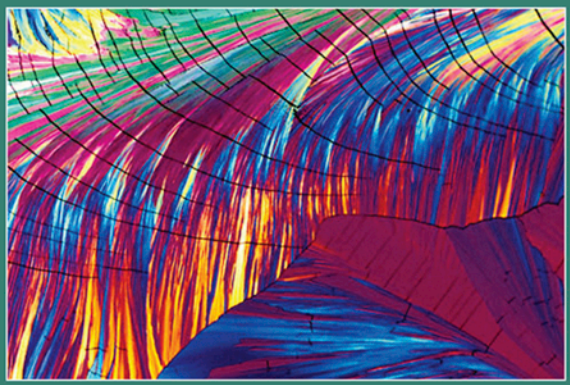
MEYLER'S
Side Effects of

Cardiovascular Drugs



J.K. Aronson

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Preface

This volume covers the adverse effects of drugs used in managing cardiovascular disorders. The material has been collected from *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions* (15th edition, 2006, in six volumes), which was itself based on previous editions of *Meyler's Side Effects of Drugs*, and from the *Side Effects of Drugs Annuals* (SEDA) 28, 29, and 30. The main contributors of this material were M Andréjak, JK Aronson, JJ Coleman, A del Favero, MG Franzosi, V Gras, J Harenberg, GD Johnston, P Joubert, DM Keeling, R Latini, PO Lim, TM MacDonald, AP Maggioni, U Martin, GT McInnes, K Peerlinck, DA Sica, R Verhaeghe, P Verhamme, J Vermylen, and F Zannad. For contributors to earlier editions of *Meyler's Side Effects of Drugs* and the *Side Effects of Drugs Annuals*, see http://www.elsevier.com/wps/find/bookseriesdescription.cws_home/BS_SED/description.

A brief history of the Meyler series

Leopold Meyler was a physician who was treated for tuberculosis after the end of the Nazi occupation of The Netherlands. According to Professor Wim Lammers, writing a tribute in Volume VIII (1975), Meyler got a fever from para-aminosalicylic acid, but elsewhere Graham Dukes has written, based on information from Meyler's widow, that it was deafness from dihydrostreptomycin; perhaps it was both. Meyler discovered that there was no single text to which medical practitioners could look for information about unwanted effects of drug therapy; Louis Lewin's text "Die Nebenwirkungen der Arzneimittel" ("The Untoward Effects of Drugs") of 1881 had long been out of print (SEDA-27, xxv-xxix). Meyler therefore determined to make such information available and persuaded the Netherlands publishing firm of Van Gorcum to publish a book, in Dutch, entirely devoted to descriptions of the adverse effects that drugs could cause. He went on to agree with the Elsevier Publishing Company, as it was then called, to prepare and issue an English translation. The first edition of 192 pages (*Schadelijke Nevenwerkingen van Geneesmiddelen*) appeared in 1951 and the English version (*Side Effects of Drugs*) a year later.

The book was a great success, and a few years later Meyler started to publish what he called surveys of unwanted effects of drugs. Each survey covered a period of two to four years. They were labelled as volumes rather than editions, and after Volume IV had been published Meyler could no longer handle the task alone. For subsequent volumes he recruited collaborators, such as Andrew Herxheimer. In September 1973 Meyler died unexpectedly, and Elsevier invited Graham Dukes to take over the editing of Volume VIII.

Dukes persuaded Elsevier that the published literature was too large to be comfortably encompassed in a four-yearly cycle, and he suggested that the volumes should be produced annually instead. The four-yearly volume could then concentrate on providing a complementary critical encyclopaedic survey of the entire field. The first *Side Effects of Drugs Annual* was published in 1977. The first encyclopaedic edition of *Meyler's Side Effects of Drugs*, which appeared in 1980, was labelled the ninth edition, and since then a new encyclopaedic edition has appeared every four years. The 15th edition was published in 2006, in both hard and electronic versions.

Monograph structure

This volume is in six sections:

- drugs used to treat hypertension, heart failure, and angina pectoris;
- diuretics—a general introduction to their adverse effects, followed by monographs on individual drugs;
- antidysrhythmic drugs— a general introduction to their adverse effects, followed by monographs on individual drugs;
- drugs that act on the cerebral and peripheral circulations;
- anticoagulants, thrombolytic agents, and anti-platelet drugs;
- cardiovascular adverse effects of non-cardiovascular drugs.

In each monograph in the Meyler series the information is organized into sections as shown below (although not all the sections are covered in each monograph).

DoTS classification of adverse drug reactions

A few adverse effects have been classified using the system known as DoTS. In this system adverse reactions are classified according to the ***Dose*** at which they usually occur, the ***Time-course*** over which they occur, and the ***Susceptibility factors*** that make them more likely, as follows:

- ***Relation to Dose***
  - Toxic reactions—reactions that occur at supratherapeutic doses
  - Collateral reactions—reactions that occur at standard therapeutic doses
  - Hypersusceptibility reactions—reactions that occur at subtherapeutic doses in susceptible individuals

- ***Time course***
  - Time-independent reactions—reactions that occur at any time during a course of therapy
  - Time-dependent reactions
    - Immediate or rapid reactions—reactions that occur only when a drug is administered too rapidly
    - First-dose reactions—reactions that occur after the first dose of a course of treatment and not necessarily thereafter

  - Early reactions—reactions that occur early in treatment then either abate with continuing treatment (owing to tolerance) or persist
  - Intermediate reactions—reactions that occur after some delay but with less risk during longer term therapy, owing to the "healthy survivor" effect
  - Late reactions—reactions the risk of which increases with continued or repeated exposure
  - Withdrawal reactions—reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced
  - Delayed reactions—reactions that occur some time after exposure, even if the drug is withdrawn before the reaction appears

- ***Susceptibility factors***
  - Genetic
  - Age
  - Sex
  - Physiological variation
  - Exogenous factors (for example drug–drug or drug–food interactions, smoking)
  - Diseases

Drug names

Drugs have usually been designated by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available, chemical names have been used. In some cases brand names have been used.

Spelling

For indexing purposes, American spelling has been used, e.g. anemia, estrogen rather than anaemia, oestrogen.

Cross-references

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-l3, SED-14, etc; the *Side Effects of Drugs Annuals* are cited as SEDA-1, SEDA-2, etc.

J K Aronson
Oxford, August 2008

Organization of material in monographs in the Meyler series (not all sections are included in each monograph)

General information
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- Comparative studies
- Drug-combination studies
- Placebo-controlled studies
- Systematic reviews

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Interference with diagnostic tests
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Management of adverse drug reactions
Monitoring therapy
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DRUGS USED TO TREAT HYPERTENSION, HEART FAILURE, AND ANGINA PECTORIS

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Antihypertensive Drugs

General information

Moving targets and patterns of prescribing antihypertensive drugs

The landscape of hypertension management has changed considerably, and changes in treatment are reviewed every few years by national and international groups with interests in cardiovascular disease. In 2003 the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure produced its seventh report (1). On the basis of data on the lifetime risk of hypertension and the risks of cardiovascular disease in patients with hypertension, their report emphasized the targets of disease treatment and pointed to new patterns of prescribing. Guidelines from the European Society of Hypertension and the European Society of Cardiology, also published in 2003 (2), gave similar perspectives.

In 2004 the British Society of Hypertension produced a comprehensive set of guidelines, endorsing the A(B)/CD algorithm (3). This strategy targets the renin–angiotensin–aldosterone system in younger Caucasian patients with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists, while first-line treatment in older Caucasian or black patients of any age is with calcium channel blockers or thiazide diuretics; beta-blockers take a less important initial role in the absence of compelling indications. There are also concerns regarding the possible adverse metabolic consequences of long-term therapy with thiazide diuretics and beta-blockers.

Since the hypertension guidelines were published new evidence that strengthens this argument has appeared. Conventional blood pressure-lowering therapy (atenolol + bendroflumethiazide) has been compared with a more contemporary regimen of drugs (amlodipine + perindopril) in a large randomized controlled trial (4). The Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) has shown that treating hypertension with amlodipine and additional perindopril as required was associated with a reduction in the incidence of all types of cardiovascular events compared with atenolol + a thiazide. The overall incidence of adverse effects was similar in the two groups, but not surprisingly the specific adverse effects profiles were different. Cough, joint swelling, and peripheral edema were more common with amlodipine + perindopril, and bradycardia, dizziness, diarrhea, dyspnea, erectile dysfunction, fatigue, and cold extremities were more common with atenolol + a thiazide. Moreover, the amlodipine-based regimen caused new-onset diabetes in significantly fewer patients than the atenolol-based regimen did.

What implications does this newer evidence have on the current pattern of prescribing in hypertension? The combination of a calcium channel blocker with an ACE inhibitor (or an angiotensin receptor antagonist) has not previously been used as often as other combinations. Fixed-dose combinations are therefore not generally available, although they are likely to become more widely available. The ASCOT-BPLA study reaffirmed that most hypertensive patients require two or more agents to reach blood pressure targets. This endorses the latest guidelines, which propose that combination treatment should be considered for patients who present with a systolic blood pressure of 160 mmHg or more or a diastolic blood pressure of 100 mmHg or more.

Monitoring therapy

The publication of clear and explicit guidance on monitoring therapy in order to maximize efficacy and minimize adverse drug reactions is rare. The publication of practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists, and angiotensin receptor antagonists in heart failure may also be helpful in the safer administration of these drugs in hypertension (5). These guidelines provide advice about how these drugs should be used safely, including what advice should be given to the patient and what monitoring needs to be undertaken. Of equal value are the recommendations about the actions to be taken if problems occur, for example what to do in the event of electrolyte imbalance or renal dysfunction in patients taking ACE inhibitors.

Choice of antihypertensive drugs in patients with diabetes and hypertension

The choice of drugs in patients with diabetes and hypertension is important because antihypertensive drugs affect the development of complications such as albuminuria and the development of nephropathy, and because the metabolic effects of antihypertensive drugs can complicate treatment or enhance the development of diabetes.

The authors of a review of the treatment of combined diabetes and hypertension pointed out the importance of tight blood pressure control (aiming for a blood pressure below 130/80 for all diabetics and below 125/75 in the presence of significant proteinuria) for the prevention of cardiovascular mortality and morbidity, and the development and progression of diabetic nephropathy (6). Adequate control of blood pressure is more important than the choice of drug, and multiple drugs are often required.

The general consensus is that ACE inhibitors should be the first-line choice, angiotensin II receptor blockers being a reasonable alternative.

Thiazide diuretics impair glucose tolerance. On the other hand the increase in renin that they cause enhances the effects of ACE inhibitors and angiotensin II receptor blockers. It also appears that the adverse effect on blood glucose can be eliminated by avoiding hypokalemia.

Beta-blockers reduce proteinuria and cardiovascular mortality. They can worsen glycemic control, reduce awareness of hypoglycemia, and adversely affect lipid profiles. However, in patients with diabetes and hypertension and a history of myocardial infarction, the benefits may outweigh the risks.

Calcium channel blockers combined with ACE inhibitors appear to provide additional renoprotection.

The LIFE study

Further commentaries on the LIFE study in over 9000 patients (7) have appeared in 2003.

The key findings alluded to in a commentary (8), in terms of hypertension and diabetes, were that atenolol or losartan as monotherapy reduced blood pressure in patients with diabetes and hypertension, but not to the target blood pressure, suggesting that more intensive therapy is required than was used in the LIFE study. The data suggest that the onset of diabetes can be prevented or delayed by losartan, and losartan is also more effective than atenolol in reducing cardiovascular mortality and morbidity in patients with diabetes taking suboptimal treatment. In another commentary (9) it was suggested that losartan is clearly better and that elderly patients with hypertension should not be exposed to beta-blockers.

The ALPINE study

In a 1-year study, 392 newly diagnosed patients with hypertension were randomized to either candesartan 16 mg/day or hydrochlorothiazide 25 mg/day; if the blood pressure did not fall below 135/85 in patients aged under 65 years or 140/90 in patients aged 65 years or older, extended-release felodipine 2.5–5.0 mg was added to candesartan or atenolol 50–100 mg to hydrochlorothiazide (10). The fall in blood pressure was similar in the two groups and most patients required two drugs. Fasting insulin and glucose concentrations increased in the hydrochlorothiazide + atenolol group, but were unaffected in the candesartan + felodipine group. Eight patients in the thiazide group developed diabetes mellitus compared with one in the candesartan group.

Other studies in diabetes

In 463 patients with type II diabetes and hypertension, a combination of atenolol + chlortalidone produced worse metabolic control (HbA_{1c}), whereas metabolic control was minimally affected with verapamil + trandolapril (11). Both regimens produced similar suboptimal falls in mean blood pressure.

In 457 patients with type II diabetes, hypertension, and albuminuria, the effect of daily perindopril 2 mg + indapamide 0.625 mg was compared with the effect of daily enalapril 10 mg (12). Based on blood pressure, doses could be increased to a maximum of 8.0 mg of perindopril + 2.5 mg of indapamide or 40 mg of enalapril. The combination produced a statistically significant greater fall in blood pressure, but it is difficult to see this as clinically relevant (3.0 and 1.5 mm more for systolic and diastolic pressures respectively). There was a significantly greater reduction in albuminuria with the combination (−40%), than with monotherapy (−27%).

Combination therapy

Several smaller studies have suggesting that monotherapy is usually not optimal for patients with diabetes and hypertension, and that combination therapy would be required in most cases. In 24 patients with diabetes and hypertension, dual renin-angiotensin blockade with lower doses of an ACE inhibitor and an angiotensin II receptor blocker was superior to maximal doses of either alone (13). In 38 patients with diabetes and hypertension benazepril + amlodipine produced better reduction in blood pressure and a more favorable effect on fibrinolytic balance than either drug alone (14).

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Acebutolol

See also Beta-adrenoceptor antagonists

General Information

Acebutolol is a beta-adrenoceptor antagonist with membrane-stabilizing activity that is sometimes cited as being cardioselective but has considerable effects on bronchioles and peripheral blood vessels.

Organs and Systems

Respiratory

Bronchiolitis obliterans has been attributed to acebutolol (1).

Liver

Six cases of reversible hepatitis have been attributed to acebutolol (2).

Skin

Various drugs can cause a lupus-like syndrome. Beta-adrenoceptor antagonists have been implicated only infrequently and there have been no cases of subacute cutaneous lupus erythematosus associated with the use of beta-adrenoceptor antagonists. Subacute cutaneous lupus erythematosus has been attributed to acebutolol (3).

- A 57-year-old woman with hypertension developed a cutaneous eruption taking acebutolol for 1 month. She had no history of photosensitivity, photodermatosis, or immunological diseases. A complete blood cell count, liver and kidney tests, rheumatoid factor, and complement fractions were all within the refrence ranges. There was a positive titer of antinuclear antibodies. A biopsy specimen showed atrophy of the epidermis. A positive lupus band test was found at direct immunofluorescence. Acebutolol was withdrawn, and she was given chloroquine sulfate associated with photoprotection. The cutaneous eruption resolved progressively. After 4 months the skin lesions had completely cleared. A Seroly test was negative for antihistone antibodies.

While several cases of subacute cutaneous lupus erythematosus have been described with other antihypertensive agents, such as captopril, calcium channel blockers, and hydrochlorothiazide, this seems to have been the first case described in a patient taking a beta-adrenoceptor antagonist. This case and its evolution suggest a link between acebutolol therapy and the onset of a lupus-like syndrome, whose pathogenesis is unclear.

Immunologic

Patients taking acebutolol relatively commonly develop antinuclear antibodies (4,5).

Drug Administration

Drug overdose

The membrane-stabilizing activity of beta-blockers can play a major role in toxicity. Of 208 deaths in subjects who had taken beta-blockers, 206 occurred with drugs that have membrane-stabilizing activity. This quinidine-like effect can be reversed by sodium bicarbonate, which is also used to counteract the cardiotoxic effects of cyclic antidepressants, which also have membrane-stabilizing activity.

- An overdose of acebutolol (6.4 mg) in a 48-year-old man caused cardiac arrest with ventricular tachycardia (6). An intravenous bolus of sodium bicarbonate 50 mmol produced sinus rhythm.

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Alfuzosin

See also Alpha-adrenoceptor antagonists

General Information

Alfuzosin is a uroselective alpha$_1$-adrenoceptor antagonist used to relieve the symptoms of prostatic hyperplasia (1). Its safety has been investigated in a large prospective 3-year

open trial in 3228 patients with benign prostatic hyperplasia. There were no unexpected adverse effects. Only 4.2% of the patients dropped out owing to adverse effects.

In a large database of 7093 patients with lower urinary tract symptoms related to benign prostatic hyperplasia treated for up to 3 years with alfuzosin in general practice, adverse events were reported in a very complex and uninformative way (2). In another paper, the same authors reported on a subcohort of 2829 patients, with special focus on effects on quality of life. Adverse events occurred in 15% of the patients, 1.7% died during the study, and 5.2% had serious effects, which the authors did not detail, but which they stated were not related to treatment. Most adverse effects occurred during the first 3 months of treatment (3). In another database of 3095 Spanish patients taking alfuzosin 5 mg bd for 60 days, adverse events were reported in 3.3% of the patients, and led to drug withdrawal in 1.6%; postural hypotension occurred in 1.8% (4).

In a systematic review 11 trials of alfuzosin in 3901 men were analysed (5). Alfuzosin was safe and well tolerated. Most of the reported adverse events, such as dizziness and syncope, were related to its vasodilatory action.

Organs and Systems

Nervous system

Dizziness, headache, postural hypertension, and other symptoms familiar from the older alpha-blockers occur primarily during the first 2 weeks of treatment with alfuzosin (1).

Liver

Hepatitis potentially related to alfuzosin has been reported.

- A 63-year-old man, who had taken amiloride and alfuzosin for 9 months for hypertension and benign prostatic hyperplasia, became jaundiced (6). His aspartate transaminase was 3013 IU/l, alanine transaminase 2711 IU/l, alkaline phosphatase 500 IU/l, and total bilirubin 415 μmol/l. Viral causes, autoimmune hepatitis, and biliary obstruction were excluded. After withdrawal of alfuzosin, his liver function tests gradually returned to normal within 6 months.
- An 80-year-old man with chronic liver disease due to hepatitis B virus took alfuzosin for 3 weeks for benign prostatic hyperplasia and developed raised liver enzymes, which settled rapidly on withdrawal of alfuzosin (7).

Immunologic

Dermatomyositis has been attributed to alfuzosin.

- A 75-year-old man, who had taken alfuzosin for 1 year, developed muscle pain and weakness over 4 days, accompanied by tenderness and swelling of the deltoid muscles (8). There was erythema, with rash, periungual purpura, and erythematous plaques over the finger joints. Serum CK, LDH, and transaminase activities were raised and ANA was positive. An MRI scan showed findings consistent with inflammation of muscle and a biopsy confirmed the diagnosis of dermatomyositis. Three days after drug withdrawal there was no improvement, so prednisone was started and he recovered within a few days. The temporal relation in this case was weak.
- Dermatomyositis, with typical clinical effects, biochemical tests, electromyography, and muscle biopsy, occurred in a 75-year-old man who had taken alfuzosin for 1 year (9). There was no malignancy and he recovered fully after alfuzosin withdrawal (timing not given).

Drug Administration

Drug formulations

The pharmacology, including the tolerability and drug-interaction potential, of a modified-release formulation of alfuzosin, relating mainly to studies in patients symptomatic benign prostatic hyperplasia, has been reviewed (10).

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Alpha-adrenoceptor antagonists

See also Alfuzosin, Doxazosin, Indoramin, Prazosin, Terazosin

General Information

The postsynaptic alpha-adrenoceptor antagonists, indoramin, prazosin, and related quinazoline derivatives, block $alpha_1$-adrenoceptor-mediated vasoconstriction of peripheral blood vessels (both arterial and venous) and are effectively peripheral vasodilators (1,2). Qualitatively and quantitatively common adverse effects are generally similar, although indoramin has additional effects on other neurotransmitter systems and therefore tends to be considered separately. Their use in benign prostatic hyperplasia has been reviewed (3,4).

Several recent articles have reviewed the pharmacology, pharmacokinetics, mode of action, use, efficacy, and adverse effects of the selective $alpha_1$-adrenoceptor blockers doxazosin, prazosin, and terazosin in benign prostatic hyperplasia (5).

The frequencies and the profile of adverse effects of five major classes of antihypertensive agents have been assessed in an unselected group of 2586 chronically drug-treated hypertensive patients (6). This was accompanied by a questionnaire-based survey among patients attending a general practitioner. The percentage of patients who reported adverse effects spontaneously, on general inquiry, and on specific questioning were 16, 24, and 62% respectively. With alpha-blockers the figures were 15, 25, and 50%. The percentage of patients in whom discontinuation was due to adverse effects was 6.8% with alpha-blockers. Alpha-blockers were associated with less fatigue, cold extremities, sexual urge, and insomnia, and more bouts of palpitation than other antihypertensive drugs (RR = 2.5; CI = 1.2, 5.4). The authors did not find a significant effect of age on the pattern of adverse effects. Women reported more effects and effects that were less related to the pharmacological treatment.

The first-dose effect (profound postural hypotension and reflex tachycardia) is a well-recognized complication of the first dose of prazosin and related agents. This phenomenon is dose-related and can usually be avoided by using a low initial dosage taken at bedtime. During long-term treatment, orthostatic hypotension and dizziness is reported by about 10% of patients.

Current guidelines on the use of postsynaptic alpha-adrenoceptor antagonists have been reviewed (7).

Drug-drug interactions

Inhibitors of phosphodiesterase type V

Postsynaptic alpha-adrenoceptor antagonists are used both in hypertension and for urological conditions, and can cause orthostatic hypotension due to vasodilatation. This adverse effect can be potentiated considerably if they are co-administered with inhibitors of phosphodiesterase type V for the treatment of erectile dysfunction (8).

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Ambrisentan

General Information

Ambrisentan is an endothelin ET_A receptor antagonist (1). It has been used in pulmonary arterial hypertension and there have been one dose-ranging study, two randomized, double-blind, placebo-controlled studies, and one drug-conversion study. In the dose-ranging study, ambrisentan 1–10 mg produced significant improvements from baseline in walking distance at 12 weeks (2). In the placebo-controlled studies, ambrisentan 2.5–10 mg/day was associated with significant improvement in walking distance at 12 weeks and sustained for up to 1 year. The most common adverse effects associated with ambrisentan in clinical trials were peripheral edema (17%), nasal congestion (6%), palpitation (5%), constipation (4%), flushing (4%), abdominal pain (3%), nasopharyngitis (3%), and sinusitis (3%). In the placebo-controlled studies, the incidence of liver aminotransferase and bilirubin abnormalities at 12 weeks was lower with ambrisentan than with placebo (0.8% versus 2.3% respectively). Patients who had had raised serum transaminase activities during previous therapy with bosentan or sitaxsentan were switched to ambrisentan without further abnormalities in liver function. In a double-blind, dose-ranging study in 64 patients with pulmonary hypertension adverse events reflected those common to the endothelin receptor antagonist class, but two patients developed raised serum transaminase activities, one of whom required

treatment withdrawal (3). Raised liver enzymes have been seen with bosentan and other drugs in this class.

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Amlodipine

See also Calcium channel blockers

General Information

Amlodipine is a long-acting dihydropyridine calcium channel blocker. It has an adverse effects profile similar to those of other dihydropyridines, but at a lower frequency (1). Along with felodipine (2), but unlike other calcium channel blockers, it may also be safer in severe chronic heart failure when there is concurrent angina or hypertension (3).

The effects of amlodipine and isosorbide-5-mononitrate for 3 weeks on exercise-induced myocardial stunning have been compared in a randomized, double-blind, crossover study in 24 patients with chronic stable angina and normal left ventricular function (4). Amlodipine attenuated stunning, evaluated by echocardiography, significantly more than isosorbide, without difference in antiischemic action or hemodynamics. Amlodipine was better tolerated than isosorbide, mainly because of a lower incidence of headache (4).

Vasodilatory calcium channel blockers have been reported to improve exercise tolerance in some preliminary studies. A multicenter, randomized, placebo-controlled trial was therefore performed in 437 patients with mild to moderate heart failure to assess the effects of amlodipine 10 mg/day in addition to standard therapy (5). Over 12 weeks amlodipine did not improve exercise time and did not increase the incidence of adverse events.

Mental stress is a risk factor for cardiovascular disease. In 24 patients with mild to moderate hypertension, amlodipine reduced the blood pressure rise during mental stress compared with placebo, but increased plasma noradrenaline concentrations (6).

Hypertension leading to cardiac dysfunction is very frequent in patients with the inherited syndrome called Ribbing's disease, which is characterized by multiple epiphyseal dystrophy. In a randomized, double-blind comparison of amlodipine (10 mg/day) and enalapril (20 mg/day) in 50 patients for 6 months, both drugs significantly reduced blood pressure, but amlodipine increased heart rate and plasma concentrations of noradrenaline and angiotensin II (7). These undesired effects make ACE inhibitors a better choice for prevention of cardiac dysfunction.

Placebo-controlled studies

The efficacy and safety of amlodipine have been assessed in a multicenter, double-blind, placebo-controlled trial in 268 children with hypertension aged 6–16 years (8). Amlodipine produced significantly greater reductions in systolic blood pressure than placebo. Twelve patients withdrew from the study because of adverse events, six of which were attributed to the study drug: three cases of worsening hypertension, one of facial edema, one of finger edema and rash, and one of ventricular extra beats. The maximal dose, 5 mg/day, was not high, and the target to reduce blood pressure below the 95th centile was reached in 35% of children with systolic hypertension and in 55% of those with diastolic hypertension.

Organs and Systems

Nervous system

- A 35-year-old woman with benign intracranial hypertension and high blood pressure was given amlodipine, with good control of her blood pressure (9). However, her headache worsened and she developed papilledema. The CSF pressure was 30 cm. Her symptoms disappeared shortly after amlodipine withdrawal.

Fluid balance

Calcium channel blockers often cause peripheral edema, usually limited to the lower legs; periocular and perioral edema are less common. Occasionally edema can be more severe, and a case of anasarca has been reported in a 77-year-old woman with essential hypertension taking amlodipine 10 mg/day (10).

Hematologic

Thrombocytopenia has been attributed to amlodipine (11).

- A 79-year-old man developed epistaxis and gum bleeding; his platelet count was 1×109/l. Amlodipine was withdrawn and immunoglobulins and glucocorticoids were given. The platelet count returned to 204×109/l in 7 days. Amlodipine was restarted, and 2 days later bleeding recurred and resolved after amlodipine was withdrawn for the second time. ELISA (enzyme-linked immunosorbent assay) showed an IgG antibody reactive with patient's platelets only in the presence of amlodipine.

The authors suggested that drug-related thrombocytopenia can occur after long-term treatment with a drug, such as in this patient who had been taking amlodipine for 10 years before the event.

Liver

Hepatitis has been attributed to amlodipine.

- A 77-year-old man took amlodipine for 1 month and developed jaundice and raised aspartate transaminase, alanine transaminase, and bilirubin (12). A liver biopsy suggested a drug-induced hepatitis and the amlodipine was withdrawn. His symptoms and laboratory values normalized. Other drugs (metformin, fluindione, and omeprazole) were not withdrawn.
- A 69-year-old hypertensive man who had taken amlodipine for 10 months abruptly developed jaundice, choluria, raised serum bilirubin, and increased transaminases (13). After amlodipine withdrawal he progressively recovered in a few weeks without sequelae or relapses. However, after several months he presented again with jaundice and an enlarged liver, having started to take diltiazem 5 months before. He recovered completely in a few weeks after drug withdrawal.

In the second case the authors hypothesized an idiosyncratic mechanism.

- An 87-year-old woman who had taken amlodipine for several years for hypertension developed pruritus and 2 weeks later painless jaundice (14). She had a raised bilirubin concentration and raised aspartate and alanine transaminase activities. Infectious causes were not found and a liver biopsy suggested drug-induced liver damage. After withdrawal of amlodipine the transaminases and measures of cholestasis improved markedly within 2 weeks.

Skin

Recognized skin eruptions associated with amlodipine include erythematous and maculopapular rashes, skin discoloration, urticaria, dryness, alopecia, dermatitis, erythema multiforme, and lichen planus. A granuloma annulare-like eruption has been reported (15).

- A 64-year-old Caucasian woman, with a history of ankylosing spondylitis, hypertension, and osteoporosis, took amlodipine for 13 days and developed a rash on her lower legs. Amlodipine was withdrawn, but the rash progressed to involve both of her hands. The eruption consisted of multiple erythematous pruritic papules. Histology showed focal collagen degeneration and a significant interstitial histiocytic dermal infiltrate, suggestive of granuloma annulare. Within 3 months of withdrawal of amlodipine the reaction cleared and did not recur during follow-up for 3 years.

Amlodipine can cause generalized pruritus, which usually happens within 24 hours and resolves within 24 hours of withdrawal (16).

Photosensitivity presenting with telangiectasia can be caused by calcium channel blockers.

- A 57-year-old hypertensive man developed telangiectasia, initially on the forehead and rapidly extending to the upper back, shoulders, and chest, particularly during the summer (17). The eruption began 1 month after starting amlodipine and diminished considerably 3 months after withdrawal.
- A 3-year-old girl developed telangiectases on the cheeks and gingival hyperplasia while taking furosemide, captopril, and amlodipine for hypertension due to hemolytic–uremic syndrome (18). Both lesions disappeared on withdrawal of amlodipine.

Calcium channel blockers can cause lichen planus.

- A 56-year-old Nigerian woman, with a previous history of sickle cell trait, osteoarthritis, and non-insulin-dependent diabetes mellitus, took amlodipine 5 mg/day for hypertension for 2 weeks and developed a lichenoid eruption (19). Histological examination confirmed the diagnosis of lichen planus. Amlodipine was withdrawn and there was rapid symptomatic and clinical improvement after treatment with glucocorticoids and antihistamines.

Generalized hyperpigmentation has been reported (20).

- A 45-year-old Turkish man with a history of hypertension who had taken amlodipine 10 mg/day for 3 years developed Fitzpatrick's skin type III after a 2-year history of gradually increasing, asymptomatic, generalized hyperpigmentation. Although cutaneous hyperpigmentation was more prominent on the photoexposed areas, there was no history of previous photosensitivity, pruritus, or flushing. Photo protection and withdrawal of amlodipine was advised. The skin discoloration faded slightly 8 months after changing amlodipine to metoprolol and strict avoidance of sun exposure.

Nails

Longitudinal melanonychia is tan, brown, or black longitudinal streaking in the nail plate due to increased melanin deposition and Hutchinson's sign is periungual pigmentation. In a 75-year-old Indian man longitudinal melanonychia and periungual pigmentation affecting several fingernails and toenails were attributed to amlodipine, which he had taken for 2 years for hypertension (21).

Musculoskeletal

A patient presented with severe, generalized muscle stiffness, joint pain, and fatigue while taking amlodipine for hypertension and zafirlukast for asthma. Stopping zafirlukast did not change her symptoms; the dose of amlodipine was increased at different times up to 15 mg to control blood pressure better. The neurological symptoms worsened, in the absence of any evidence of immunological or neurological disorders, and so amlodipine was withdrawn: the symptoms disappeared within 4 days (22).

Reproductive system

Gynecomastia is not uncommon in men undergoing hemodialysis for end-stage renal disease. Two cases of gynecomastia have been reported in patients taking amlodipine 10 mg/day (23). In both cases the gynecomastia abated within a month or so of substituting amlodipine with an angiotensin receptor blocker. In one case, amlodipine was re-administered because of worsening of hypertension, and gynecomastia reappeared.

Second-Generation Effects

Pregnancy

Subcutaneous fat necrosis in a neonate has been attributed to maternal use of amlodipine during pregnancy (24).

- A boy weighing 4 kg was born by spontaneous normal delivery at 39 weeks to a 38-year-old Afro-Caribbean woman, whose pregnancy was complicated by essential hypertension treated with amlodipine. On day 1 the child developed firm, red, pea-sized nodular lesions on the face, buttocks, back, shoulders, and arms.

Subcutaneous fat necrosis of the newborn is relatively uncommon. It is said to be benign and painless and to resolve within a few weeks. However, in this case it was extremely painful and was relieved only by opiates. The skin changes persisted beyond the age of 6 months and remained extremely symptomatic until the age of 9 months, when the skin had become normal. Calcium abnormalities have often been reported in association with subcutaneous fat necrosis, and exposure to amlodipine during pregnancy may have resulted in impairment of enzyme systems dependent on calcium fluxes for their action; it may also have affected calcium homeostasis in the neonate. Since previous reports of teratogenicity in animals have been published, few women take calcium channel blockers during pregnancy and there are no reports to date of an association between these drugs and subcutaneous fat necrosis (24).

Drug Administration

Drug overdose

Amlodipine overdose has been reported (25).

- A 23-year-old woman took 60 tablets of amlodipine intentionally and developed tachycardia and severe hypotension. She did not improve with intensive therapy and developed left ventricular failure and oliguria and underwent hemodiafiltration. Her condition slowly improved over 4 days.

Drug–Drug Interactions

Chloroquine

A possible interaction of amlodipine with chloroquine has been reported (26).

- A 48-year-old hypertensive physician, who had optimal blood pressure control after taking oral amlodipine 5 mg/day for 3 months, developed a slight frontal headache and fever, thought that he had malaria, and took four tablets of chloroquine sulfate (total 600 mg base). Two hours later he became nauseated and dizzy and collapsed; his systolic blood pressure was 80 mmHg and his diastolic pressure was unrecordable, suggesting vasovagal syncope, which was corrected by dextrose–saline infusion.

There was no malaria parasitemia in this case, and hence the syncope may have resulted from the acute synergistic hypotensive, venodilator, and cardiac effects of chloroquine plus amlodipine, possibly acting via augmented nitric oxide production and calcium channel blockade. Since malaria fever is itself associated with orthostatic hypotension, this possible interaction may be unrecognized and unreported in these patients.

Ciclosporin

Ciclosporin increases the survival of allografts in man. However, it causes renal vasoconstriction and increases proximal tubular reabsorption, leading in some cases to hypertension (27). The concomitant use of calcium channel blockers can prevent most of these adverse effects of ciclosporin. However, some calcium channel blockers (verapamil, diltiazem, nicardipine) can increase plasma concentrations of ciclosporin up to three-fold through inhibition of cytochrome P450. Eight different studies have been performed on the combination of amlodipine and ciclosporin given for 1–6 months to kidney transplant recipients, and the results have been reviewed (28). In three studies, in a total of 41 patients, amlodipine increased ciclosporin concentrations, while in the others, a total of 85 patients, there was no evidence of an interaction.

In normotensive renal transplant recipients treated for 2 months with amlodipine there was a small but significant nephroprotective effect (29). Thus, amlodipine, in contrast to other calcium channel blockers, does not affect ciclosporin blood concentrations and can be safely added in transplant recipients.

Sildenafil

The effect of sildenafil on arterial pressure has been tested in 16 hypertensive men taking amlodipine 5–10 mg/day (30). Sildenafil did not affect amlodipine pharmacokinetics, but caused a further additive fall in blood pressure. Adverse events with the combination of sildenafil and amlodipine, headache, dyspepsia, and nausea, did not require drug withdrawal.

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Angiotensin-converting enzyme inhibitors

See also Benazepril, Captopril, Cilazapril, Enalapril, Fosinopril, Imidapril, Lisinopril, Perindopril, Quinapril, Ramipril, Temocapril, Trandolapril, Zofenopril

General Information

Angiotensin-converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to angiotensin II. The ACE is also a kininase, and so ACE inhibitors inhibit the breakdown of kinins. Some of the adverse effects of these drugs are related to these pharmacological effects. For example, cough is thought to be due to the action of kinins on axon fibers in the lungs and hypotension is due to vasodilatation secondary to reduced concentrations of the vasoconstrictor angiotensin II.

Our knowledge of the use of ACE inhibitors has expanded dramatically during recent years, thanks to the publication of the results of a number of large clinical trials (1).

The Heart Outcomes Prevention Evaluation (HOPE) study showed that virtually all patients with a history of cardiovascular disease, not only those who have had an acute myocardial infarction or who have heart failure, benefit from ACE inhibitor therapy (2). The authors selected 9297 patients at increased risk of cardiovascular disease, defined as a history of a cardiovascular event or evidence of disease, such as angina. People with diabetes but no indication of heart disease were included, but they had to have an additional risk factor. They were allocated to receive the ACE inhibitor ramipril 10 mg/day or placebo. The trial was stopped early, according to the

predefined rules, because of an overwhelming effect of ramipril on the primary end-point, a 22% reduction in a composite measure of myocardial infarction, stroke, and death from cardiovascular causes. Significance was also achieved on outcomes as diverse as myocardial infarction, revascularization, heart failure, cardiac arrest, and worsening angina. Patients with diabetes had a similar 25% reduction for the composite cardiovascular end-point. Moreover, patients taking ramipril had 16% less overt nephropathy (defined as urine albumin over 300 mg/24 hours, or urine total protein excretion over 500 mg/24 hours, or a urine albumin/creatinine ratio over 36 mg/mmol). They also needed 22% less laser therapy for retinopathy. Since all the patients in the HOPE study were not hypertensive, and since the cardiovascular benefit was greater than that attributable to the fall in blood pressure, the authors suggested that ACE inhibitors are cardioprotective, vasculoprotective, and renal protective, independently of their blood pressure lowering effect.

Relative to the dosage issue, the dosage–plasma concentration relation for enalaprilat (the active metabolite of enalapril) in patients with heart failure and its relation to drug-related adverse effects has been investigated (3). In patients taking enalapril for more than 3 months, in dosages of 5–20 mg bd, there were highly variable trough concentrations of enalaprilat. They were affected by serum creatinine, the severity of heart failure, and body weight. Adverse effects, such as cough and rises in serum creatinine and potassium, were more common at high enalaprilat trough concentrations. The authors concluded that these results provide a rationale for individually adjusting ACE inhibitor doses in case of adverse effects.

Use in hypertension

In hypertension, the Captopril Prevention Project (CAPPP) trial evaluated an ACE inhibitor as an alternative first-line agent in mild to moderate hypertension. It was a prospective randomized open study with blinded end point evaluation (PROBE design), comparing an antihypertensive strategy based on either captopril or conventional therapy with a beta-blocker or a diuretic in patients with mild to moderate hypertension. At the end of follow-up the incidence of cardiovascular events was equal with the two strategies. However, imbalances in the assignment of treatment resulted in a 2 mmHg higher average diastolic blood pressure at entry in the group assigned to captopril. This difference in blood pressure alone would be sufficient to confer an excess of cardiovascular risk within this group, could mask real differences between the regimens in their effects on coronary events, and could explain the greater risk of stroke among patients who took captopril. The authors claimed that the overall results support the position that from now on one should consider ACE inhibitors as first-line agents, equal to diuretics and beta-blockers (4). The CAPPP study also reported a reduced risk of diabetes with captopril, which may be explained by the fact that thiazides and beta-blockers cause changes in glucose metabolism and by favorable effects of ACE inhibition on insulin responsiveness.

The second Swedish Trial in Old Patients with hypertension, STOP-2, was designed to compare the effects of conventional antihypertensive drugs on cardiovascular mortality and morbidity with those of newer antihypertensive drugs, including ACE inhibitors, in elderly patients (5). The study was prospective, randomized, and open, but with a blinded end-point evaluation. It included 6614 patients aged 70–84 years with hypertension (blood pressure over 180 mmHg systolic, or over 105 mmHg diastolic, or both). The patients were randomly assigned to conventional drugs (atenolol 50 mg/day, metoprolol 100 mg/day, pindolol 5 mg/day, or hydrochlorothiazide 25 mg/day plus amiloride 2.5 mg/day) or to newer drugs (enalapril 10 mg/day or lisinopril 10 mg/day, or felodipine 2.5 mg/day or isradipine 2.5 mg/day). Blood pressure fell similarly in all treatment groups. There were equal incidences of the primary end-points (fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease combined) in all groups (20 events per 1000 patient years). Subgroup analyses showed that conventional therapy, ACE inhibitors, and calcium antagonists had similar efficacy in preventing cardiovascular mortality and major morbidity. This finding argues against the hypothesis that some classes of antihypertensive drugs have efficacy advantages over others, at least in this population of elderly hypertensive patients. Therefore, the choice of antihypertensive treatment will be related to other factors, such as cost, co-existing disorders, and adverse effects. With respect to the reported adverse effects, since the study was open, causality cannot be established. Nevertheless, the size of the study and its naturalistic design allowed accurate assessment of the incidence of adverse effects in this population of elderly hypertensive patients. With ACE inhibitors the most frequently reported adverse effects were cough 30%, dizziness 28%, ankle edema 8.7%, headache 7.7%, shortness of breath 7.3%, and palpitation 5.5%. Actually, little detail was given in the section devoted to safety in the main publication of the results of the trial.

Use in heart failure

In heart failure much debate has been generated by the observation of general "under-use" of ACE inhibitors and the use of smaller doses than have been beneficial in clinical trials. This was partly related to concern about safety with the highest doses, especially in high-risk groups, such as the elderly and patients with renal insufficiency (6). Actually, outcome trials effectively excluded elderly patients (75–80 years and over) and usually patients with renal insufficiency. As elderly patients have poorer renal function, they are more likely to have vascular disease in their renal and carotid arteries, and may be more prone to symptomatic hypotension, it cannot be assumed that the benefit to harm balance observed in younger patients will be the same, at the same doses, in elderly people. The NETWORK trial, a comparison of small and large doses of enalapril in heart failure, was poorly designed and is not conclusive. However, it suggested that apart from a trend to more fatigue with higher doses (10 mg bd), the incidence of adverse effects,

including symptomatic hypotension, was similar across the three dosages (2.5, 5, and 10 mg bd) (7).

In heart failure the issue of whether it is justified to use doses of ACE inhibitors substantially smaller than the target doses used in the large-scale studies that established the usefulness of these drugs has been examined in the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial (8). This trial randomized 3164 patients with New York Heart Association (NYHA) class II–IV heart failure and ejection fractions less than 30% to double-blind treatment with either low doses (2.5–5.0 mg/day) or high doses (32.5–35 mg/day) of the ACE inhibitor lisinopril for 39–58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a non-significant 8% lower risk of death but a significant 12% lower risk of death plus hospitalization for any reason and 24% fewer hospitalizations for heart failure. Dizziness and renal insufficiency were more frequent in the high-dose group, but the two groups were similar in the number of patients who required withdrawal of the study medication. These findings suggest that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor, unless higher doses cannot be tolerated. However, the ATLAS trial did not address this issue properly. The doses in the small-dose arm were actually very small, and much smaller than those used in routine practice, as reported in several other studies (9). The doses in the large-dose arm may have been unnecessarily high. The recommendation of using target doses proven to be effective in large-scale trials remains unchallenged.

In the studies of left ventricular dysfunction (SOLVD), adverse effects related to the long-term use of enalapril have been thoroughly investigated (10).

Use in myocardial infarction

In the acute infarction ramipril efficacy (AIRE) study, oral ramipril in 2006 patients with heart failure after acute myocardial infarction resulted in a substantial reduction in deaths within 30 days (11).

More trials during and after myocardial infarction have been published and subjected to meta-analysis (12). This very large database provides valuable information on the rate of the most common adverse effects. Of all trials of the effects of ACE inhibitors on mortality in acute myocardial infarction, only the CONSENSUS II trial did not show a positive effect. In this trial, enalaprilat was infused within 24 hours after the onset of symptoms, followed by oral enalapril. The reasons for the negative result of CONSENSUS II remain unresolved, but hypotension and a proischemic effect linked to a poorer prognosis have been suggested.

Use in nephropathy

The results of two trials in patients with chronic nephropathy have reinforced the benefit of ACE inhibitors in slowing the progression of chronic renal insufficiency due to renal diseases other than diabetic nephropathy (13–15) and have provided sufficient information on the safety profile of these agents in chronic renal insufficiency. This was found to be essentially the same as in patients with normal renal function. The current practice of avoiding ACE inhibitors in severe renal insufficiency, to prevent further renal impairment and hyperkalemia, is no longer justified, although careful monitoring should still be observed.

Ramipril has a renal protective effect in non-diabetic nephropathies with nephrotic and non-nephrotic proteinuria (14). It also improves cardiovascular morbidity and all-cause mortality in patients with some cardiovascular risk (2).

The Ramipril Efficacy in Nephropathy (REIN) trial was designed to test whether glomerular protein traffic, and its modification by an ACE inhibitor, influenced disease progression in non-diabetic chronic nephropathies (13). Patients were stratified before randomization by 24-hour proteinuria. Treatment with ramipril or placebo plus conventional antihypertensive therapy was targeted at the same bloodpressure control. At the second interim analysis, ramipril had slowed the fall in glomerular filtration rate (GFR) more than expected from the degree of blood pressure reduction. In the follow-up study GFR almost stabilized in patients who had been originally randomized to ramipril and had continued to take it for more than 36 months. The combined risk of doubling of the serum creatinine or end-stage renal insufficiency was half that found in those taking placebo plus conventional therapy. In patients with proteinuria of 1–3 g/day the fall in GFR per month was not significantly affected, but progression to end-stage renal insufficiency was significantly less common with ramipril (9/99 versus 18/87) for a relative risk of 2.72 (CI = 1.22, 6.08) (14); and so was progression to overt proteinuria (15/99 versus 27/87; RR = 2.40; CI = 1.27, 4.52).

The results of this trial show that ramipril was well tolerated and even protective in cases of advanced renal insufficiency. One major reason for the current practice of underprescription and of prescription of suboptimal doses of ACE inhibitors, especially in patients with heart failure, is the presence of renal insufficiency (16). In such patients, not only should ACE inhibitors no longer be avoided, they are indeed indicated for preservation of renal function.

General adverse effects

The commonest unwanted effects of ACE inhibitors are related to their pharmacological actions (that is inhibition of angiotensin-converting enzyme and kininase II): renal insufficiency, potassium retention, pronounced first-dose hypotension, cough, and the serious but less common angioedema. Skin rashes and taste disturbances are uncommon, but may be more likely with sulfhydryl-containing drugs, particularly captopril. Rare hypersensitivity reactions include rashes, bone-marrow suppression, hepatitis, and alveolitis. If administered in the second or third term of pregnancy, ACE inhibitors can cause a number of fetal anomalies, including growth retardation, renal impairment, oligohydramnios, hypocalvaria, fetal pulmonary hypoplasia, and fetal death. Neonatal anuria and neonatal death can also occur (17,18). Tumor-inducing effects have not been reported.

The frequencies and the profile of adverse effects of five major classes of antihypertensive agents have been assessed in an unselected group of 2586 chronically drug-treated hypertensive patients (19). This was accompanied by a questionnaire-based survey among patients visiting a general practitioner. The percentages of patients who reported adverse effects spontaneously, on general inquiry, and on specific questioning were 16, 24, and 62% respectively. With ACE inhibitors the figures were 15, 22, and 55%. The percentage of patients in whom discontinuation was due to adverse effects was 8.1% with ACE inhibitors (significantly higher than diuretics). Compared with beta-blockers, ACE inhibitors were associated with less fatigue (RR = 0.57; 95% CI = 0.38, 0.85), cold extremities (RR = 0.11; CI = 0.07, 0.18), sexual urge (RR = 0.52; CI = 0.33, 0.82), insomnia (RR = 0.10; CI = 0.04, 0.26), dyspnea (RR = 0.38; CI = 0.17, 0.85), and more coughing (RR = 13; CI = 5.6, 30). The authors did not find a significant effect of age on the pattern of adverse effects. Women reported more effects and effects that were less related to the pharmacological treatment.

Organs and Systems

Cardiovascular

Marked reductions in blood pressure, without any significant change in heart rate, can occur at the start of ACE inhibitor therapy. Such reductions, which are not orthostatic, are sometimes symptomatic but rarely fatal. The volume of evidence is greatest with the longer established agents, but continues to suggest that the problems of first-dose hypotension are most likely to occur in patients whose renin–angiotensin system is stimulated (renin-dependent states), such as in renovascular hypertension or other causes of renal hypoperfusion, dehydration, or previous treatment with other vasodilators (20). These conditions can co-exist, particularly in severe heart failure (21–23). Similar problems have occurred in the treatment of hypertensive neonates and infants (24), but again were particularly likely in the setting of high plasma renin activity associated with either renovascular disease or concurrent diuretic treatment.

The use of very low doses to avoid first-dose hypotension is common, although the rationale remains unclear (25). It is even less clear whether or not there are differences between different ACE inhibitors, that is whether first-dose hypotension is agent-specific or a class effect (26,27).

Respiratory

Cough

DoTS classification
Dose-relation: collateral effect
Time-course: time-independent
Susceptibility factors: genetic (polymorphisms of the bradykinin B_2 receptor gene and the ACE gene); sex (men); exogenous factors (non-smokers).

A non-productive irritant cough was reported as an adverse effect of ACE inhibitors in the mid 1980s. It can be distressing and inconvenient, leading to withdrawal of therapy. Certain susceptibility factors are clearly recognized (for example non-smoking and female sex), but racial group can also affect the incidence.

Frequency

In different studies there has been large variability in the absolute incidence of cough (0.7–48%), the discontinuation rate (1–10%), and the relative incidences with different ACE inhibitors (28). However, the placebo-controlled, randomized, HOPE study has provided a remarkable database, with the largest cohort and the longest follow-up ever reported with such therapy (over 9000 patients followed for 5 years on average). Compared with placebo, ACE inhibitor therapy with ramipril caused cough leading to drug withdrawal in 7.3% of patients (compared with 1.8% for placebo) (13).

HOPE TIPS was a prospective study of patients with high cardiovascular risk, in which the practicability and tolerability of ramipril titration was tested in 1881 patients (29). Cough occurred in 14% over a period of up to 3 months, and 4% discontinued ramipril as a result. The author of an accompanying editorial (30) pointed out that the true incidence of ramipril-induced cough had conceivably been overestimated in the study, owing to the large proportions of patients with type 2 diabetes (52%) and non-smokers (80%) and the high doses used. The authors suggested that cough was not necessarily more common in Asian patients (79% of the patients in this study), although within this broad category the differential susceptibility to cough may quite large, and the editorial examined this; on the balance of evidence, Chinese patients (and perhaps some other racial groups in Asian countries) probably develop cough more commonly with ACE inhibitors than Caucasian patients do.

Mechanism

The mechanism of this effect has been explored (31–33). It may be more complicated than just an increase in concentrations of bradykinin and substance P, increased microvasculature leakage, and stimulation of vagal C fibers (34). Sulindac and indometacin may abolish or reduce the intensity and frequency of cough, supposedly because of inhibition of prostaglandin synthesis (35,36). Common variant genetics of ACE, chymase, and the bradykinin B_2 receptor do not explain the occurrence of ACE inhibitor-related cough (37). In general, bronchial hyper-reactivity has been causally implicated and may also be associated with exaggerated dermal responses to histamine (31,33). However, in one report, airways hyper-responsiveness was not a consistent finding (38).

Susceptibility factors

Cough is more common in non-smokers (39) and in women (39,40). It has been speculated that the risk of cough is genetically predetermined. The possibility that polymorphisms of the human bradykinin B_2 receptor gene may be involved in ACE inhibitor-related cough

has been investigated in a case-control study (41). The DNA of 60 subjects with and without cough who were treated with ACE inhibitors was compared with that of 100 patients with untreated essential hypertensive and 100 normotensive subjects. The frequencies of the TT genotype and T allele were significantly higher in the subjects with cough than in subjects without. These tendencies were more pronounced in women. Subjects with the CC genotype were less susceptible to cough. According to the authors, high transcriptional activity of the bradykinin B_2 receptor promoter may be related to the risk of ACE inhibitor-related cough. This is the first demonstration that a genetic variant is involved in ACE inhibitor-related cough. It may therefore be possible to predict the occurrence of cough related to ACE inhibitor use.

The genetic basis of ACE inhibitor-induced cough and its relation to bradykinin have been further explored in a study of the effect of cilazapril in two groups of healthy volunteers genotyped for ACE insertion/deletion (I/D) polymorphism (42). The cough threshold to inhaled capsaicin was significantly lower in the genotype II group than in the DD group. Skin responses to intradermal bradykinin were significantly enhanced in the genotype II group. There was no difference in responsiveness to intradermal substance P. The authors suggested that these findings provide further evidence of the link between ACE inhibitor-induced cough and I/D polymorphism of the ACE gene, and that this supports the hypothesis that ACE inhibitors cause cough by modulating tissue concentrations of bradykinin.

Chinese patients experience more cough from ACE inhibitors than Caucasians. A review of the pharmacokinetics and blood pressure-lowering efficacy of ACE inhibitors as well as of ACE and angiotensinogen gene polymorphism did not find significant differences between Chinese and Caucasians to account for the difference in cough incidence (43).

Management

ACE inhibitor-associated cough seems to be a class effect: switching to another ACE inhibitor rarely solves the problem, although there are occasional anecdotal reports (40,44). However, most patients who develop a cough related to an ACE inhibitor are able and willing to continue therapy. In a small randomized study inhaled sodium cromoglicate relieved the symptom (45). In those in whom the symptom is intolerable, a switch to an angiotensin receptor antagonist is justified.

Obstructive airways disease

It has been suggested that ACE inhibitors are also associated with an increased incidence of symptomatic obstructive airways disease, leading to bronchospasm and asthma (46). However, a prescription event monitoring study of more than 29 000 patients taking ACE inhibitors, compared with 278 000 patients taking other drugs, failed to confirm this association (47).

Endocrine

Gynecomastia has been reported in a patient taking captopril 75 mg/day; it resolved when captopril was withdrawn but recurred when the patient was given enalapril (48). This suggests that gynecomastia may not be simply attributable to the sulfhydryl group of captopril.

Metabolism

ACE inhibition has been associated with increased insulin sensitivity in diabetic patients, and it has therefore been hypothesized that ACE inhibitors can precipitate hypoglycemia in such patients. A Dutch case-control study suggested that among users of insulin or oral hypoglycemic drugs, the use of ACE inhibitors was significantly associated with an increased risk of hospital admission for hypoglycemia (49). However, a French case/non-case study from the pharmacovigilance database did not confirm this finding (50).

In a matched case-control study of 404 cases of hospitalization for hypoglycemia in diabetic patients and 1375 controls, the risk of hypoglycemia was greater in those who used insulin versus a sulfonylurea and was not influenced by the use of ACE inhibitors (51). However, the use of enalapril was associated with an increased risk of hypoglycemia (OR = 2.4; CI = 1.1, 5.3) in sulfonylurea users. Although the authors emphasized the fact that previous reports of ACE inhibitor-related hypoglycemia were more frequent with enalapril, it is unclear why only enalapril, and not ACE inhibitors as a class, was associated with a significantly increased risk of hypoglycemia, and why this occurred only in sulfonylurea users.

Conversely, it has been suggested that the protective effect of ACE inhibitors against severe hypoglycemia should be tested in high-risk patients with high ACE activity. About 10–20% of patients with type 1 diabetes mellitus have a risk of severe hypoglycemia. In 307 unselected consecutive diabetic outpatients, those with the ACE DD genotype had a relative risk of severe hypoglycemia of 3.2 (95% CI = 1.4, 7.4) compared with those with the genotype II (52). There was a significant relation between serum ACE activity and the risk of severe hypoglycemia.

Electrolyte balance

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired kidney function and/or in patients taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, and especially aldosterone antagonists, hyperkalemia can occur. In two cases, hypoaldosteronism with diabetes was implicated (53,54).

Hyponatremia, defined as a plasma sodium concentration of 133 mmol/l or under, has been investigated in a prospective study of elderly patients with hip fractures. ACE inhibitors were the most frequently used drugs (five of 14 cases) (55). Of course, this does not prove a cause and effect relation, since in elderly people ACE inhibitors are likely to be among the most frequently prescribed drugs. However, hypoaldosteronism would be a likely mechanism.