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Today's Treatment

Diseases of the urinary system

High blood pressure and renal disease

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High blood pressure is almost invariably found at some stage in patients with renal disease. This is unsurprising for not only does the kidney control sodium and water balance but it also secretes renin, which through angiotensin II is the most powerful arteriolar and venous constrictor known. Damage to the kidney, particularly that predominantly affecting the cortex, disturbs this finely balanced system and leads to an inability to control sodium and water excretion. On a normal salt intake there is retention of sodium and water so that sodium balance can be maintained. At the same time accompanying damage to the small arterioles leading to and from the glomeruli or directly to the juxtaglomerular cells themselves, leads to inappropriately high renin secretion for the state of sodium balance. These two factors—an increase in sodium and water or volume and inappropriately high renin—are the most important underlying mechanisms for the high blood pressure seen in renal disease. It must be remembered, however, that some patients with renal disease predominantly affecting the medulla—for instance, phenacetin nephropathy—may be unable to conserve sodium on a normal salt intake. These patients have a low or normal blood pressure, which in advanced renal disease is often the first sign of progressive sodium depletion.

While a rise in blood pressure may therefore be seen as an appropriate response, high blood pressure can of itself further damage the kidney and compound the underlying disease. Reduction of the high blood pressure slows down or halts the progressive development of renal failure. An interruption of this vicious circle of renal disease leading to high blood pressure, which further damages the kidney, leading to a higher blood pressure, is one of the few therapeutic moves that prevents or delays the need for long-term dialysis.

Risks of high blood pressure

Patients with a raised blood pressure in renal disease are as likely to develop a stroke or heart attack as hypertensive patients without renal disease. Moderately or mildly raised blood pressure leads to thickening of the arteriolar wall, which does not seriously impair renal function in a previously normal kidney but will do so if there is underlying renal disease. Severely raised blood pressure may cause damage to small arterioles causing fibrinoid necrosis and proliferation of arterioles. This leads to glomerular ischaemia and malignant hypertension. Malignant hypertension, whether caused by an underlying renal disease or causing the destruction of the kidney itself invariably leads, if *not* treated immediately and adequately, to progressive renal failure, and therefore to a lifetime of dialysis or transplantation.

An interruption of this vicious circle by reducing blood pressure is known to halt or even improve the renal failure. Despite this knowledge many patients with malignant hypertension are inadequately treated. They are referred to renal units with terminal renal failure when it is too late to reverse the process. The importance of early and effective reduction of blood pressure in malignant hypertension cannot be over-emphasised.

Mechanism

Recent advances in the more accurate measurement of the renin angiotensin system and the use of inhibitors have shown that raised blood pressure can be caused by excessive renin secretion. Measurements of body composition have shown that at the opposite extreme raised blood pressure can be due to excess sodium and water or volume. These two extremes are best illustrated by some patients on maintenance haemodialysis.

There are a few patients whose raised blood pressure does not fall with progressive weight reduction or sodium and water removal. These patients have high levels of plasma renin activity and angiotensin II. Infusion of saralasin, a competitive inhibitor of angiotensin II, reduces the raised blood pressure to normal,

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showing that the raised angiotensin II level is directly causing the high blood pressure. The opposite extreme is illustrated by anephric patients in whom the high blood pressure is directly related to sodium and water excess. Removal of sodium and water at dialysis and thereby a reduction in weight causes a fall in blood pressure. Plasma renin activity in these anephric patients is low, irrespective of sodium and water balance, and infusion of saralasin causes a small rise in blood pressure, confirming that the renin-angiotensin system is not implicated in the maintenance of their high blood pressure. In most patients being treated with dialysis, and patients with renal disease whose blood pressure is raised, the hypertension appears to be caused by one or both of these mechanisms—that is, inappropriately high renin or excess volume or both.

Renal disease, particularly if it is predominantly in the cortex and is associated with progressive renal failure, is accompanied by some degree of sodium and water retention if the patient is eating a normal amount of salt. Simultaneously, the damage to the arterioles and juxtaglomerular apparatus leads to inappropriately high renin secretion for the state of sodium balance. In addition, the vasoconstrictor effect of angiotensin II is directly related to sodium balance. Not surprisingly, therefore, most patients with renal disease have a raised blood pressure.

Investigations

CORRECTABLE CAUSE

Much time and effort has and can be spent investigating hypertensive patients for a benefit that is not always apparent. On the other hand, patients with malignant hypertension should be fully investigated with renal arteriograms and measurement of the renin concentration in the renal veins, if available, to exclude a renin-secreting tumour or some potentially curable cause such as renal artery stenosis or a unilateral renal disease. All patients with renal disease should have an intravenous pyelogram. If this shows changes suggesting renal artery stenosis further investigations may be indicated. Renovascular hypertension is probably best looked for by measuring plasma renin activity or using a competitive inhibitor of angiotensin II such as saralasin or both. Neither of these are as yet freely available. A detailed discussion of renovascular hypertension is outside the scope of this article.

UNDERLYING RENAL DISEASE AND SEVERITY OF BLOOD PRESSURE

Appropriate investigations to establish the underlying cause of the renal disease as well as assessing the severity of the raised blood pressure are indicated. Several measurements of blood pressure, examination of fundi, chest radiography, and an electrocardiogram are essential, with some measurement of catecholamine excretion—for instance, 24-hour urinary vanillyl mandelic acid—to exclude a pheochromocytoma. The severity of renal impairment must be assessed by at least measuring plasma creatinine concentrations and creatinine clearance.

SODIUM AND RENIN

Measurement of renin and the state of sodium and water balance should indicate to some extent the mechanism of the raised blood pressure in renal disease. Renin measurements and measurement of body composition, however, are not readily available. An assessment of dietary sodium intake by measuring 24-hour urinary sodium is useful to determine whether the patient is consuming large or small quantities of sodium. A large sodium intake (>200 mmol/24 h) may improve renal function but may make it difficult to control the blood pressure. A low sodium intake (<75 mmol/24 h) will impair renal function.

Management

Lowering severely raised blood pressure associated with renal disease slows or prevents the deterioration in renal function that would otherwise occur. This benefit is less certain for less severe hypertension but probably occurs. The outcome will also depend on the underlying renal disease. Lowering the blood pressure also incurs an additional benefit in that the incidence of strokes will be reduced, and if beta-blockers are used probably heart attacks as well, as they are in patients who have hypertension without renal disease.

Aim

Treatment aims to reduce the blood pressure towards or into the normal range—that is, systolic <160 mm and diastolic <90 mm Hg—without reducing renal blood flow. Transiently, the renal function may be reduced as blood pressure is lowered, but provided over-enthusiastic treatment does not produce hypotension or sodium and water depletion, this deterioration in renal function is not permanent.

Ways of lowering blood pressure

ALTERATION OF SODIUM AND WATER BALANCE

Dietary—If the raised blood pressure is predominantly caused by sodium and water retention or volume excess a reduced dietary sodium intake will cause a loss of sodium and water. This volume reduction will cause a fall in blood pressure provided that the sodium and water loss has not stimulated a large reactive rise in renin release. A reduction in volume or sodium and water balance, however, will cause a considerable deterioration in renal function. A reduction in sodium intake is *not* indicated unless sodium intake is excessive—for instance, >150 mmol/24 h—or there is persistent clinical evidence of sodium and water retention despite using diuretics. Unfortunately many patients are still being advised to restrict their sodium intake severely. This may cause a deterioration in renal function without necessarily altering the blood pressure. An increase in sodium intake to normal amounts in such patients often results in a remarkable improvement in renal function and in wellbeing.

Diuretics will cause a loss of sodium and water, and like dietary sodium restriction would appear to be rational treatment in those patients whose blood pressure is maintained by volume excess, but diuretics cause severe deterioration in renal function and should *not* be used unless there is gross—that is, clinical evidence of—sodium and water retention. If there is oedema, thiazide or more potent diuretics such as frusemide may be used. Potent diuretics like frusemide should be reserved for patients with severe renal failure who are resistant to thiazide diuretics. Conventional doses of diuretics may be used (such as, bendroflumazide 5 mg/day). Some patients with severe renal failure not on dialysis may require large amounts of frusemide—250–500 mg/day. Potassium-sparing diuretics such as spironolactone must be used with great caution because of the risk of hyperkalaemia in the presence of renal failure. They are contraindicated unless the plasma potassium concentration can be frequently monitored.

REDUCTION IN RENIN-RELEASE BETA-BLOCKERS

Beta-blockers will reduce renin release and thereby angiotensin II concentrations. Beta-blockers are effective in patients whose blood pressure is being directly raised by excess renin release and angiotensin II. In such patients beta-blockers appear to be the treatment of choice. Patients whose blood pressure is predominantly raised because of sodium and water retention, however,

must combine the beta-blocker with a vasodilator—for instance, hydralazine.

The beta-blocker most widely used in patients with renal disease is propranolol. Necessary adjustments in dose must always be remembered in patients with renal failure. There is some evidence that the half life of the active metabolites of propranolol may be reduced in renal failure, suggesting that it may have to be given more often. Generally, however, the dosage used is no different from that for patients with normal renal function (around 80-160 mg twice a day). Other beta-blockers are equally useful.

VASODILATORS COMBINED WITH BETA-BLOCKERS

Interest in vasodilators, particularly hydralazine, was renewed because of the synergistic, or at the very least additive antihypertensive, effect when they are combined with beta-blockers. When vasodilators are given by themselves compensatory mechanisms, probably mediated by the sympathetic nervous system, increase the heart rate, cardiac output, and renin release. Given alone, vasodilators are therefore not very effective. When a vasodilator is combined with a beta-blocker, however, the heart rate, cardiac output, and renin release do not increase, and there is a greater fall in blood pressure with both drugs than with either drug alone. This combination is effective in all forms of renal hypertension and will even lower blood pressure in patients who appear to be predominantly volume-dependent. Vasodilators will directly increase renal blood flow and may maintain renal blood flow even when there has been a large fall in blood pressure. Clinical experience supports this, in that when vasodilators and beta-blockers are combined the renal function does not deteriorate, and, indeed, often improves. The other advantage of this combination, apart from its powerful antihypertensive effect, is that postural reflexes remain intact, and there is no postural or exercise hypotension.

The most widely used vasodilator is hydralazine. This drug has the advantage of many years' use. When used in amounts below 200 mg/day it does not appear to have any serious side effects. Dosage does not appear to need modification in renal failure—starting dose 25 mg twice a day up to 100 mg twice a day. Patients who do not respond to this combination of beta-blocker and hydralazine can try two further vasodilators—diazoxide and minoxidil. Experience with diazoxide has shown it to be very effective but it has the major disadvantage of causing diabetes. Minoxidil, the most potent oral vasodilator known, is effective in most resistant hypertensive patients when combined with a beta-blocker. The main side effect of minoxidil is excessive hair growth, which makes its use in women difficult. The use of minoxidil is currently restricted to specialised units, and should probably be reserved for patients with severe or malignant hypertension who do not respond to the combination of hydralazine and beta-blocker. Vasodilators, particularly minoxidil, may

cause some retention of sodium and water, and if this occurs, a diuretic should be added. This may have an additional antihypertensive effect, but care must be taken with diuretics not to cause sodium and water depletion with consequent deterioration in renal function.

SUGGESTED TREATMENT SCHEDULE

Patients with renal disease whose diastolic pressure is consistently >100 mm Hg or systolic >160 mm Hg should be treated. Beta-blockers should be started in all patients unless there is a specific contraindication, such as severe heart failure or severe asthma. If the beta-blocker is not effective in conventional doses hydralazine should be added, increasing the dose up to 100 mg twice a day. If this is not effective and the patient is taking tablets with no clinical evidence of sodium and water excess minoxidil should be substituted for the hydralazine. A diuretic or an increase in diuretics may be needed.

SPECIAL CASES

Malignant hypertension

Malignant hypertension is a medical emergency. These patients, therefore, need urgent effective treatment, and treatment should not wait for referral to hospital. Propranolol (160 mg) and hydralazine (50 mg) by mouth will lower blood pressure smoothly in most patients within two to three hours. Parenteral drugs are *not* necessary unless there is hypertensive encephalopathy or left ventricular failure. The parenteral drug of choice is probably intravenous diazoxide. Conventional doses (300 mg) may cause severe hypotension, so that it is better to start with a bolus of 50-100 mg intravenously. If this amount is not effective a larger amount can then be given.

Patients on dialysis

In patients being treated with long-term intermittent dialysis prevention of deterioration in renal function is no longer of overwhelming importance. Most (90%) hypertensive patients on dialysis can be controlled by gradually reducing the predialysis weight by removing sodium and water at dialysis (ultrafiltration) and restricting water intake between dialyses. Some patients, however, will not respond to volume removal alone because this stimulates excessive renin production, which maintains their blood pressure. It is then necessary to give antihypertensive drugs. Usually propranolol and hydralazine will control their blood pressure. In more resistant cases minoxidil with propranolol is effective. In these cases bilateral nephrectomy to control blood pressure is no longer necessary.

Is high intake of vitamin C or liver in dried capsules of any value as a preventive against cancer in general and brain tumours in particular?

Several drugs are secondary amines. Nitrites are used to preserve meats and other foodstuffs. Under certain circumstances, vitamin C prevents the formation of carcinogenic nitrosamines from nitrites and secondary amines in the stomach. In laboratory animals fed nitrites and secondary amines it has been shown that vitamin C may protect against cancer development. Whether a high intake of vitamin C protects humans from developing cancer of any kind under the ordinary conditions of everyday life is not known. Liver is rich in, *inter alia*, vitamin A. Vitamin A deficiency leads to squamous metaplasia of normally glandular epithelium and squamous metaplasia is thought to be a step in the direction of cancer development. In

laboratory animals tumour development after exposure to known carcinogens has been shown to be delayed or prevented by high intakes of vitamin A or its analogues. Vitamin A, however, is toxic at dose levels not far above those regarded as necessary to sustain life, so that caution is needed in exploring the value of the vitamin as a cancer preventive in man. Synthetic vitamin A analogues, which possess the cancer-preventing activity but are less toxic, are currently the subject of controlled clinical trial in high cancer risk groups (such as heavy cigarette smokers) in the USA. Relatively few chemicals have been shown in laboratory animals to cause brain tumours. Among them are several nitrosamines. Conceivably, therefore, vitamin C might protect against the development of brain tumours, although not against their enlargement once they have begun to grow. There is no evidence that vitamin A or its analogues specifically prevent brain tumour development.