pocket companion

Stockley's Drug Interactions 2014

Edited by
Claire L Preston

Pharmaceutical Press

Stockley's Drug Interactions Pocket Companion 2014

Editor

Claire L Preston, BPharm, PGDipMedMan, MRPharmS

Editorial Staff

Elaina E Crehan, MChem
Samuel Driver, BSc
Elizabeth S Foan, BA (Cantab)
Nilufer Karim, BSc, MPharm, MRPharmS
Sonia Z Khan, MPharm, PGCertPharmPrac
Rebecca E Luckhurst, BSc
Deirdre M McGuirk, BComm, MPharm, MRPharmS

Based on data produced by the Stockley Editorial Team

Ian A Baxter BSc, PhD, MRPharmS
Mildred Davis, BA, BSc, PhD, MRPharmS
Rebekah Raymond, BSc, DipPharmPrac
Julia Sawyer, BPharm, DipPharmPrac, MRPharmS

Expert Contributor

C Rhoda Lee, BPharm, PhD, MRPharmS

Editorial Director

Karen Baxter, BSc, MSc, MRPharmS

Pharmaceutical Press

Published by Pharmaceutical Press

1 Lambeth High Street, London SE1 7JN, UK

Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society

First published 2014

Typeset by Data Standards Ltd, Frome, Somerset
Printed in Italy by Rotolito Lombarda SpA

ISBN 978 0 85711 142 5

A catalogue record for this book is available from the British Library

Disclaimer
Stockley's Drug Interactions Pocket Companion (SDIPC) provides healthcare professionals with practical information on drug interactions and their management. SDIPC is published annually and the Publisher works to ensure that the information is accurate and up-to-date as at the date of publication, but changes do regularly occur and the Publisher does not warrant that it is accurate.

SDIPC is designed as a digest for rapid reference and it may not always include all information necessary for prescribing or dispensing. Also less detail is given on certain specialties since those involved are expected to have specialist knowledge and access to specialist literature. SDIPC should be interpreted in light of professional knowledge and supplemented as necessary with a complete reference source and by reference to product literature.

To the fullest extent permitted by law the publisher assumes no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information. The Publisher does not exclude any liability for death or personal injury resulting from negligence, fraud, or any liability which cannot be excluded by applicable law.

Stockley's Drug Interactions Pocket Companion 2014

Preface

What is *Stockley's Drug Interactions Pocket Companion*?

Stockley's Drug Interactions is a reference work that provides concise, accurate, and clinically relevant information to healthcare professionals. Monographs are based on published sources including clinical studies, case reports, and systematic reviews, and are fully referenced. *Stockley's Drug Interactions Pocket Companion* has summarised this comprehensive work to create a small and conveniently-sized quick-reference text.

Stockley's Drug Interactions Pocket Companion provides the busy healthcare professional with quick and easy access to clinically relevant, evaluated and evidence-based information about drug interactions. As with the full reference work this publication attempts to answer the following questions:

- Are the drugs or substances in question known to interact or is the interaction only theoretical and speculative?
- If they do interact, how serious is it?
- Has it been described many times or only once
- Are all patients affected or only a few?
- Is it best to avoid some drug combinations altogether or can the interaction be accommodated in some way?
- What alternative and safer drugs can be used instead?

Coverage

Stockley's Drug Interactions Pocket Companion 2014 contains over 2200 interaction monographs pertaining to specific drugs or drug groups. Each monograph in *Stockley's Drug Interactions* was assessed by practising clinical pharmacists for its suitability for inclusion in the *Pocket Companion*. Broadly speaking interactions involving anaesthesia, the specialist use of multiple antiretrovirals, the specialist use of multiple antineoplastics or intravenous antineoplastics, and non-interactions were omitted. However, exceptions were made, particularly where there has been controversy over whether or not a drug interacts.

Monographs

Following the familiar format of the Stockley products, the information in this publication is organised into a brief summary of the evidence for the interaction and a description of how best to manage it. The information is based on the most recent quarterly update of *Stockley's Drug Interactions* at the time of going to press. This data is fully referenced and available at www.medicinescomplete.com. These references have not been included in the *Pocket Companion* to keep size to a minimum. Anyone interested in seeing our sources can consult *MedicinesComplete*, or the full reference work of *Stockley's Drug Interactions*.

Ratings

Each monograph has been assigned a rating symbol to offer guidance to the user on the clinical significance of the interaction. These ratings are the same as those used in *Stockley's Interaction Alerts*. The Alerts are rated using three separate categories:

- Action – This describes whether or not any action needs to be taken to accommodate the interaction. This category ranges from 'avoid' to 'no action needed'.
- Severity – This describes the likely effect of an unmanaged interaction on the patient. This category ranges from 'severe' to 'nothing expected'.
- Evidence – This describes the weight of evidence behind the interaction. This category ranges from 'extensive' to 'theoretical'.

These ratings are combined to produce one of four symbols:

- ⊗ For interactions that have a life-threatening outcome, or where concurrent use is contraindicated by the manufacturers.
- ⚠ For interactions where concurrent use may result in a significant hazard to the patient and so dose adjustment or close monitoring is needed.
- ? For interactions where there is some doubt about the outcome of concurrent use, and therefore it may be necessary to give patients some guidance about possible adverse effects, and/or consider some monitoring.
- ✓ For interactions that are not considered to be of clinical significance, or where no interaction occurs.

We put a lot of thought in to the original design of these symbols, and have deliberately avoided a numerical or colour coding system as we did not want to imply any relationship between the symbols or colours. Instead we chose internationally recognisable symbols, which in testing were intuitively understood by our target audience of healthcare professionals.

Structure

Stockley's Drug Interactions Pocket Companion is structured alphabetically for ease of use, with International Nonproprietary Names (INNs) to identify drug names. Cross references to US Approved Names (USANs) are also included where drug names differ significantly. Consequently an interaction between aspirin and beta blockers will appear under A, and an interaction between beta blockers and digoxin will appear under B. We have only used drug groups where they are considered to be widely recognised, hence beta blockers is used, but alpha agonists is not. The drug groups we have used are as follows:

ACE inhibitors
Alpha blockers
Amfetamines
Aminoglycosides
Angiotensin II receptor antagonists
Antimuscarinics
Antidiabetics
Antihistamines
Antimuscarinics
Antipsychotics
Azoles
Benzodiazepines
Beta blockers
Bisphosphonates
Calcium-channel blockers
Cephalosporins
Contraceptives
Corticosteroids
Diuretics
Dopamine agonists
Endothelin receptor antagonists
Ergot derivatives
Fibrates
H_2-receptor antagonists
HRT
HIV-protease inhibitors
5-HT_3-receptor antagonists
Inotropes and Vasopressors
Low-molecular-weight heparins
Macrolides
MAO-B inhibitors
MAOIs
Nasal decongestants
Nitrates
NNRTIs
NRTIs
NSAIDs
Opioids
Penicillins
Phosphodiesterase type-5 inhibitors
Proton pump inhibitors
Quinolones
Salbutamol (Albuterol) and related bronchodilators
SSRIs
Statins
Sulfonamides
Tetracyclines
Tricyclics
Triptans
Vaccines
Warfarin and related oral anticoagulants

Acknowledgements

Aside from the editorial staff many other people have contributed to this publication and the Editors gratefully acknowledge the assistance and guidance they have provided. In particular, we would like to express our gratitude to David Granger and Karl Parsons for their support in producing the final dataset, particularly the indexing, and to Linda Paulus who has handled the various aspects of the production of this book. Thanks are also due to Ivan Stockley and Alina Lourie for their support with this project.

Individual users of this product continue to take the time to provide us with feedback on the contents and structure of the data, and for that we

are grateful. These comments are always useful to us in developing the products to better meet the needs of end-users.

Contact details

We are always very pleased to receive feedback from those using our products. Anyone wishing to comment can contact us at the following e-mail address: stockley@rpharms.com.

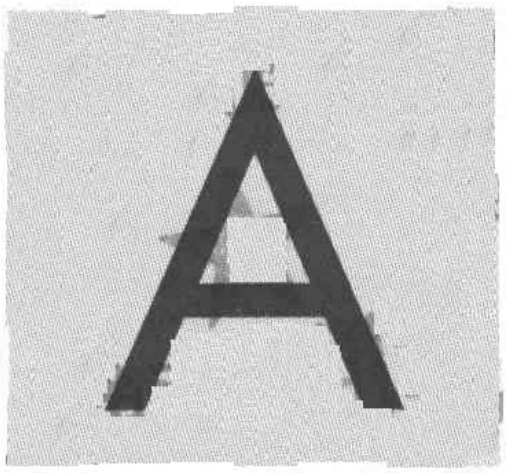
Abbreviations

ACE	angiotensin-converting enzyme
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time–concentration curve
BPH	benign prostatic hyperplasia
bpm	beats per minute
CNS	central nervous system
CSF	cerebrospinal fluid
CSM	Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines)
DMARD	disease modifying antirheumatic drug
ECG	electrocardiogram
e.g.	*exempli gratia* (for example)
FFPRHC	The UK Faculty of Family Planning and Reproductive Health Care
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
i.e.	*id est* (that is)
INR	international normalised ratio
IUD	intra-uterine device
LFT	liver function test
MAO	monoamine oxidase
MAO-A	monoamine oxidase, type A
MAO-B	monoamine oxidase, type B
MAOI	monoamine oxidase inhibitor
mg	milligram(s)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
mL	millilitre(s)
mmHg	millimetre(s) of mercury
mol	mole
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
pH	the negative logarithm of the hydrogen ion concentration
PPI	proton pump inhibitor
RNA	ribonucleic acid
SSRI	selective serotonin reuptake inhibitor
TSH	thyroid-stimulating hormone
UK	United Kingdom
US	United States of America
WHO	World Health Organization

About the Editor

Claire L. Preston studied pharmacy at the University of Nottingham, graduating in 1998. She completed her pre-registration year in Ashford, Kent before working as a community pharmacist for several years. She then became a medicines management pharmacist at a Primary Care Trust in Kent where she undertook her Clinical Diploma. Claire started at the Pharmaceutical Press in 2007 as a Staff Editor on the *British National Formulary* and later became an Assistant Editor. Claire has been the Lead Editor for Drug Interactions for the Pharmaceutical Press since March 2012.

Contents



ACE inhibitors

Most ACE inhibitor 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 as a whole. The ACE inhibitors do not appear to undergo interactions via cytochrome P450 isoenzymes.

ACE inhibitors + Aliskiren ⚠

The concurrent use of ACE inhibitors and aliskiren increases the risk of hyperkalaemia. Additive hypotension is likely to occur, which can be clinically beneficial, see also antihypertensives, page 97.

Monitor potassium concentrations with concurrent use, particularly in patients at high risk of hyperkalaemia (such as those with reduced renal function and/or diabetes). Note that, in December 2011, the European Medicines Agency stated that aliskiren-containing medicines should not be given to diabetic patients in combination with ACE inhibitors.

ACE inhibitors + Allopurinol ⚠

A case of hypersensitivity has been attributed to the concurrent use of captopril and allopurinol. Other ACE inhibitors may interact similarly. Anaphylaxis and myocardial infarction occurred in one man taking enalapril with allopurinol. The combination of ACE inhibitors and allopurinol might increase the risk of leucopenia and serious infection.

Patients taking both drugs should be very closely monitored for any signs of hypersensitivity (e.g. skin reactions) or low white cell count (sore throat, fever), especially if they have renal impairment. White blood cell counts should be monitored periodically: some manufacturers suggest checking before starting allopurinol, then every 2 weeks during the first 3 months of treatment, and periodically thereafter.

ACE inhibitors + Alpha blockers ?

The first-dose hypotensive effect seen with alpha blockers (particularly alfuzosin,

prazosin and terazosin) is likely to be potentiated by ACE inhibitors. It is unclear whether there are real differences between the alpha blockers in their propensity to cause this first-dose effect. Note that the acute hypotensive reaction appears to be short-lived. In one small study tamsulosin did not have any clinically relevant effects on blood pressure that was already well controlled by enalapril.

Minimise the risk of hypotensive reactions by starting with a low dose of alpha blocker, preferably given at bedtime, and increase the dose slowly over a couple of weeks. It is recommended that the dose of the ACE inhibitor is reduced during initiation. If adding an ACE inhibitor to an alpha blocker, consider decreasing the dose of the alpha blocker and re-titrate as necessary. Patients should be warned to lie down and raise their legs if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until symptoms abate.

ACE inhibitors + Antacids

Fosinopril ⚠

The bioavailability of fosinopril is moderately reduced by an aluminium/magnesium hydroxide-containing antacid.

The manufacturers suggest separating fosinopril administration from that of antacids by at least 2 hours.

Other ACE inhibitors ✓

Antacids have been reported to reduce the bioavailability of some ACE inhibitors but this seems unlikely to be clinically important (except perhaps in the case of fosinopril, see above).

The manufacturers of some ACE inhibitors warn that antacids may reduce their bioavailability, but there seems to be no evidence of a clinically significant interaction in practice.

ACE inhibitors + Antidiabetics ?

The concurrent use of ACE inhibitors and antidiabetics normally appears to be uneventful. However, hypoglycaemia, marked in some instances, has occurred in a small number of diabetics taking insulin or sulfonylureas with captopril, enalapril, lisinopril, or perindopril. This has been attributed, but not proven, to be due to an interaction. Sitagliptin appears to alter the hypotensive effects of enalapril.

It would be advisable to warn all patients taking insulin or oral antidiabetics who are just starting any ACE inhibitors that excessive hypoglycaemia has been seen very occasionally and unpredictably. It might be prudent to temporarily increase the frequency of blood glucose monitoring. Any problem seems easily resolved by reducing the sulfonylurea dose. The risk of an interaction appears low, and the use of ACE inhibitors in diabetes is considered beneficial. The reported effect of sitagliptin on the blood pressure-lowering effects of ACE inhibitors requires further study, until more is known it would seem prudent to bear the possibility of an interaction in mind should any otherwise unexplained changes in blood pressure occur on concurrent use.

ACE inhibitors + Aspirin ?

The antihypertensive efficacy of captopril and enalapril may be reduced by high-dose aspirin in about 50% of patients. Low-dose aspirin (less than or equal to 100 mg daily) appears to have little effect. It is unclear whether aspirin attenuates the benefits of ACE inhibitors in heart failure. The likelihood of an interaction may depend on disease state and its severity.

For hypertension, no action is needed if antiplatelet dose aspirin is used. Suspect an interaction with analgesic dose aspirin if the ACE inhibitor seems less effective, or blood pressure control is erratic. Increase the ACE inhibitor dose or consider an alternative analgesic, but note that NSAIDs interact in the same way as high-dose aspirin. For heart failure it is generally advised that concurrent use is best avoided, unless a specific indication (e.g. coronary heart disease, stroke) exists.

ACE inhibitors + Azathioprine ⚠

Anaemia has been seen in kidney transplant patients given azathioprine with enalapril or captopril. Leucopenia occasionally occurs when captopril is given with azathioprine. Azathioprine is rapidly and extensively metabolised to mercaptopurine. Mercaptopurine is therefore expected to share the interactions of azathioprine.

The manufacturer of captopril recommends that it should be used with extreme caution in patients taking immunosuppressants, especially if there is renal impairment. They advise that differential white blood cell counts should be checked before starting captopril, then every 2 weeks in the first 3 months of captopril use, and periodically thereafter, although this is most likely to already be occurring or planned because of the azathioprine. Any effect seems likely to be a group interaction, and it would therefore seem prudent to consider monitoring with any ACE inhibitor.

ACE inhibitors + Ciclosporin (Cyclosporine) ⚠

Acute renal failure has developed in kidney transplant patients taking ciclosporin with enalapril. Oliguria was seen in another patient taking ciclosporin with captopril. There is a possible increased risk of hyperkalaemia when ACE inhibitors are given with ciclosporin, as both drugs may raise potassium levels. It is anticipated that all ACE inhibitors will interact similarly.

The incidence of renal failure appears to be low, nevertheless care and good monitoring are needed if ACE inhibitors and ciclosporin are used concurrently. Monitor potassium levels more closely in the initial weeks of concurrent use.

ACE inhibitors + Clonidine ✓

ACE inhibitors may potentiate the antihypertensive effects of clonidine, and this can be clinically useful. However, limited evidence suggests that the effects of captopril may be delayed when patients are switched from clonidine. Note that sudden withdrawal of clonidine may cause rebound hypertension.

The general importance of this interaction is unknown, but be aware that it may occur.

A

ACE inhibitors + Contraceptives ?

Drospirenone, which is given as the progestogen component of oral combined hormonal contraceptives, might increase the risk of hyperkalaemia when given with other drugs that can cause hyperkalaemia such as ACE inhibitors. However, two studies found no evidence of an increased risk of hyperkalaemia on the concurrent use of with enalapril and drospirenone (given as *HRT*). Oral combined hormonal contraceptives are associated with increased blood pressure and might antagonise the efficacy of antihypertensive drugs, see Antihypertensives + Contraceptives, page 98.

The risk of hyperkalaemia appears to be low, especially if renal function is normal. In the US, it is recommended that consideration be given to monitoring potassium concentrations during the first cycle in women [with normal renal function] who regularly take an ACE inhibitor, whereas the UK manufacturer recommends that the potassium concentration is measured during the first cycle or month of treatment in women with mild or moderate renal impairment only. For women with severe renal impairment, the UK manufacturer contraindicates the use of drospirenone-containing contraceptives, whereas, in the US, its use in renal impairment [to any degree] is contraindicated. In patients at higher risk of developing hyperkalaemia (e.g. in renal impairment) it is generally recommended that potassium concentrations are measured during the first cycle of treatment with drospirenone.

ACE inhibitors + Co-trimoxazole ⚠

Two reports describe serious hyperkalaemia, apparently caused by the concurrent use of trimethoprim (given as co-trimoxazole) and enalapril or quinapril, in association with renal impairment. In elderly patients taking an ACE inhibitor, the use of co-trimoxazole appears to increase the risk of hospitalisation for hyperkalaemia.

Trimethoprim or ACE inhibitors alone can cause hyperkalaemia, particularly with other factors such as renal impairment. Monitor plasma potassium concentrations if this combination is used in those with renal impairment. Note that co-trimoxazole is a combination preparation containing trimethoprim, and might therefore interact similarly. It has been suggested that trimethoprim should probably be avoided in elderly patients, with or without chronic renal impairment, taking ACE inhibitors and patients with AIDS taking an ACE inhibitor for associated nephropathy should probably discontinue their ACE inhibitor during treatment with high-dose co-trimoxazole.

ACE inhibitors + Digoxin ✓

No clinically significant interaction has been seen between digoxin and most ACE inhibitors. Some studies have found that serum digoxin levels rise by about 20% or more if captopril is used, but others have found no significant changes. It has been suggested that any interaction is likely to occur only in those patients who have pre-existing renal impairment.

No action usually needed. In patients with renal impairment given digoxin and captopril it may be prudent to be alert for increased digoxin effects (e.g. bradycardia).

ACE inhibitors + Diuretics

Loop diuretics and Thiazides ?

The use of ACE inhibitors with loop or thiazide diuretics is normally safe and effective, but first-dose hypotension (dizziness, fainting) can occur, particularly if the dose of diuretic is high (greater than furosemide 80 mg daily or equivalent) and often in association with predisposing conditions (heart failure, renovascular hypertension, haemodialysis, high levels of renin and angiotensin, low-sodium diet, dehydration, diarrhoea or vomiting, etc.). In addition, renal impairment, and even acute renal failure, have been reported, and diuretic-induced hypokalaemia can still occur when ACE inhibitors are used with potassium-depleting diuretics.

First-dose hypotension is well established. In patients taking high-dose diuretics, ACE inhibitors should be initiated under close supervision. Consider temporarily stopping the diuretic or reducing its dose at least 24 hours before the ACE inhibitor is added. If this is not clinically appropriate the response to the first dose of the ACE inhibitor should be monitored for at least 2 hours, or until blood pressure has stabilised. ACE inhibitors should be started with a very low dose, even in patients at low risk (e.g. those with uncomplicated essential hypertension taking low-dose thiazides). All patients should be warned about what can happen, and advised to lie down if dizziness, lightheadedness or faintness occurs. Any marked hypotension is normally transient, but if problems persist it might be necessary to temporarily reduce the diuretic dose. Taking the first dose of the ACE inhibitor just before bedtime is also preferable. Severe reactions (e.g. renal impairment or hypokalaemia) are rare, and routine monitoring of the ACE inhibitor should suffice. However, if increases in urea and creatinine occur, a dose reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

Potassium-sparing diuretics ⚠

The use of ACE inhibitors with potassium-sparing diuretics, such as amiloride, eplerenone, spironolactone, and triamterene, can result in hyperkalaemia, particularly in the presence of other risk factors (e.g. advanced age, diabetes, doses of spironolactone greater than 25 mg daily, and renal impairment).

The concurrent use of ACE inhibitors and amiloride or triamterene is normally not advised, but if both drugs are appropriate potassium concentrations should be closely monitored. The presence of a loop or thiazide diuretic might not necessarily prevent hyperkalaemia. The combination of an ACE inhibitor and spironolactone or eplerenone is beneficial in some indications, but close monitoring of serum potassium concentrations and renal function is needed, especially with any changes in treatment or in the patient's clinical condition. It has been suggested that spironolactone should not be given with ACE inhibitors in those with a glomerular filtration rate of less than 30 mL/minute.

ACE inhibitors + Epoetin ?

Epoetin can cause hypertension and thereby reduce the effects of ACE inhibitors, and an additive hyperkalaemic effect is theoretically possible. ACE inhibitors appear to reduce the efficacy of epoetin, but any interaction could take many months to develop.

Blood pressure and electrolytes, particularly potassium, should be routinely monitored in those given epoetin. An increase in the ACE inhibitor dose appears