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Remains the world’s most comprehensive and authoritative international reference book on drug interactions. Stockley's Drug Interactions is a source book of interactions, their mechanisms, clinical importance and management.Covers interactions between therapeutic drugs, proprietary medicines, herbal medicines, foods, drinks, and drugs of abuse Contains in-depth yet concise monographs in an easy-to-read format Provides comprehensive details of the clinical evidence for the interactions under discussion, an assessment of their clinical importance, and clear guidance on managing the interaction in practice Has a brief summary of the interaction in each monograph – perfect for the busy healthcare professionalIs fully referenced throughoutContains almost 4500 monographsIs global in coverage – inclusion of drugs used worldwideNew in the 12th edition are over 300 new monographs, with reviews and updates for the existing 4500 monographs. £240.00 (£240.00 inc VAT) Almost 500 new monographs, with reviews and updates for the existing 4500 monographs. 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Ask the publishers to restore access to 500,000+ books. 14th January 2025For January, 458 new interactions have been added, and 69 existing interactions have been updated. Stockley’s Drug Interactions, edited by Claire L Preston, remains the world’s most comprehensive and authoritative international reference book on drug interactions. Based upon thousands of published papers and reports this eleventh edition: Covers interactions between therapeutic drugs, proprietary medicines, herbal medicines, foods, drinks, and drugs of abuse Contains in-depth yet concise monographs in an easy-to-read format Provides comprehensive details of the clinical evidence for the interactions under discussion, an assessment of their clinical importance, and clear guidance on managing the interaction in practice Has a brief summary of the interaction in each monograph – perfect for the busy healthcare professional Is fully referenced throughout Contains almost 4500 monographs Is global in coverage – inclusion of drugs used worldwide New in the 11th edition: Over 350 new monographs added Many existing monographs have been reviewed, revalidated, and updated A comprehensive update and restructure of the chapter on Antidiabetic drugs, in-line with published literature Addition of new advice regarding the concurrent use of aliskiren, ACE inhibitors, and angiotensin-II receptor antagonists An updated list of drugs that have a risk of prolonging the QT interval The addition of new drugs, including apixaban, apremilast, dolutegravir, lomitapide, mirabegron, the NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir), the NS5B inhibitors (dasabuvir, sofosbuvir), the sodium-glucose co-transporter-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), and telavancin Stock Status: In Stock (Only 2 left) STOCKLEYS UNIQUE BENEFITS A Source Book of Interactions, their Mechanisms, Clinical Importance and Management. 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Preston Edition 12th Edition Format (Paperback, Hardback etc) Hardback Total Pages 1840 Brand / Publisher Stockley's Publisher Pharmaceutical Press Delivery We offer customers a wide range of delivery options from Free (7-10 working days) ... right up to by Next Day by 9am (subject to location and stock availability). Simply choose your preferred service when checking out We show "live" stock levels for all publications Orders received after 3:45pm will be processed on the next working day. Unless specifically requested, our delivery partners will not attempt a weekend delivery Returns We offer all customers a "No Quibble" 28 day returns policy. If you need to return a title for any reason ... Contact our customer services team first to explain what you are returning and the reason Request a Returns Authorisation Number We will email you this and a link to arrange your return quickly & easily via Royal Mail Take your return to your nearest Post Office and they will do the rest Please refer to our Returns page for full details & charges. SPS has a variety of resources on drug interactions which we recommend you check first. For example Using miconazole oral gel with statins describes the potential interaction and provides advice on prescribing miconazole for patients taking different statins. If the information is not available on the SPS website or the information resources listed, or if your clinical scenario is complex, we would suggest you seek further advice from our Medicines Advice service. Other primary resources In addition to our own resources, we particularly recommend the following resources. They are free to access unless indicated otherwise: British National Formulary When looking for interactions between medicines, we recommend using the BNF and BNFC as mobile apps (registration required) or via Medicines Complete (needs an NHS England OpenAthens account). This allow users to search for interactions between multiple medicines. Information is provided for each pair of interacting drugs. Register for an NHS England OpenAthens account Summaries of Product Characteristics SmPCs/SPCs are available via electronic Medicines Compendium and MHRA. They list interactions with other medicinal products and other forms of interaction in section 4.5. Other useful sections include: contraindications (4.3) special warnings and precautions for use (4.4) pharmacodynamic properties (5.1) pharmacokinetic properties (5.2) Stockley’s Drug Interactions Available to subscribers via Medicines Complete, monographs in Stockley’s Drug Interactions describe the evidence, mechanism, clinical importance and management of over 4,500 drug interactions. The Interaction Checker allows users to search for interactions between multiple medicines; information is provided for each pair of interacting drugs, with links to the full Stockley monographs. The following resources are useful for finding information in specific areas and are freely available: The interactive Cancer drug interaction checker allows users to select cancer medicines and co-medications. Results are graded from ‘medicines should not be co-administered’ to ‘no clinically significant interaction expected’ and note if further monitoring or dose adjustment are required. The Faculty of Reproductive and Sexual Healthcare has issued advice on interactions with hormonal contraceptives. The interactive HIV interaction checker allows users to select HIV drugs and co-medications they are interested in. Results are graded from ‘these medicines should not be co-administered’ to ‘no clinically significant interaction expected’ and note if further monitoring or dose adjustment are required. The prescribing resources section of the site provides further information including summary tables of drugs interactions and fact sheets for HIV medicines. The US site CredibleMeds (access is free but users must be registered) provides a searchable database of medicines that prolong the QT interval and/or induce Torsades de Pointes (TdP). Drugs are categorised according to risk: known risk, possible risk or conditional risk of TdP. A page showing therapeutic options not on the QT drugs list shows, by indication, medicines that are and are not in the QT risk categories. Questions around TdP risk, including the criteria used to assign drugs a risk category for the database, are answered in FAQs for Healthcare Professionals. The hepatology drug interaction checker provides information on interactions with medicines used in chronic hepatitis C infection. Users can select hepatology drugs and co-medications. Results are graded from ‘these medicines should not be co-administered’ to ‘no clinically significant interaction expected’ and note if further monitoring or dose adjustment are required. Training resources If you would like more information on how to approach answering questions on drug interactions we recommend: Medicines Learning Portal The Medicines Learning Portal is aimed at trainee hospital pharmacists but the content is also relevant to clinical primary care healthcare professionals. The portal includes a tutorial on drug interactions which provides advice on: questions to ask when considering questions relating to drug interactions mechanisms of drug interactions managing and monitoring drug interactions how to talk to patients about drug interactions Update history 20 March 2023 19 January 2023 HomebookStockley’s Drug Interactions (9th Edition) Stockley’s Drug Interactions (9th Edition)This, the 9th edition of Stockley’s Drug Interactions, continues to build on the experience gained by the editorial team, from a history of more than 30 years of analysing the literature on drug interactions. In the words of Ivan Stockley, from his original guidance to us: ‘most readers want answers quickly, and therefore we have to write concisely and crisply to produce a picture which emerges very rapidly. We are not in the business of writing a discursive essay or great literature. Our busi-ness is bread-and-butter, rapid and unambiguous communication, for which we use direct and simple English, avoiding jargon wherever we can, recognising that our readers have varied backgrounds. Some may have forgotten (or never known) some of what we, with our familiarity with the subject, come to regard as basic pharmacology or medicine. At the same time we need to avoid patronising the well-informed reader by “mickey-mousing” it.’ This is the philosophy we work with, and we hope to continue to pay due respect to Ivan Stockley’s intentions by adhering to this fitting guidance.In some areas we have become slightly more discursive, in the hope of better explaining the relevance of an interaction to specific patient groups. However, we have addressed the needs of those in a hurry by in-cluding a short summary of the interaction, with the advice on the man-agement of the interaction discussed separately from the detailed clinical evidence and mechanism information. For those with more time, or those wishing to know the full picture, the clinical evidence and mecha-nism sections provide more detailed background on the interaction. Whichever approach is taken, the aim of Stockley’s Drug Interactions is, as ever, to inform busy doctors, pharmacists, nurses and other healthcare professionals of the facts about drug interactions, without their having to do the time-consuming literature searches and full assessment of the pa-pers for themselves. If you need some insight into the general philosophy underlying the way the information is handled in this publication, you should have a look at the section, ‘Before using this book. . .’.This publication is unique in the Stockley family of products by not in-cluding a symbol to rate the severity of the interaction. We continue to review this decision, but we currently believe that, in this fully compre-hensive text, it is not always possible to simply assign one rating – cer-tainly drug groups are often not identical in the way they interact, and to assign one symbol to the discussion of a group of drugs risks incorrectly implying that all members may interact similarly. Further, it overlooks the range of differences in the individual patient that a practitioner may need to consider. An otherwise fit and healthy patient will react very dif-ferently to a patient with a multitude of medical problems, and, in some instances, the interaction may only occur in the presence of certain dis-ease states, for example renal impairment, or perhaps only in children. We therefore prefer to discuss these various risks and differences, where applicable, and allow the reader to make the decision on the severity of the interaction with the full knowledge of their particular patient. We be-lieve that the ratings symbols have a useful place in our other products, such as Stockley’s Drug Interactions Pocket Companion, where the in-teraction information is designed to be abridged, and summarised in a few lines: in this situation the symbol presents a worst-case scenario. For this edition of Stockley’s Drug Interactions, the concise and easy-to-read format of the monographs has been maintained. As with previous editions, all of the existing interactions monographs have been reviewed, revalidated and updated, and many new ones have been added, making a total in excess of 3700 monographs, representing at 20% increase in content on the previous edition. This serves to highlight the ever-increas-ing wealth of information on this topic. Indeed we now cite well over 22,000 references, more, we think, than any other reference text on this subject. We also review relevant information provided by regulatory bodies outside of the UK, in particular the EMEA in Europe and the FDA in the US, which continues to enhance the international flavour of the publication. In addition, we have created three new chapters, covering Nutritional agents, Supplements and Vitamins, Thyroid hormones, and Urological drugs, to reflect the increasing literature available on these particular topic areas. Previous editions have found us struggling with the best way to deal with the interactions of herbal medicines in this reference, which is primarily an evidence-based text. As before, we have included the interactions of herbal medicines for which clinical evidence is available. However, we have long felt that the overwhelming numbers of theoretical and in vitro papers are worthy of analysis alongside the modest amount of clinical data on herbal medicines interactions. Our sister publication Stockley’s Herbal Medicines Interactions, first published in 2009, has therefore been written to deal with this theoretical data, which does not fit with the philosophy of Stockley’s Drug Interactions.This edition has also seen a growth in our editorial team, which includes experienced clinical pharmacists and medical writers, and we have been pleased to have the advice and assistance of pharmacists with a greater knowledge of community pharmacy and specialist clinical subjects than those in our existing team. In particular, the advice of Rosy Weston, a specialist HIV pharmacist, has been of great help, and our thanks go out to her. The diverse practical experience of our team and advisors helps us to maintain the quality and realistic nature of the management advice given. The Editorial team have also had assistance from many other people in developing this publication, and the Editor gratefully acknowledges the assistance and guidance that they have provided. The Martindale team continue to be a great source of advice and support, and particular thanks is due to the editor, Sean Sweetman, both for his direct assistance with producing the publication, and for allowing us access to the Martindale databases, from which we derive much of our nomenclature. We greatly appreciate the help of Chloë Hatwal in putting together the final typeset pages. Thanks are also due to Tamsin Cousins, for patiently handling the various aspects of producing our publications in print. We are also grate-ful for the support of both Paul Weller and Robert Bolick. Stockley’s Drug Interactions continues to be available on the Pharm-aceutical Press electronic platform, MedicinesComplete (available at www.medicinescomplete.com), where it is updated quarterly; as well as being available on other platforms as an e-book. With the continued de-velopment of the integratable Alerts product and the MedicinesComplete platform, we remain indebted to Julie McGlashan, Elizabeth King, and all those involved in the technical aspects of these products, for their ad-vice and support. For more details about these digital products please visit: www.pharmpress.com/Stockley Finally, thanks are due to those who take the time to provide us with feedback, either directly, or in the form of questions about the publica-tion. We continue to value this input to evolve the publication and to en-sure it meets the needs of the users. We are particularly grateful to those who have taken the time to answer our questions about specific aspects of practice. General considerations and an outline survey of some basic interaction mechanisms(a) What is a drug interaction?An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some en-vironmental chemical agent. Much more colourful and informal definitions by patients are that it is “. . . when medicines fight each other. . .”, or “. . . when medicines fizz together in the stomach . . .”, or “. . .what happens when one medicine falls out with another. . .” The outcome can be harmful if the interaction causes an increase in the toxicity of the drug. For example, there is a considerable increase in risk of severe muscle damage if patients taking statins start taking azole antifungals (see ‘Statins + Azoles’, p.1321). Patients taking monoamine ox-idase inhibitor antidepressants (MAOIs) may experience an acute and po-tentially life-threatening hypertensive crisis if they eat tyramine-rich foods such as cheese (see ‘MAOIs or RIMAs + Tyramine-rich foods’, p.1395). A reduction in efficacy due to an interaction can sometimes be just as harmful as an increase: patients taking warfarin who are given rifampicin (rifampin) need more warfarin to maintain adequate anticoagulation (see ‘Coumarins + Antibacterials; Rifamycins’, p.424), while patients taking ‘tetracyclines’, (p.390) or ‘quinolones’, (p.374) need to avoid antacids and milky foods (or separate their ingestion) because the effects of these antibacterials can be reduced or even abolished if admixture occurs in the gut. These unwanted and unsought interactions are adverse and undesirable but there are other interactions that can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics in or-der to achieve antihypertensive effects possibly not obtainable with either drug alone (see ‘Antihypertensives + Other drugs that affect blood pres-sure’, p.1051). The mechanisms of both types of interaction, whether ad-verse or beneficial, are often very similar, but the adverse interactions are the focus of this publication. Definitions of a drug interaction are not rigidly adhered to in this publica-tion because the subject inevitably overlaps into other areas of adverse re-actions with drugs. So you will find in these pages some ‘interactions’ where one drug does not actually affect another at all, but the adverse out-come is the simple additive effects of two drugs with similar effects (for ex-ample the combined effects of two or more CNS depressants, or two drugs which affect the QT interval). Sometimes the term ‘drug interaction’ is used for the physico-chemical reactions that occur if drugs are mixed in intrave-nous fluids, causing precipitation or inactivation. The long-established and less ambiguous term is ‘pharmaceutical incompatibilities’. Incompatibili-ties are not covered by this publication.(b) What is the incidence of drug interactions?The more drugs a patient takes the greater the likelihood that an adverse reaction will occur. One hospital study found that the rate was 7% in those taking 6 to 10 drugs but 40% in those taking 16 to 20 drugs, which repre-sents a disproportionate increase.1 A possible explanation is that the drugs were interacting. Some of the early studies on the frequency of interactions uncritically compared the drugs that had been prescribed with lists of possible drug in-teractions, without appreciating that many interactions may be clinically trivial or simply theoretical. As a result, an unrealistically high incidence was suggested. Most of the later studies have avoided this error by looking at only potentially clinically important interactions, and incidences of up to 8.8% have been reported.2-4 Even so, not all of these studies took into account the distinction that must be made between the incidence of potential interactions and the incidence of those where clinical problems actu-ally arise. The simple fact is that some patients experience quite serious reactions while taking interacting drugs, while others appear not to be af-fected at all. A screening of 2 422 patients over a total of 25 005 days revealed that 113 (4.7%) were taking combinations of drugs that could interact, but ev-idence of interactions was observed in only 7 patients, representing an in-cidence of 0.3%.2 In another study of 44 hospital inpatients taking 10 to 17 drugs over a 5-day period, 77 potential drug interactions were identi-fied, but only one probable and four possible adverse reactions (6.4%) were detected.5 A further study, among patients taking antiepileptic drugs, found that 6% of the cases of toxicity were due to drug interactions.6 These figures are low compared with those of a hospital survey that monitored 927 patients who had received 1004 potentially interacting drug combina-tions. Changes in drug dose were made in 44% of these cases.7 A review of these and other studies found that the reported incidence rates ranged from 2.2 to 70.3%, and the percentage of patients actually experiencing problems was less than 11.1%. Another review of 639 elderly patients found a 37% incidence of interactions.8 Yet another review of 236 geriat-ric patients found an 88% incidence of clinically significant interactions, and a 22% incidence of potentially serious and life-threatening interac-tions.9 A 4.1% incidence of drug interactions on prescriptions presented to community pharmacists in the US was found in a further survey,10 where-as the incidence was only 2.9% in another American study,11 and just 1.9% in a Swedish study.12 An Australian study found that about 10% of hospital admissions were drug-related, of which 4.4% were due to drug in-teractions.13 A very high incidence (47 to 50%) of potential drug interac-tions was found in a study carried out in an Emergency Department in the US.14 One French study found that 16% of the prescriptions for a group of patients taking antihypertensive drugs were contraindicated or unsuita-ble,15 whereas another study in a group of geriatric patients found only a 1% incidence.16 The incidence of problems would be expected to be high-er in the elderly because ageing affects the functioning of the kidneys and liver.17,18 These discordant figures need to be put into the context of the under-re-porting of adverse reactions of any kind by medical professionals, for rea-sons that may include pressure of work or the fear of litigation. Both doctors and patients may not recognise adverse reactions and interactions, and some patients simply stop taking their drugs without saying why. None of these studies give a clear answer to the question of how frequently drug interactions occur, but even if the incidence is as low as some of the studies suggest, it still represents a very considerable number of patients who appear to be at risk when one thinks of the large numbers of drugs prescribed and taken every day.(c) How seriously should interactions be regarded and handled?It would be very easy to conclude after browsing through this publication that it is extremely risky to treat patients with more than one drug at a time, but this would be an over-reaction. The figures quoted in the previous sec-tion illustrate that many drugs known to interact in some patients, simply fail to do so in others. This partially explains why some quite important drug interactions remained virtually unnoticed for many years, a good ex-ample of this being the increase in serum digoxin levels seen with quini-dine (see ‘Digoxin and related drugs + Quinidine’, p.1111). Examples of this kind suggest that patients apparently tolerate adverse interactions remarkably well, and that many experienced physicians ac-commodate the effects (such as rises or falls in serum drug levels) without consciously recognising that what they are seeing is the result of an inter-action. ACE inhibitors and Angiotensin II receptor antagonistsACE inhibitors (angiotensin-converting enzyme inhibitors) prevent the production of angiotensin II from angiotensin I. The angiotensin II recep-tor antagonists are more selective, and target the angiotensin II type I(AT1) receptor, which is responsible for the pressor actions of angiotensin II. Angiotensin II is involved in the renin-angiotensin-aldosterone system, which regulates blood pressure, sodium and water homoeostasis by the kidneys, and cardiovascular function. Angiotensin II stimulates the syn-thesis and secretion of aldosterone and raises blood pressure via a direct vasoconstrictor effect. Angiotensin converting enzyme (ACE) is identical to bradykinase, so ACE inhibitors may additionally reduce the degradation of bradykinin and affect enzymes involved in the production of prostaglandins. Many of the interactions of the ACE inhibitors and angiotensin II recep-tor antagonists involve drugs that affect blood pressure. Consequently in most cases the result is either an increase in the hypotensive effect (e.g. ‘alcohol’, (p.51)) or a decrease in the hypotensive effect (e.g. ‘indomet-acin’, (p.32)). In addition, due to their effects on aldosterone, the ACE inhibitors and angiotensin II antagonists may increase potassium concentrations and can therefore have additive hyperkalaemic effects with other drugs that cause elevated potassium levels. Furthermore, drugs that affect renal function may potentiate the adverse effects of ACE inhibitors and angiotensin II an-tagonists on the kidneys. Most ACE inhibitor and angiotensin II receptor antagonist interactions are pharmacodynamic, that is, interactions that result in an alteration in drug effects rather than drug disposition, so in most cases interactions of individual drugs will be applicable to the group. In vitro experiments sug-gest that the role of cytochrome P450 isoenzymes in the metabolism and interactions of the angiotensin II receptor antagonists (candesartan, epro-sartan, irbesartan, losartan and valsartan) is small, although losartan, irbe-sartan, and to a minor extent, candesartan, are metabolised by CYP2C9. Only losartan and irbesartan were considered to have a theoretical poten-tial for pharmacokinetic drug interactions involving CYP2C9.1 See ‘An-giotensin II receptor antagonists + Azoles’, p.39. The ACE inhibitors do not appear to undergo interactions via cytochrome P450 isoenzymes. ‘Table 2.1’, (see below) lists the ACE inhibitors and the angiotensin II receptor antagonists. Although most of the interactions of the ACE inhib-itors or angiotensin II receptor antagonists are covered in this section, if the ACE inhibitor or angiotensin II receptor antagonist is the affecting drug, the interaction is dealt with elsewhere.AlcoholFor social and historical reasons alcohol is usually bought from a store or in a bar or restaurant, rather than from a pharmacy, because it is considered to be a drink and not a drug. However, pharmacologically it has much in common with medicinal drugs that depress the central nervous system. Objective tests show that as blood-alcohol levels rise, the ability to per-form a number of skills gradually deteriorates as the brain becomes pro-gressively disorganised. The myth that alcohol is a stimulant has arisen because at parties and social occasions it helps people to lose some of their inhibitions and it allows them to relax and unwind. Professor JH Gaddum put it amusingly and succinctly when, describing the early effects of mod-erate amounts of alcohol, he wrote that “logical thought is difficult but af-ter dinner speeches easy.” The expansiveness and loquaciousness that are socially acceptable can lead on, with increasing amounts of alcohol, to unrestrained behaviour in normally well-controlled individuals, through to drunkenness, unconsciousness, and finally death from respiratory failure. These effects are all a reflection of the progressive and deepening depres-sion of the CNS. ‘Table 3.1’, (p.47) gives an indication in very broad terms of the reac-tions of men and women to different amounts and concentrations of alco-hol. On the whole women have a higher proportion of fat in which alcohol is not very soluble, their body fluids represent a smaller proportion of their total body mass, and their first-pass metabolism of alcohol is less than men because they have less alcohol dehydrogenase in their stomach walls. Consequently if a man and woman of the same weight matched each other, drink for drink, the woman would finish up with a blood alcohol level about 50% higher than the man. The values shown assume that the drink-ers regularly drink, have had a meal and weigh between 9 and 11 stones (55 to 70 kg). Higher blood-alcohol levels would occur if alcohol was drunk on an empty stomach and lower values in much heavier individuals. The liver metabolises about one unit of alcohol per hour so the values will fall with time. Since alcohol impairs the skills needed to drive safely, almost all nation-al and state authorities have imposed maximum legal blood alcohol limits. In a number of countries this has been set at 80 mg/100 mL (35 micrograms per 100 mL in the breath) but impairment is clearly de-tectable at lower concentrations, for which reason some countries have imposed much lower legal limits, even down to 0 mg/100 mL in some cases. Even within countries the legal limit can vary, depending on the type of vehicle being driven and the age of the driver. Alcohol can interact with many drugs both by pharmacokinetic and/or pharmacodynamic mechanisms. The quantity and frequency of alcohol consumption can affect the bioavailability of alcohol and other drugs. Sev-eral hepatic enzymes are important in the metabolism of alcohol; primarily alcohol dehydrogenases convert alcohol into acetaldehyde, but other en-zymes, in particular the cytochrome P450 isoenzyme CYP2E1, are also in-volved, especially in moderate to heavy alcohol consumption. The cytochrome P450 isoenzymes CYP3A4 and CYP1A2 may also have a role in the metabolism of alcohol. Alcohol can induce CYP2E1 (and possibly other isoenzymes) after pro-longed heavy intake, and this can result in an increased metabolic rate and lower blood levels of drugs metabolised via this system. Conversely, short term binge drinking is likely to cause inhibition of this enzyme group by direct competition for binding sites and therefore decrease the metabolism of other drugs. Probably the most common drug interaction of all occurs if alcohol is drunk by those taking other drugs that have CNS depressant activity, the result being even further CNS depression. Blood-alcohol levels well with-in the legal driving limit may, in the presence of other CNS depressants, be equivalent to blood-alcohol levels at or above the legal limit in terms of worsened driving and other skills. This can occur with some antihista-mines, antidepressants, anxiolytics, hypnotics, opioid analgesics, and oth-ers. This section contains a number of monographs that describe the results of formal studies of alcohol combined with a number of recognised CNS depressants, but there are still many other drugs that await study of this kind, and which undoubtedly represent a real hazard. A less common interaction that can occur between alcohol and some drugs, chemical agents, and fungi, is the flushing (Antabuse) reaction. This is exploited in the case of disulfiram (Antabuse) as a drink deterrent (see ‘Alcohol + Disulfiram’, p.66), but it can occur unexpectedly with some other drugs, such as some antifungals and cephalosporins, chlo-rpropamide and metronidazole, and can be both unpleasant and possibly frightening, but it is not usually dangerous.Alpha blockersThe selective and non-selective alpha blockers are categorised and listed in ‘Table 4.1’, (see below). The principal interactions of the alpha blockers are those relating to enhanced hypotensive effects. Early after the introduction of the selective alpha blockers it was discovered that, in some individuals, they can cause a rapid reduction in blood pressure on starting treatment (al-so called the ‘first-dose effect’ or ‘first-dose hypotension’). The risk of this may be higher in patients already taking other antihypertensive drugs. A similar hypotensive effect can occur when the dose of the alpha blocker is increased, or if treatment is interrupted for a few days and then re-intro-duced. The first-dose effect has been minimised by starting with a very low dose of the alpha blocker, and then escalating the dose slowly over a couple of weeks. Some manufacturers recommend giving the first dose on retiring to bed, or if not, avoiding tasks that are potentially hazardous if syncope oc-curs (such as driving) for the first 12 hours. If symptoms such as dizziness, fatigue or sweating develop, patients should be warned to lie down, and to remain lying flat until they abate completely. It is unclear whether there are any real differences between the alpha blockers in their propensity to cause this first-dose effect. However, tamsu-losin is reported to have some selectivity for the alpha receptor 1A subtype, which are found mostly in the prostate and so have less effect on blood pres-sure: an initial titration of the dose is therefore not considered to be neces-sary. Nevertheless, it would be prudent to exercise caution with all the drugs in this class. Other alpha blockers are also used to increase urinary flow-rate and im-prove obstructive symptoms in benign prostatic hyperplasia. In this setting, their effects on blood pressure are more of an adverse effect, and their ad-ditive hypotensive effect with other antihypertensives may not be benefi-cial. Some alpha blockers (e.g. alfuzosin, doxazosin, tamsulosin) are metabo-lised via the cytochrome isoenzyme system, particularly by CYP3A4, and so potent CYP3A4 inhibitors may possibly increase their plasma levels, see ‘Alpha blockers + CYP3A4 or CYP2D6 inhibitors’, p.96.Anaesthetics and Neuromuscular blockersMany patients undergoing anaesthesia may be taking long-term medica-tion, which may affect their haemodynamic status during anaesthesia. This section is limited to drug interactions and therefore does not cover the many precautions relating to patients taking long-term medication and un-dergoing anaesthesia.(a) General anaestheticsIn general anaesthesia a balanced approach is often used to meet the main goals of the anaesthetic procedure. These goals are unconsciousness/am-nesia, analgesia, muscle relaxation, and maintenance of homoeostasis. Therefore general anaesthesia often involves the use of several drugs, in-cluding benzodiazepines, opioids, and anticholinesterases, as well as gen-eral anaesthetics (sometimes more than one) and neuromuscular blockers. The use of several different types of drugs in anaesthesia means that there is considerable potential for drug interactions to occur in the peri-opera-tive period, but this section concentrates on the effects of drugs on general anaesthetics and neuromuscular blockers. The interactions of other drugs used peri-operatively are mainly covered under ‘anticholinesterases’,(p.396), ‘benzodiazepines’, (p.831), and ‘opioids’, (p.149). There may be difficulty in establishing which of the drugs being used in a complex regimen are involved in a suspected interaction. It should also be borne in mind that disease processes and the procedure for which an-aesthesia is used may also be factors to be taken into account when evalu-ating a possible interaction. Some established interactions are advantageous and are employed clini-cally. For example, the hypnotic and anaesthetic effects of ‘propofol and midazolam’, (p.106), are found to be greater than the expected additive ef-fects and this synergy allows for lower dosage regimens in practice. Sim-ilarly nitrous oxide reduces the required dose of inhalational generalanaesthetics (see ‘Anaesthetics, general + Anaesthetics, general’, p.103). The general anaesthetics mentioned in this section are listed in ‘Table 5.1’, (p.101). Barbiturates used as anaesthetics (e.g. thiopental) are largely covered here, whereas barbiturates used predominantly for their antiepi-leptic or sedative properties (e.g. phenobarbital or secobarbital) are dealt with in the appropriate sections. Many anaesthetics have been associated with arrhythmias, due to their sensitising effects on the myocardium. A suggested listing of inhalational anaesthetics in order of decreasing sensitising effect on the myocardium is as follows: cyclopropane, halothane, enflurane/methoxyflurane, desflu-rane/isoflurane/sevoflurane.(b) Local anaestheticsThe interactions discussed in this section mainly involve the interaction of drugs with local anaesthetics used for epidural or spinal anaesthesia. The interactions of lidocaine used as an antiarrhythmic is dealt with in ‘An-tiarrhythmics’, (p.273). The local anaesthetics mentioned in this section are listed in ‘Table 5.1’, (p.101).(c) Neuromuscular blockersThe competitive (non-depolarising) neuromuscular blockers and depolar-ising neuromuscular blockers mentioned in this section are listed in ‘Table 5.2’, (p.101). The modes of action of the two types of neuromuscular blocker are discussed in the monograph ‘Neuromuscular blockers + Neu-romuscular blockers’, p.142. It should be noted that mivacurium (a com-petitive blocker) and suxamethonium (a depolarising blocker) are hydrolysed by cholinesterase, so share some interactions in common that are not relevant to other competitive neuromuscular blockers.Analgesics and NSAIDsThe drugs dealt with in this section include aspirin and other salicylates, NSAIDs, opioid analgesics, and the miscellaneous analgesics, such as ne-fopam and paracetamol. ‘Table 6.1’, (p.150) contains a listing, with a fur-ther classification of the NSAIDs.Interactions(a) Aspirin and NSAIDsAspirin and the NSAIDs generally undergo few clinically significant pharmacokinetic interactions. The majority are highly protein bound, and have the potential to interact with other drugs via this mechanism. How-ever, with a few exceptions, most of these interactions are not clinically important (see ‘Protein-binding interactions’, (p.3)). Of the newer NSAIDs, celecoxib is metabolised by the cytochrome P450 isoenzyme CYP2C9, and inhibits CYP2D6. Rofecoxib, now withdrawn, inhibits CYP1A2, see ‘Tizanidine + CYP1A2 inhibitors’, p.1572. Never-theless, most of the important interactions with NSAIDs and aspirin are pharmacodynamic. Aspirin and all non-selective NSAIDs inhibit platelet aggregation, and so can increase the risk of bleeding and interact with oth-er drugs that have this effect. NSAIDs that are highly selective for cyclo-oxygenase-2 (COX-2) do not inhibit platelet aggregation. synthesis of renal prostaglandins, and so can cause salt and water reten-tion. This can increase blood pressure and affect antihypertensive therapy. Aspirin and non-selective NSAIDs inhibit the mechanisms that protect the gastrointestinal mucosa and so cause gastrointestinal toxicity. COX-2 selective NSAIDs (coxibs) are less likely to have this effect, but they can still cause gastrointestinal toxicity.(b) OpioidsMorphine is metabolised by glucuronidation by UDP-glucuronyltrans-ferases, mainly to one active and one inactive metabolite. The glucuroni-dation of morphine can be induced or inhibited by various drugs. Morphine is not significantly affected by cytochrome P450 isoenzymes. The semi-synthetic morphine analogues, hydromorphone and oxymor-phone, are metabolised similarly. and require metabolic activation, possibly by CYP2D6 or glucuronyl-transferases. Inhibitors of these enzymes may therefore reduce their effi-cacy. Oxycodone is also metabolised by CYP2D6 and CYP3A4. Pethidine (meperidine) is metabolised by several cytochrome P450 isoenzymes. If the metabolism of pethidine is increased it can lead to increased production of the toxic metabolite, norpethidine, and increased CNS adverse effects. Methadone is metabolised by several cytochrome P450 isoenzymes in-cluding CYP3A4, CYP2B6, and CYP2D6, although CYP2C8, CYP2C9 and CYP2C19 may also play a role. Buprenorphine is metabolised by CYP3A4, and alfentanil is extensively metabolised by CYP3A4, and has been used as a probe drug for assessing CYP3A4 activity. Fentanyl and sufentanil are also metabolised by CYP3A4, but because they are high hepatic-extraction drugs (see ‘Chang-es in first-pass metabolism’, (p.4)) they are less affected by inhibitors or inducers of CYP3A4, although in some instances this may still lead to clinically significant effects.(c) ParacetamolParacetamol is not absorbed from the stomach, and the rate of absorption is well correlated with the gastric emptying rate. Paracetamol has therefore been used as a marker drug in studies of gastric emptying. Paracetamol is primarily metabolised by the liver to a variety of metabolites, principally the glucuronide and sulfate conjugates. Hepatotoxicity of paracetamol is thought to be due to a minor metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is inactivated with glutathione and excreted as mercaptu-rate and cysteine conjugates. When the liver stores of glutathione are de-pleted, and the rate of production of NAPQI exceeds the rate of production of glutathione, excess NAPQI attaches to liver proteins and causes liver damage. CYP2E1 may be involved in the formation of this hepatotoxic metabolite.Anorectics and StimulantsThis section covers the drugs used in the management of obesity (such as orlistat, rimonabant and sibutramine) as well as the older drugs, such as the amfetamines, which are now no longer widely indicated for this con-dition and are now more generally considered as drugs of abuse. However, it should not be forgotten that the amfetamines (largely dexam