whose potassium concentrations are moderately raised and in whom there is no electrocardiographic upset.

We conclude that although hyperkalaemia is common in patients in hospital, it is rarely life threatening. Those with rapidly increasing potassium concentrations, in the presence of renal failure, are most at risk of developing potassium cardiotoxicity. Patients in this high risk group should undergo continuous biochemical and electrocardiographic monitoring. Acute cardiac toxicity induced by hyperkalaemia should be reversed promptly with calcium gluconate, while severe abnormalities will respond readily to glucose and insulin treatment. Cation exchange resins should be used to correct moderate hyperkalaemia due to excess potassium loading and dialysis when hyperkalaemia is severe or due to diminished potassium excretion.

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New Drugs

Alpha-blockers and converting enzyme inhibitors

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Alpha-blockers and converting enzyme inhibitors have been introduced for the treatment of hypertension and more recently in refractory congestive cardiac failure. These drugs cause dilatation of both the arterial and venous side of the circulation by specific mechanisms: antagonism of catecholamines at alpha receptors and prevention of angiotensin II generation respectively.

The principal role of these drugs at present is in the more severe or resistant grades of hypertension. Several new treatment strategies have emerged, however, for the management of congestive cardiac failure. Traditional therapeutic approaches have included the use of diuretics and cardiac glycosides. In addition, drug treatment is now used also to produce vasodilatation. On the arterial side of the circulation this will reduce the load against which the heart must pump (afterload), while on the venous side there will be a reduction in blood volume load delivered to the failing heart (preload). Alpha-blockers and converting enzyme inhibitors not only have beneficial acute

haemodynamic effects but may lead to longer term improvement in patients who are refractory to more conventional management.

Alpha-blockers

Prazosin, labetalol, and indoramin are alpha-adrenoceptor antagonists, but only prazosin shows this as its sole effect at doses used and concentrations achieved therapeutically. Labetalol is primarily a beta-adrenoceptor antagonist with modest alpha-blocking activity. Indoramin is an alpha-adrenoceptor antagonist but also has a range of additional pharmacological effects.

Alpha-adrenoceptors exist in at least two forms. Alpha₁-receptors are found on postsynaptic membranes such as the smooth muscle of arteries and veins. Stimulation of these receptors by catecholamines leads to vasoconstriction. Alpha₂-receptors are found both peripherally and in the central nervous system. In the periphery they have been identified on pre-synaptic nerve terminals and here their stimulation by catecholamines or other agonists results in a diminished release of noradrenaline. Recent reports suggest that these receptors may also be located postsynaptically and respond particularly to circulating catecholamines. In the central nervous system alpha₂-receptors are found primarily on postsynaptic nerve cell membranes, and their stimulation results in diminished sympathetic outflow. Alpha₂-receptors in the brain are also intimately concerned in the mechanisms controlling sleep, and thus a consequence of central alpha₂-receptor stimulation is sedation.

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The classical α -blockers phentolamine and phenoxybenzamine affect both α_1 -receptors and α_2 -receptors.

PRazosin (HYPOVASE, MINIPRESS)

Prazosin is a quinazoline derivative that was originally thought to act by direct vasodilatation, possibly by phosphodiesterase inhibition. It is now known, however, that at the concentrations achieved in clinical practice prazosin is a selective antagonist of α_1 -adrenoceptors. There were suggestions that prazosin lowers blood pressure without producing reflex increases in heart rate or renin release, but these claims have not stood the test of careful study. Prazosin acts on both arterial and venous sides of the circulation.

Pharmacokinetics

Prazosin undergoes first pass liver metabolism. About 50-70% of a swallowed dose reaches the systemic circulation unchanged. The drug is more than 95% protein bound both to albumin and to acute phase proteins such as α_1 -acid glycoprotein. Patients with hypoalbuminaemia show a threefold to fourfold increase in the concentration of unbound, and therefore pharmacologically active, drug. Elimination from the body is almost exclusively by liver metabolism, and clinically important changes in elimination will probably occur in patients with severe cirrhosis, but no data in this area are available. The pharmacokinetics of prazosin are not appreciably altered in elderly patients.

Adverse reactions

In general, prazosin is well tolerated. During its earlier clinical use the only problem that occurred with any frequency was the so-called first dose reaction. This was a syncopal attack resulting from a precipitous fall in blood pressure and usually occurred after the first dose, particularly in patients receiving beta-blockers or diuretics, but was also seen after a substantial and abrupt increase in dose. The use of a small starting dose (0.5 mg) together with cautious increments of the dose will virtually eliminate this problem. Additional adverse effects occasionally encountered are nausea and headache. Occasional cases of urinary incontinence have been attributed to prazosin and probably result from its α -blocking activity on smooth muscles of the neck of the bladder.

Prazosin in hypertension

The starting dose of prazosin should be 0.5 mg given in the evening, and the patient should be told of the possibility that an orthostatic reaction might occur and be asked to remain at home after the first dose. Subsequently the dose is 0.5 mg twice a day, increasing by small increments every two to three days to whatever dose is necessary to control the blood pressure. It is usually unnecessary to administer prazosin more often than twice a day. In the more severe forms of hypertension doses of 20 mg a day or more are often necessary.

The major clinical role of prazosin is as a third line drug in managing hypertension. It is rarely used as a first line drug because the reflex cardiovascular responses to the fall in blood pressure produced by prazosin may limit its antihypertensive efficacy. If a beta-blocker and diuretic alone have failed to control the blood pressure or if one or other are contraindicated or poorly tolerated then prazosin would be an appropriate drug to consider. It has been claimed that prazosin causes a more

favourable change in plasma lipids and lipoproteins than beta-blockers or diuretics. This observation and its relevance remain controversial.

Prazosin in congestive cardiac failure

In acute haemodynamic studies prazosin has been shown to improve performance in some patients with refractory congestive cardiac failure. This action seems to depend mainly on a reduction in preload after venodilatation. Longer term treatment with prazosin has led to symptomatic improvement, although there is doubt as to whether it influences mortality in severe heart failure. In some patients tolerance appears to develop after treatment for weeks or months. Whether this has a metabolic or dynamic basis remains unclear.

LABETALOL (TRANDATE)

Mechanism of action

Labetalol is marketed as a mixture of four diastereoisomers which combine α - and beta-adrenoceptor antagonist activity. In practice the beta-blocking activity predominates, and labetalol has a range of clinical activity similar to non-selective beta-blockers such as propranolol. It also has a mild vasodilating action resulting from its α_1 -blocking properties.

Pharmacokinetics

Labetalol undergoes extensive first pass metabolism, and the bioavailability of unchanged drug is substantially increased in patients with cirrhosis. Clearance is by liver metabolism, and reduced elimination is seen in patients with cirrhosis.

Adverse reactions

Adverse reactions are generally similar to those of the non-selective beta-blockers, and labetalol should not be given to patients with asthma, heart failure, or cardiac conduction abnormalities. Nausea and postural hypotension may occur, particularly at higher doses. A transient tingling of the scalp is common after intravenous administration.

Labetalol in hypertension

Labetalol has to be given two to three times a day and this clearly puts the drug at a disadvantage compared with those beta-blockers that are effective when given once daily. In most patients the possession of mild α -blocking activity probably does not outweigh this major disadvantage. The dose is 100 mg three times a day initially, increasing as required to control blood pressure. Lower doses should be used in patients with cirrhosis.

The main indication for labetalol is essential hypertension. It has also been used intravenously for the emergency reduction of blood pressure when 50 mg is given over one minute and repeated if necessary. Labetalol has been used to manage hypertension during pregnancy but there is no evidence to suggest that it is superior to methyldopa.

INDORAMIN (BARATOL)

Mechanism of action

Indoramin has several pharmacological effects. *In vitro* it shows selective antagonism at α_1 -adrenoceptors. In addition

it has membrane stabilising effects and also antagonises the actions of histamine and serotonin.

Pharmacokinetics

Indoramin seems to undergo extensive first pass metabolism and is eliminated by liver metabolism. There is currently no evidence concerning the behaviour of the drug in patients with liver disease. It is more than 90% protein bound.

Adverse reactions

Sedation is the most frequent effect and may be encountered in up to half the patients receiving indoramin. It appears to be dose related. This effect may interfere with the patient's ability to drive or operate machinery. Failure of ejaculation is also a relatively common problem, though it is said to resolve with continued treatment. The negative inotropic effect may exacerbate heart failure in patients with cardiac disease. Several other unwanted effects include dryness of the mouth, depression, weight gain, and fluid retention. Fluid retention is common with alpha-blockers and is minimised by the concomitant use of a diuretic.

Indoramin in hypertension

Unlike prazosin indoramin does not have a first dose effect and does not cause a reflex bradycardia. Like prazosin it does not carry the risk of exacerbating peripheral ischaemia or bronchospasm associated with treatment with beta-blockers. The starting dose is 25 mg twice daily and may be increased every two weeks to a maximum of 100 mg twice daily.

The drug seems to be as effective (but more expensive) as methyldopa or prazosin in lowering blood pressure but its range of unwanted effects will limit its use.

Converting enzyme inhibitors

Inhibition of angiotensin converting enzyme is a novel approach to the treatment of several cardiovascular diseases, including hypertension and congestive cardiac failure. Converting enzyme is found in many sites including plasma, lung, and blood vessels. It forms active angiotensin II from the inactive decapeptide angiotensin I. Angiotensin II raises blood pressure directly by vasoconstriction and indirectly by increasing aldosterone release. Converting enzyme inhibition reduces these effects. The earliest converting enzyme inhibitors were derived from the venom of the Brazilian pit viper. Later synthetic peptide analogues (Teprotide or SQ20881) lowered blood pressure in animals and man but were only active when given intravenously. These results encouraged the search for orally active converting enzyme inhibitors. At present one of these, captopril (SQ14225), is available for clinical use, and several others are at advanced stages of development in clinical trials.

CAPTOPRIL (CAPOTEN)

Mechanism of action

Captopril is a proline derivative containing a sulphydryl group and is a competitive antagonist of angiotensin converting enzyme. In addition, by blockade of kininase II it prevents bradykinin breakdown and may also interfere with degradation of enkephalins. Captopril lowers blood pressure in hypertensive patients and normotensive subjects without any pronounced

postural effect. The fall in blood pressure lasts for six to eight hours and is not usually accompanied by a tachycardia or other reflex consequences of peripheral vasodilatation. The intensity of cardiovascular effects depends on the sodium balance of the subject and the activity of the renin-angiotensin system. Increased plasma renin activity, resulting from sodium restriction, diuretic treatment, or renovascular disease, leads to greater falls in blood pressure than in those with a normal or high intake of salt. Haemodynamic studies in patients with hypertension or cardiac failure suggest an action on venous capacitance vessels in addition to arteriolar resistance.

Pharmacokinetics

Captopril is well absorbed after oral administration but data on drug disposition and pharmacokinetics are limited as reliable measurement of the drug in body fluids is difficult. Although hepatic metabolism does occur, the prolonged duration of drug action in patients with renal failure suggests that renal excretion of the drug or active metabolites is also important. The paucity of information on drug disposition has led to problems in optimisation of dose and frequency of administration. The high doses used in early studies may have influenced the pattern of adverse reactions noted in clinical trials.

Adverse reactions

Adverse effects of captopril include relatively frequent (5% or more) reports of rashes, loss of taste, and gastrointestinal symptoms. Dermatological reactions have taken a wide variety of forms and while usually seen at higher dose levels have not always been closely dose related. Depression, sedation, or drowsiness have not, however, been a feature of treatment with captopril. Serious adverse effects are fortunately rare (less than 1%) and include proteinuria and bone marrow depression. These effects have usually been seen in patients receiving high doses (greater than 450 mg/day), who either have pre-existing renal disease or proteinuria, or both, or have underlying immunological disturbances (systemic lupus erythematosus). They may also occur in severely ill patients taking other drugs with known renal and marrow toxicity. The mechanism of toxicity is not known, but the range of effects, including proteinuria, marrow depression, rash, and taste disturbance, is similar to that seen with D-penicillamine, another drug containing sulphydryl. The frequency of life threatening side effects remains to be established in wider clinical practice. At present, however, it is reasonable to limit the use of captopril to severe hypertension resistant to conventional treatment.

Captopril in hypertension

Captopril has been at least as effective as triple treatment with beta-blocker, diuretic, and vasodilator drugs and is particularly useful in hypertension associated with renal artery stenosis, characterised by high plasma renin activity and secondary hyperaldosteronism. In essential hypertension a proportion of patients will respond to captopril alone and up to 80% to captopril with a thiazide diuretic. In these patients lower doses (75 mg daily or less) are at least as effective as higher doses.

Captopril is usually given in three divided daily doses, although patients with renal impairment may require lower doses given less frequently. The starting dose of 25 mg three times daily may be increased to 150 mg thrice daily over two to six weeks depending on response. Patients who are sodium depleted or are already receiving diuretics should be given a lower starting dose (6-25 mg) as they may show an exaggerated response to the first few doses.

Further experience in essential hypertension with low doses of captopril will be required to determine whether converting enzyme inhibition can be extended to the much larger group of mild to moderate hypertensive patients.

Captopril in congestive cardiac failure

Captopril can produce considerable short term haemodynamic improvement in patients with refractory heart failure, and there is evidence of long term symptomatic relief. Its beneficial effects appear to result from actions on both arterial and venous sides of the circulation. As with other recent developments in managing heart failure by reduction of preload or afterload, or both, captopril should at present be reserved for patients with persistent symptoms and signs not responding to conventional treatment with diuretics or digoxin or both. Patients taking diuretics should start with a low dose of captopril, which may then be increased under close supervision.

Conclusion

Since most patients with hypertension can be adequately controlled by once daily treatment with a beta-blocker or a thiazide diuretic and with few adverse reactions the drugs described above will have limited appeal for first line treatment at present. Prazosin and captopril have a place in treating the more resistant forms of hypertension and prazosin might also be used in low doses, combined with a diuretic, for those patients who are unable to take a beta-blocker. Labetalol has the disadvantage of its dosing frequency while indoramin has the disadvantage of its unwanted effects.

Both prazosin and captopril may improve symptoms in patients with refractory congestive cardiac failure. There is no evidence, however, that these agents alter the clinical course of

the disease. For the present their use should be restricted to those patients who remain symptomatic despite conventional treatment with diuretics or digitalis preparations, or both.

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New Devices

Drug convertarule

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Abstract

A convenient pocket ruler has been developed that allows conversion between metric and molar measurements of many of the drugs for which therapeutic monitoring in the circulation is commonly used. The ruler also gives information to the clinician on suggested therapeutic ranges for the incorporated drugs.

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Introduction

The fine tuning of plasma drug concentration to optimise pharmacological response and avoid toxicity is an attractive concept that is finding increasing favour with clinicians. In most hospitals departments of biochemistry provide estimations of drug concentrations. Clinical pharmacists and clinical pharmacologists may help to interpret the figures and provide advice on adjustment of the dosage to help attain a therapeutic concentration. Drug concentrations are increasingly being provided in the molar units favoured by scientists, despite the fact that drugs are still prescribed in metric amounts. Several conversion scales have been produced.¹ To avoid possible errors of interpretation, we have developed a convenient pocket ruler that not only converts molar units to metric units but also provides information on the therapeutic ranges of several drugs for which routine plasma monitoring is commonly used.