

(*a*) patients with acute or chronic renal failure, as it can aggravate renal failure. If a tetracycline is needed doxycycline should be used as it does not seem to have this effect.

(*b*) Persons hypersensitive to any tetracycline.

(*c*) Patients with systemic lupus erythematosus, which it can exacerbate.

In pregnant women tetracycline depresses bone growth and discolours the teeth in the fetus, and in children up to the age of 8 years it likewise discolours growing teeth. The drug should therefore be avoided in these groups unless it is needed for a serious infection (see uses (*a*)) for which no good alternative is available.

Precautions

See interactions.

Adverse effects and warnings

Most of the adverse effects are common to all tetracyclines.

Gastrointestinal effects are the commonest and include anorexia, epigastric distress, nausea, flatulence, vomiting, diarrhoea, sore mouth, and anal irritation. The incidence is related to dosage and duration of treatment.

Superinfection by resistant organisms may follow suppression of the normal bacterial flora in the gastrointestinal tract. Overgrowth with *Candida albicans* can lead to sore mouth, anorectal inflammation, diarrhoea, and vaginitis. Resistant coliform organisms or staphylococci may cause life-threatening infection in debilitated patients and in those receiving immunosuppressive or corticosteroid therapy.

Renal toxicity—In patients who develop renal insufficiency while taking the drug it may seriously worsen renal function.

Acute benign intracranial hypertension (pseudotumur cerebri) sometimes follows the use of tetracycline in therapeutic doses in infants; they become irritable, vomit, and develop a tense bulging fontanelle. Adults show meningeal irritation and papilloedema. The spinal fluid is normal and the condition disappears when the drug is stopped.

Hepatotoxicity—Liver damage may follow intravenous use of tetracycline in large doses and has occasionally followed oral use. Such damage (which can be fatal) is more likely to occur in patients with pre-existing hepatic or renal insufficiency, particularly in pregnancy or post partum.

Photosensitivity reactions may occur and manifest as exaggerated sunburn and marked erythema on exposure to sunlight.

Hypersensitivity reactions may take the form of fixed eruptions, urticaria, angioneurotic oedema, non-thrombocytopenic purpura, and rarely anaphylactic shock.

Changes in children's teeth and nails—All tetracyclines are deposited in growing deciduous and permanent teeth, causing yellowish discoloration, enamel hypoplasia and tendency to caries if given to women after the 6th month of pregnancy and to children up to the age of 8 years. They are also deposited in the nails when given to infants and late in pregnancy. The incidence and intensity is related to the total dose of tetracyclines ingested.

Interactions

Milk, iron, calcium, magnesium, and aluminium salts (present in many antacid preparations) diminish the absorption of tetracycline and therefore none of these should be given at the same time. Oral anticoagulants are potentiated because the drug inhibits vitamin K-synthesising bacteria in the gut. The doses of the oral anticoagulant may thus have to be reduced during tetracycline therapy.

The anaesthetic methoxyflurane has precipitated fatal kidney failure in patients taking tetracycline, and should therefore be avoided.

Dosage required (average dose and dose range)

Oral dose—Uses (*a*) and (*b*).

Adults— 1 g in 2-4 divided doses daily, or 500 mg six-hourly for more serious infections. For long-term prophylaxis in chronic bronchitis 250 mg twice or three times daily.

Children—(see contraindications) 20-40 mg/kg body weight/day in four divided doses.

(*c*) Acne vulgaris: 250-500 mg daily as a single dose. The effect may not appear until the drug has been used for two months. Rosacea: 250 mg daily or less usually suffices; some patients need only 250 mg on alternate days or twice weekly.

The eye ointment is applied three or four times daily.

Duration of treatment depends on the use.

PHARMACEUTICAL INFORMATION

Selected dosage forms

Capsules contain tetracycline hydrochloride or tetracycline phosphate complex. Usual strengths 250 and 500 mg of tetracycline base.

Oral suspension contains tetracycline hydrochloride or tetracycline phosphate complex. Usual strength 125 mg/5 ml (tetracycline base).

Eye ointment—strength 1%.

Storage conditions

Tetracycline should be stored in an airtight container. The suspension should be protected from light and at a temperature not exceeding 30°C. Expiry date, two to three years from the date of manufacture, depending on the formulation.

Legal category

Prescription drug.

Package inserts for prescribed medicines: what minimum information do patients need?

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Summary and conclusions

The information a patient needs about a prescribed medicine can be determined by considering what responsibilities he can assume in relation to taking medicine. When the medicine has been dispensed the patient needs to know how to take the drug; how to store the drug; how it is expected to help; and how to recognise problems and what to do about them. A guide was designed to specify what information is required to meet these needs. Using this guide, a set of minimum information on tetracycline was prepared that aimed at being brief, specific, and readable. The best format for the information remains to be determined.

Since leaflets produced by professional organisations are generally unsuitable for these purposes, information sets should be put together by small independent groups consisting of clinical pharmacologists, clinicians, pharmacists, and consumers. Each country should produce its own sets, adapting model sets to the circumstances of local practice.

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Introduction

If patients are expected to take their medicines, they must be given information. The content, quantity, and format of such information are not easily decided. Patients often demand more (presumably better) information, and indeed, better information may result in better care, though few facts have been presented