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Stockley's Drug Interactions

Ninth edition

Stockley's Drug Interactions

A source book of interactions, their mechanisms, clinical importance and management

Ninth edition

Edited by

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Preface

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 business 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 including a short summary of the interaction, with the advice on the management 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 mechanism 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 papers 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 including a symbol to rate the severity of the interaction. We continue to review this decision, but we currently believe that, in this fully comprehensive text, it is not always possible to simply assign one rating – certainly 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 differently to a patient with a multitude of medical problems, and, in some instances, the interaction may only occur in the presence of certain disease 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 believe that the ratings symbols have a useful place in our other products, such as *Stockley's Drug Interactions Pocket Companion*, where the interaction 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-increasing 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 grateful for the support of both Paul Weller and Robert Bolick.

Stockley's Drug Interactions continues to be available on the Pharmaceutical 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 development 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 advice 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 publication. We continue to value this input to evolve the publication and to ensure 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. Anyone who wishes to contact the Stockley team can do so at the following address: stockley@rpsgb.org

London, February 2010

Abbreviations

ACE—angiotensin-converting enzyme
ADP—adenosine diphosphate
AIDS—acquired immunodeficiency syndrome
ALT—alanine aminotransferase
am—*ante meridiem* (before noon)
aPTT—activated partial thromboplastin time
AST—aspartate aminotransferase
AUC—area under the time–concentration curve
$AUC_{0–12}$—area under the time–concentration curve measured over 0 to 12 hours
AV—atrioventricular
BCRP—breast cancer resistance protein (ABCG2)
BNF—British National Formulary
BP—blood pressure
BP—British Pharmacopoeia
BPC—British Pharmaceutical Codex
BPH—benign prostatic hyperplasia
bpm—beats per minute
BUN—blood urea nitrogen
CAPD—continuous ambulatory peritoneal dialysis
CDC—Centers for Disease Control (USA)
CNS—central nervous system
COMT—catechol-*O*-methyl transferase
COPD—chronic obstructive pulmonary disease
COX—cyclo-oxygenase
CSF—cerebrospinal fluid
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines)
DNA—deoxyribonucleic acid
ECG—electrocardiogram
ECT—electroconvulsive therapy
ED_{50}—the dose at which 50% of subjects respond
EEG—electroencephalogram
e.g.—*exempli gratia* (for example)
EMEA—European Agency for the Evaluation of Medicinal Products
FDA—Food and Drug Administration (USA)
$FEF_{25–75}$—maximum expiratory flow over the middle 50% of the vital capacity
FEV_1—forced expiratory volume in one second
FSH—follicle simulating hormone
FVC—forced vital capacity
g—gram(s)
GABA—gamma-aminobutyric acid
h—hour(s)
HAART—highly active antiretroviral therapy
HbA_{1c}—glycosylated (glycated) haemoglobin
HIV—human immunodeficiency virus
HRT—hormone replacement therapy
ibid—*ibidem*, in the same place (journal or book)
i.e.—*id est* (that is)
INR—international normalised ratio
ITU—intensive therapy unit
IU—International Units
IUD—intra-uterine device
kg—kilogram(s)
L—litre(s)
LDL—low-density lipoprotein
LFT—liver function test
LH—luteinising hormone
LMWH—low-molecular-weight heparin
MAC—minimum alveolar concentration
MAO—monoamine oxidase
MAOI—monoamine oxidase inhibitor
MAO-A—monoamine oxidase, type A
MAO-B—monoamine oxidase, type B
MCA—Medicines Control Agency (UK) (now MHRA)
MHRA—Medicines and Healthcare products Regulatory Agency (UK)
MIC—minimum inhibitory concentration
mEq—milliequivalent(s)
mg—milligram(s)
mL—millilitre(s)
mmHg—millimetre(s) of mercury
mmol—millimole
mol—mole
MRSA—methicillin resistant *Staphylococcus aureus*
NICE—National Institute for Health and Clinical Excellence (UK) (formerly the National Institute for Clinical Excellence)
nM—nanomole
nmol—nanomole
NNRTI—non-nucleoside reverse transcriptase inhibitor
NRTI—nucleoside reverse transcriptase inhibitor
NSAID—non-steroidal anti-inflammatory drug
NYHA—New York Heart Association
PABA—para-amino benzoic acid
PCP—pneumocystis pneumonia
pH—the negative logarithm of the hydrogen ion concentration
pm—*post meridiem* (after noon)
pO_2—plasma partial pressure (concentration) of oxygen
PPI—proton pump inhibitor
ppm—parts per million
RIMA—reversible inhibitor of monoamine oxidase type A
RNA—ribonucleic acid
sic—written exactly as it appears in the original
SNRI—serotonin and noradrenaline reuptake inhibitor
SSRI—selective serotonin reuptake inhibitor
SVT—supraventricular tachycardia
T3—Triiodothyronine
TPN—total parenteral nutrition
TSH—thyroid-stimulating hormone
UGT—uridine diphospho glucuronosyltransferase
UK—United Kingdom
US and USA—United States of America
USP—United States Pharmacopeia

Before using this book . . .

. . . you should read this short explanatory section so that you know how the drug interaction data have been set out here, and why – as well as the basic philosophy that has been followed in presenting it.

The monographs

This publication has over 3700 monographs with a common format, which are subdivided into sections like these:

- An abstract or summary for quick reading.
- **Clinical evidence**, detailing one, two or more illustrative examples of the interaction, followed by most or all of other supportive clinical evidence currently available.
- **Mechanism**, in brief.
- **Importance and management**, a short discussion designed to aid rapid clinical decision making. For example:
  – Is the interaction established or not?
  – What is its incidence?
  – How important is it?
  – How can it be managed?
  – And what, if any, are the non-interacting alternatives?
- **References**, a list of all of the relevant references. The length of the references list gives a very fair indication of the extent of the documentation. A long list indicates a well documented interaction, whereas a short list indicates poor documentation.

Some of the monographs have been compressed into fewer subsections instead of the more usual five, simply where information is limited or where there is little need to be more expansive.

The monographs do not carry the drug interaction Hazard/Severity ratings as used in the electronic *Stockley Interactions Alerts*, but what is written in each monograph should speak for itself.

Quality of information on interactions

The data on interactions are of widely varying quality and reliability. The best come from clinical studies carried out on large numbers of patients under scrupulously controlled conditions. The worst are anecdotal, uncontrolled, or based solely on *animal* studies. Sometimes they are no more than speculative and theoretical scaremongering guesswork, hallowed by repeated quotation until they become virtually set in stone.

The aim has been to filter out as much useless noise as possible, so wherever possible 'secondary' references are avoided, and 'primary' references which are available in good medical and scientific libraries are used instead – although sometimes unpublished, good quality, in-house reports on drug company files have been used where the drug company has kindly allowed access to the information. Product literature (for example, the Summary of Product Characteristics in the UK and the Prescribing Information in the US) rather than the research reports that lie behind them are also cited because they are the only source of published information about new drugs.

The quality of drug company literature is very variable. Some of it is excellent, helpful and very reliable, but regrettably a proportion contains a welter of speculative and self-protective statements, probably driven more by the company's medico-legal policy than anything else, and the nervousness of drug regulatory authorities. It is almost unbelievable (but true all the same) that drug companies that are scrupulous in the way they do their research, come out with statements about possible interactions that are little more than guesswork.

When drawing your own conclusions

The human population is a total mixture, unlike selected batches of laboratory animals (same age, weight, sex, and strain etc.). For this reason human beings do not respond uniformly to one or more drugs. Our genetic make up, ethnic background, sex, renal and hepatic functions, diseases and nutritional states, ages and other factors (the route of administration, for example) all contribute towards the heterogeneity of our responses. This means that the outcome of giving one or more drugs to any individual for the first time is never totally predictable because it is a new and unique 'experiment'. Even so, some idea of the probable outcome of using a drug or a pair of drugs can be based on what has been seen in other patients: the more extensive the data, the firmer the predictions.

The most difficult decisions concern isolated cases of interaction, many of which only achieved prominence because they were serious. Do you ignore them as 'idiosyncratic' or do you, from that moment onwards, contraindicate the use of the two drugs totally?

There is no simple 'yes' or 'no' answer to these questions, but one simple rule-of-thumb is that isolated cases of interaction with old and very well-tried pairs of drugs are unlikely to be of general importance, whereas those with new drugs may possibly be the tip of an emerging iceberg and should therefore initially be taken much more seriously until more is known. The delicate balance between these two has then to be set against the actual severity of the reaction reported and weighed up against how essential it is to use the drug combination in question.

When deciding the possible first-time use of any two drugs in any particular patient, you need to put what is currently known about these drugs against the particular profile of your patient. Read the monograph. Consider the facts and conclusions, and then set the whole against the backdrop of your patients unique condition (age, disease, general condition, and so forth) so that what you eventually decide to do is well thought out and soundly based. We do not usually have the luxury of knowing absolutely all the facts, so that an initial conservative approach is often the safest.

I

General considerations and an outline survey of some basic interaction mechanisms

Drug interactions overview

(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 environmental 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 oxidase inhibitor antidepressants (MAOIs) may experience an acute and potentially 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 order to achieve antihypertensive effects possibly not obtainable with either drug alone (see 'Antihypertensives + Other drugs that affect blood pressure', p.1051). The mechanisms of both types of interaction, whether adverse 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 publication because the subject inevitably overlaps into other areas of adverse reactions with drugs. So you will find in these pages some 'interactions' where one drug does not actually affect another at all, but the adverse outcome is the simple additive effects of two drugs with similar effects (for example 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 intravenous fluids, causing precipitation or inactivation. The long-established and less ambiguous term is 'pharmaceutical incompatibilities'. Incompatibilities 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 represents 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 interactions, 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 actually arise. The simple fact is that some patients experience quite serious reactions while taking interacting drugs, while others appear not to be affected 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 evidence of interactions was observed in only 7 patients, representing an incidence 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 identified, 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 combinations. 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 geriatric patients found an 88% incidence of clinically significant interactions, and a 22% incidence of potentially serious and life-threatening interactions.[9] A 4.1% incidence of drug interactions on prescriptions presented to community pharmacists in the US was found in a further survey,[10] whereas 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 interactions.[13] A very high incidence (47 to 50%) of potential drug interactions 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 unsuitable,[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 higher 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-reporting of adverse reactions of any kind by medical professionals, for reasons 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 section 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 example of this being the increase in serum digoxin levels seen with quinidine (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 accommodate the effects (such as rises or falls in serum drug levels) without consciously recognising that what they are seeing is the result of an interaction.