Non-prescription Drugs

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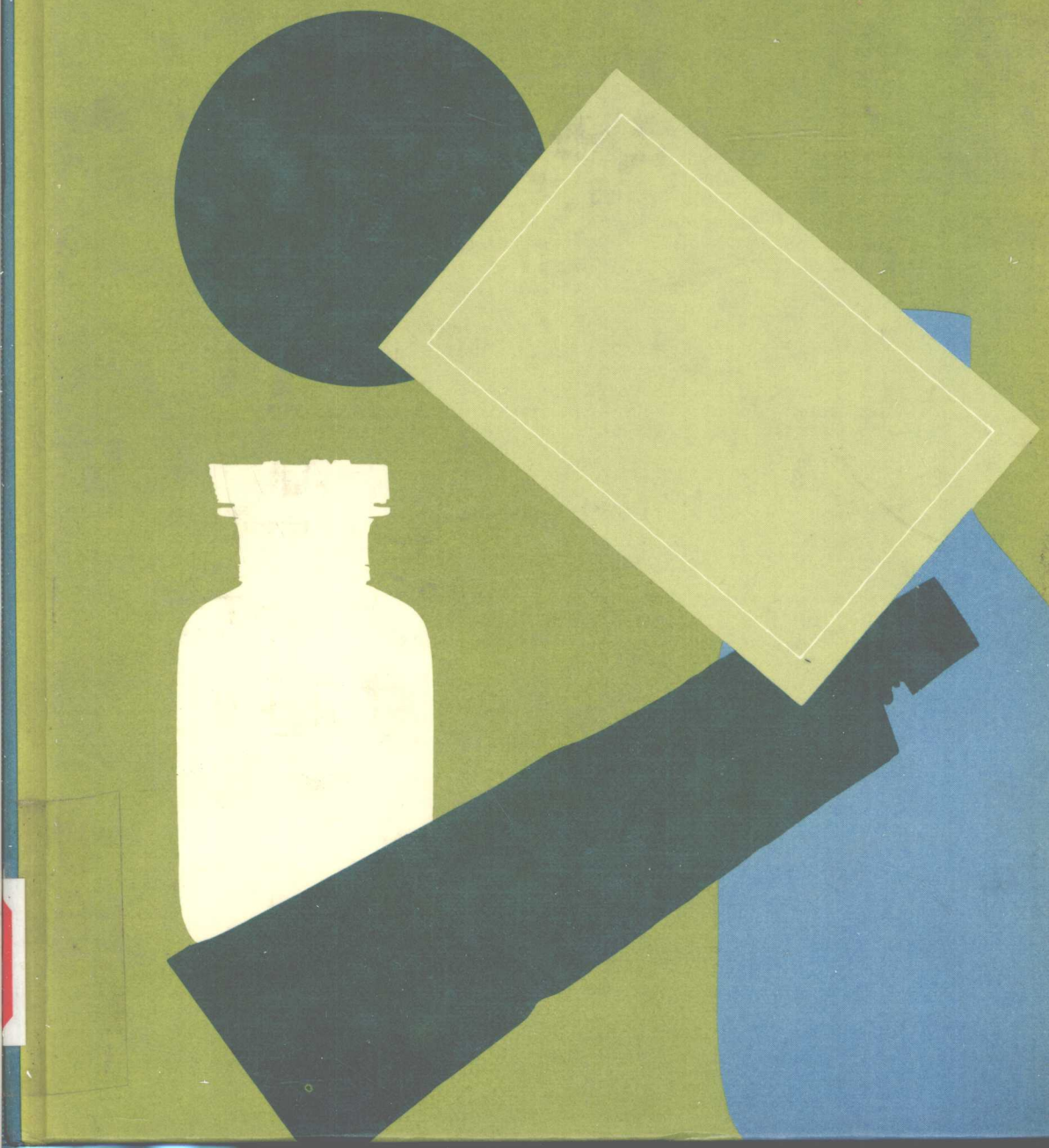

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Preface

This book is intended as a source of information on non-prescription products and on conditions for which the drugs are commonly used. Although it is primarily aimed at pharmacists and pharmacy students, it is hoped that other health professionals interested in non-prescription products will find the information it contains useful.

Non-prescription drugs and health matters have been attracting much attention lately. To bring the reader up to date with some of the controversies raised, topics of current interest, such as the role of prostaglandins in dysmenorrhoea and the safety of the psoralens in sunscreen products, have been reviewed in some detail. Many of the recent developments in our understanding of how non-prescription agents work are presented. Arguments for and against the use of specific products are discussed as objectively as possible.

Since so many factors need to be considered before recommending a suitable product it has not always been possible to make specific recommendations. In any case, there is rarely a drug which is best for every patient suffering from a particular disease or symptom. The main objective of this book is to provide information on which rational advice can be based. Practice points which can be translated into patient advice are marked ● throughout the text as are points of particular importance.

Chapter 1 deals with important aspects of therapeutics as they relate to non-prescription products. The placebo effect and combination products are discussed in some detail because of their particular importance in this respect. The remaining chapters are arragned according to the target organ as far as possible: Part 2, for example, gathers together the products acting on the skin and its appendages. In addition to categorization according to anatomical system, chapters are also grouped according to the function of the drugs, such as nutrition and analgesia.

Acknowledgements

Much of the impetus for writing this book has come from the many readers who responded so kindly to the articles, on the same topic, written by the author and published in the *Chemist and Druggist*. This book is therefore gratefully dedicated to these readers and to Mr Ronald E. Salmon, the editor of the journal.

Professor A.T. Florence gave up many hours reading and criticizing most of the chapters. His constructive and pertinent comments have been of great help to the author. All those concerned with the *American Handbook of Non-*

Prescription Drugs also deserve a special mention for leading the way and for showing that these drugs are worthy of separate consideration. The help given by staff members, previous co-authors and graduate students at Aston University is gratefully acknowledged.

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Non-prescription Drugs: Perspectives

Introduction

It is perhaps true to say that the normal reaction of a person who experiences a symptom which he does not perceive as being life-threatening is to hope that it disappears without treatment. If it persists, self-treatment using home remedies or non-prescription products is then resorted to. Only when these attempts fail does the patient seek help from a medical practitioner. The extent of self-medication is sizeable and several surveys carried out in different countries have confirmed this [1–4]. It has, for example, been shown that up to two-thirds of those suffering from symptoms sufficient to lead to absenteeism from work were not seen by a doctor [3]. The available data, while not entirely suitable for quantitative study, suggest that the misuse of non-prescription products is quite high too [3]. Laxatives, antitussives, anti-asthma preparations, antihistamines, hypnotics, appetite suppressants, antacids and nasal decongestants are non-prescription products most commonly abused. If it is accepted that educating the patient is one, if not the most effective, way of combating abuse of non-prescription products, then it is essential that the health professionals should be knowledgeable about the products which the self-medicating public uses. In this book, an attempt will be made to present the necessary information for giving rational advice to patients on common non-prescription remedies and the conditions for which they are used.

Definitions

While every country has its own system for controlling the sale of drugs, most with developed medical and pharmaceutical services categorize the available drugs into at least two major groups—those which are available without a prescription and those which require one. Within each group, subdivisions are

not unusual. Narcotics, for example, form a separate group in many countries. In Britain, non-prescription drugs are further grouped into *general sales list* items (GSL) which can be sold in most retail outlets and *pharmacy only* (P) products which can only be sold under the supervision of a qualified pharmacist. Prescription products are usually referred to as POM or *prescription-only medicines*. The ingredients discussed in this book will be those which are available without a prescription in the United Kingdom. International readers should therefore ensure that they are familiar with the medicine regulations in force in their own country. It is likely, however, that with time most of the differences will be ironed out as more and more of the regulatory bodies agree on what is safe for non-prescription use. Changes in regulations will be unavoidable as new facts emerge. While practitioners will be aware of such changes, students may be inadequately informed so that here again caution is required.

To keep in line with current international trends misleading terms such as *ethical, popular* or *patent* medicines which have sometimes been used to describe non-prescription medicines, among other things, will be avoided. The terms *non-prescription, over the counter* (OTC) and *home remedies* will be used synonymously. The term *proprietary* non-prescription product will be used to mean a branded OTC product.

Product distribution

As part of the background work for this book, 1508 non-prescription products available on the British market were classified into therapeutic groups to reflect the contents of the book as closely as possible. Figure 1.1 summarizes the results. It can be seen that vitamins, tonics and mineral supplements form the largest group. This is followed by cough and cold remedies, antacid products, analgesics and laxative agents. The relative positions of the laxative and vitamin-type products are higher than expected from available data on the frequency of symptoms. Constipation, for example, does not figure among the

Table 1.1. The ten symptoms most commonly reported by adults [5].

1.	Headaches
2.	Coughs, catarrh and phlegm
3.	Aches and pain in joints, muscles, arms or legs
4.	Backache or pain in the back
5.	Nerves, depression or irritability
6.	Corns, bunions or trouble with feet
7.	Cold, flu or running nose
8.	Indigestion
9.	Sleeplessness
10.	Undue tiredness

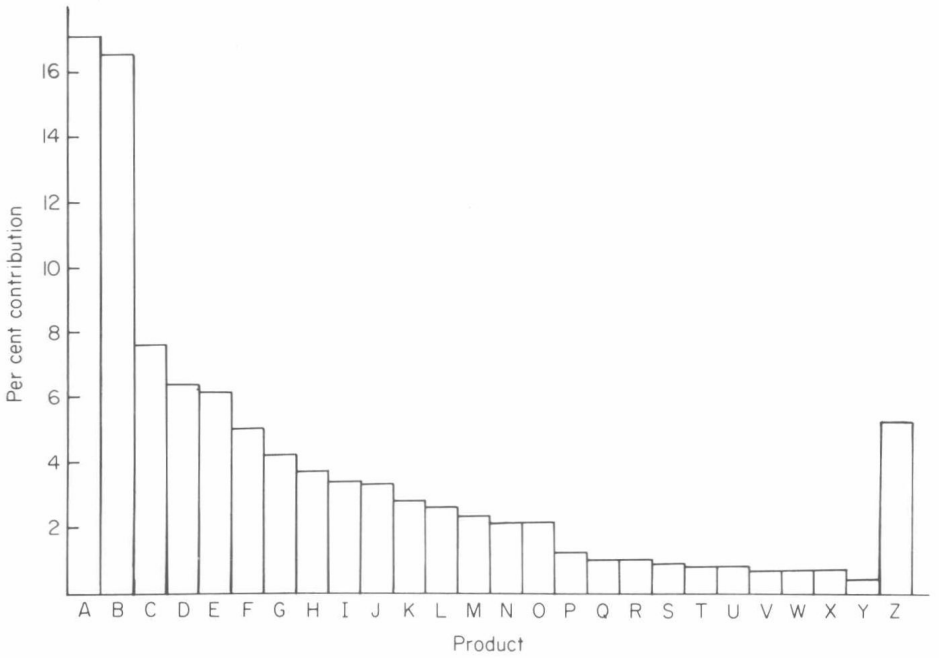

Fig. 1.1 Classification into therapeutic groups of non-prescription products on the British market.

A	Vitamin, tonics and mineral supplements	M	Ophthalmic products
B	Cough and cold remedies	N	Hay fever remedies
C	Antacids and deflatulents	O	Vasodilators
D	Internal analgesics	P	Antihaemorrhoidal products
E	Topical antiseptics	Q	Nappy rash products
F	Laxative agents	R	Ear preparations
G	External analgesics and anaesthetics	S	Antiparasitic agents
H	Other topicals	T	Anthelmintics
I	Foot care preparations	U	Contraceptive products
J	Oral hygiene products	V	Insect stings and bites products
K	Anti-acne products	W	Antidandruff products
L	Bronchodilators	X	Travel sickness products
		Y	Antimalarials
		Z	Others

ten symptoms most commonly reported by adults in Dunnell and Cartwright's study [5]. Yet, laxatives make up the sixth largest group of OTC products currently available. This perhaps indicates that these two product categories are often used for alleviating non-specific symptoms such as nerves, depression or undue tiredness, all of which are among the most commonly reported symptoms (Table 1.1). An alternative explanation of course is that the vitamin market is particularly profitable!

Use of non-prescription drugs in certain groups of patients

Paediatric patients [6–10]

Infants may be at greater risk of developing adverse reactions to drugs. Several of the hepatic enzyme systems involved in drug metabolism are immature in the newborn. Therefore, drugs which are biotransformed by the liver have longer plasma half-lives in this age-group. There is some evidence to show that with paracetamol, for example, even in older children the ratios of the metabolites formed can be different to those seen in adults. The products of metabolism are principally excreted by the kidneys. Renal function does not approach adult value until about 6 to 12 months of age. This therefore contributes to the prolongation of drug plasma half-lives in infants. The importance of the less well-developed renal excretion pathways can be illustrated by the report of an infant's death due to the systemic absorption of magnesium following the use of a magnesium sulphate enema. Absorption may also be more erratic in infants as a result of irregular peristalsis and wide fluctuations in gastric pH and emptying. For all these reasons, treatment in the infant population should normally be under professional supervision.

Geriatric patients [11–14]

With elderly subjects there appears to be greater individual variability in hepatic enzymic activity than in younger people. Protein binding is generally less because of a decrease in plasma albumin. Hence protein-bound drugs will be present in the unbound state to a higher proportion in the elderly than in the young. Renal function also generally decreases with age. It is not surprising therefore that drug pharmacokinetics have been reported to be different in the elderly when compared to those observed in younger individuals. The differences reported so far, however, have generally been small. Two factors which may be of greater importance in the elderly than altered pharmacokinetics are increased responsiveness not directly related to increased plasma concentrations and drug interactions. The latter is particularly important since the number of drugs which a person consumes concurrently usually increases with age. Non-presciption drugs are often involved and particular care should be exercised when recommending such drugs for geriatric patients.

Pregnant women

The high incidence of drug use during pregnancy is a continuing problem. Thus, one study showed that as many as 65% of a sample of over 900 pregnant women took self-prescribed drugs. Fortunately, although some association has

been claimed to exist between non-prescription drug ingestion and teratogenicity [15] it is generally accepted that any risk present is probably small [16]. There is, however, some more convincing data linking high blood salicylate levels with prolonged parturition, increased blood loss and decreased birth weight [17]. A higher incidence of stillbirths has also been suggested but a larger study [18] has failed to confirm this. The available evidence suggests that withholding the use of aspirin during the last three months of pregnancy is advisable. The absence of reports does not mean absolute safety and as a general principle all drugs including non-prescription drugs should be used with particular caution during pregnancy.

Nursing mothers

The excretion of drugs in breast-milk has recently attracted much attention [18–21] as a result of the renewed interest in breast-feeding. Of the non-precription drugs, only the anthraquinone laxatives have been reported to induce adverse effects in the newborn. However, since all drugs can be transferred into milk, vigilance is necessary. Since breast milk is more acid (pH 7.0) than plasma (pH 7.4), weak bases can be expected to be present in higher concentrations in milk than weak acids. Antihistamines, for example, are known to be excreted in breast milk. Although the significance of the concentrations observed is unclear, it is probably advisable to avoid their use by breast-feeding mothers whenever possible. (See Appendix for a discussion on ionization of weak acids and bases.) It is important to note that the absolute concentration is not always the most important parameter since only trace amounts of a drug may induce allergic reactions.

Patients with hepatic or renal pathology

Since most drugs are biotransformed by the liver and excreted by the kidneys, any pathological state affecting these organs will alter the disposition of administered drugs. Dosage adjustment therefore often becomes essential. Patients so affected should be closely supervised and self-medication by them should be discouraged.

OTC drug interactions [22–26]

Non-prescription drugs have been involved in many serious drug interactions and although some of these are well known others have only recently been reported. Many of these are discussed in detail in the individual chapters. However, it is perhaps useful to list the more potentially serious interactions in this chapter (Table 1.2).

Table 1.2. Serious potential drug interactions involving non-prescription drugs

Non-prescription drug	Interacting drug	Potential effect	Likely mechanism	Course of action
Ammonium chloride in diuretic doses	Spironolactone	Systemic acidosis may ensue	Inhibition of aldosterone and hence impairment of renal secretion of hydrogen ions by spironolactone; potentiation by urine-acidifying ammonium chloride	Avoid where possible
Antacids	Tetracyclines	Decreased bio-availability	Chelate formation	An interval of at least one hour is required between dosing with the two drugs
	Digoxin	Decreased bio-availability	Adsorption	An interval of at least one hour is required between dosing with the two drugs
Antihistamines	Alcohol and other depressant drugs	Increased side-effects and notably drowsiness	Additive effects	Concomitant use should be curtailed
	Para-amino salicylic acid	Decreased availability	Altered gastro-intestinal motility	Should be avoided where possible
	Ototoxic drugs such as the aminoglycoside antibiotics	Symptoms of ototoxicity may be masked by the antihistamine	Symptoms and side-effects confused	Extra vigilance required
Aspirin	Sulphinpyrazone	Decreased bio-availability	Antagonization of uricosuric action	Change of analgesic is required
	Probenecid	Decreased bio-availability	Antagonization of uricosuric action	Change of analgesic is required
	Methotrexate	Toxicity potentiated	Salicylates may block the renal tubular secretion of methotrexate	Aspirin and other salicylates should be avoided

	Heparin	Potentiation of anticoagulant effect	Platelet function inhibited by aspirin	Aspirin should be substituted by another analgesic such as paracetamol
Ferrous salts	Tetracyclines	Decreased bio-availability	Chelation	An interval of at least 2 h recommended between the oral administration of the 2 drugs
Hexamine or Methenamine	Acetazolamide	Activation of the urinary antiseptic impaired	Acetazolamide-induced urinary pH changes	Alternative antiseptic indicated
	Sodium bicarbonate	Activation of the urinary antiseptic impaired	Alkalization of urine by the antacid	Alternative antiseptic indicated
	Less soluble sulphonamides	Risk of crystalluria increased	Complex formation or sulphonamide precipitation	Concurrent use contra-indicated
Iodine-containing drugs	Lithium carbonate	Hypothyroid action additive	—	Iodine- or iodide-containing products should be avoided
Kaolin-pectin mixture	Lincomycin	Decreased bio-availability	Adsorption	Substitution of anti-diarrhoeal mixture by a non-adsorbing system
Pyridoxine	Laevodopa	Antiparkinson action of laevodopa antagonized	Enhancement of laevodopa metabolism by pyridoxine dependent enzymes	Peripheral decarboxylase inhibitor (e.g. carbidopa) may be substituted for laevodopa if pyridoxine judged essential
Sympathomimetic agents				
Phenylephrine Phenylpropanolamine Ephedrine Pseudoephedrine	Furazolidone	Hypertensive action of the amine enhanced	Monoamine oxidase inhibitor activity of furazolidone	Concurrent administration should be avoided
Phenylpropanolamine Pseudoephedrine Ephedrine	Monoamine oxidase inhibitors (MAOI)	Hypertensive action of the amine enhanced	MAOI–induced increase in storage of noradrenaline in the adrenergic neurons	Concurrent administration should be avoided

Table 1.2 *continued*

Non-prescription drug	Interacting drug	Potential effect	Likely mechanism	Course of action
Phenylephrine	Monoamine oxidase inhibitors (MAOI)	Hypertensive action of the amine enhanced	Increased availability of phenylephrine as a result of MAOI inhibition	Concurrent administration should be avoided
Ephedrine Pseudoephedrine	Bethanidine	Increased symptoms such as headache, visual disturbances and hearing distortion which are normally associated with hypertension	Mechanism not established	Unsupervised concurrent use not advised
	Guanethidine	Hypertension control lost	Antagonism of the adrenergic neuron blockade produced by the guanethidine	Unsupervised concurrent use not advised
Phenylpropanolamine	Bethanidine	Control of hypertension by bethanidine interfered with	Antagonism of the adrenergic neuron blockade produced by the guanethidine	Unsupervised concurrent use not advised
Phenylephrine	Debrisoquine	Control of hypertension by debrisoquine interfered with	Inhibition of monoamine oxidase by debrisoquine	Unsupervised concurrent use not advised
	Guanethidine	Control of hypertension interfered with	Increased sensitivity of receptor in the presence of guanethidine	
Vitamin D	Phenytoin	Increased requirement for vitamin D	Hyporesponsiveness of the end-organs to vitamin D	Vitamin D supplements may be required by patients on chronic phenytoin therapy

Drug interactions involving the sympathomimetic agents and the monoamine oxidase inhibitor drugs (MAOI) are perhaps the best-known examples of potentially serious interactions involving an OTC drug. Agents which have been reported to interact with the MAOIs include phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine, all of which are commonly encountered in cough and cold remedies. This interaction is not always obvious. For example, furazolidone, an antibacterial agent, also possesses MAOI activity and may therefore interact with the sympathomimetic agents although the effects can probably be expected to be milder. Prescribed drugs may render otherwise safe drugs hazardous. Spironolactone, for example, inhibits aldosterone. Renal secretion of hydrogen ions is therefore impaired. Ammonium chloride, by further acidifying urine, may lead to systemic acidosis. Although expectorant doses of the salt are unlikely to be of clinical significance, diuretic doses may be dangerous.

One of the more common types of drug interactions leads to interference with the activity of one or both of the drugs involved. The classical OTC example illustrating this is the interaction between tetracyclines and antacids containing divalent and/or trivalent cations. Concomitant administration leads to impairment of tetracycline absorption and should therefore be avoided. There should be at least a one-hour interval between the antacid and the antibacterial doses.

An OTC drug may enhance the side-effects of another non-prescription drug. Ephedrine, for example, which is present in many bronchodilator and asthma OTC products, may enhance the side-effects of theophylline. The alkaloid should therefore be avoided by patients receiving the xanthine and combination products containing the two should be reformulated.

An increased sodium intake in the form of antacids or effervescent products may add to an increased renal excretion of lithium. Loss of therapeutic control may therefore follow. Conversely, patients stabilized on lithium while on additional sodium may well develop toxic reactions when the sodium intake is curtailed.

Some of the OTC drugs require activation within the body. Examples include bisacodyl and hexamine (methenamine). With the latter a low urinary pH is a prerequisite to activity since its hydrolysis is pH dependent. Drugs which raise the urinary pH will therefore be expected to impair hexamine's activity. Antacids, acetazolamide and potassium citrate mixture are examples.

A drug may alter the physical property of another in such a way that adverse effects follow. Hexamine can again be used as an example. The concurrent use of this urinary antiseptic with the less soluble sulphonamides may lead to a precipitation of insoluble complexes. Their concurrent use is therefore unwise. It is important to note that in estimating the risk involved, in addition to the

absolute solubility of the free acid, its pK_a value should also be taken into account (see Appendix).

Drug interactions involving non-prescription remedies are therefore not uncommon and may certainly be of clinical significance. Those who are responsible for prescribing and recommending the OTC drugs should at least be aware of the interactions listed in Table 1.2. The possible mechanisms and effects of these interactions are listed together with measures which will help protect the patients.

Interference with biochemical tests [22, 27–29]

Occasionally, non-prescription drugs interfere with biochemical tests and misleading results are obtained. Thus, colourigenic substances or substances which are metabolized to highly-coloured compounds will often interfere with tests based on colourimetric determinations. Reducing substances such as

Table 1.3. Some potential non-prescription drug and biochemical test interactions

Drug	Test	Interaction
Anthraquinone Methylene blue Chloroquine Phenazopyridine Riboflavine Phenolphthalein	Colourimetric methods such as urinary phenolsulphonphthalein excretion test	Discolouration of urine by the non-prescription drug or its metabolites
Aspirin	5-hydroxyindole acetic acid determinations by fluorimetry	Interfering fluorescence
High doses	Glucose oxidase paper tests (false negative) Clinitest tablets (false positive)	Interference by reducing metabolite-gentisic acid
Paracetamol	5-hydroxyindole acetic acid	Reaction with nitrosonaphthol reagent Interaction first reported with phenacetin, the paracetamol prodrug
Glyceryl guaicolate	5-hydroxyindole acetic acid determination by nitrosonaphthol method (false positives)	Interfering metabolite of glyceryl guaicolate
Hexamine or methenamine	Urobilinogen	Formaldehyde generation by hexamine
	5-hydroxyindole acetic acid determination by nitrosonaphthol method	
	Urine glucose tests based on Benedict's solution	Formaldehyde generation by hexamine
Phenazopyridine	Glucose oxidase tests (false negative)	Delayed reaction
Promethazine	Immunological pregnancy tests	
Sodium bicarbonate (high doses)	Ames reagent strips for protein determination	Alkalization of urine