CURRENT TRENDS IN THE TREATMENT OF HYPERTENSION

By John Raftos

The purpose of this paper is to discuss recent advances in the drug therapy of hypertension with particular reference to Clonidine and the beta adrenergic blockers.

Clonidine is an imidazoline compound chemically related to the alpha adrenergic blocker tolazoline and all its affects can be reversed by that drug.

The primary site of action appears to be the bulbar apparatus controlling sympathetic constrictor activity, and, in animals, total sympathetic blockade with guanethidine prevents the hypotensive response. In addition, there may be a direct peripheral vasodilator effect. There may be some fall in cardiac output in acute experiments but this is not clinically evident in the long term. There is no direct negative inotrophic effect on the heart and coronary blood flow may be increased. Postural vasomotor responses are not impaired and in contrast to other anti hypertensive drugs, the cardiovascular response to exercise is unchanged. Renal blood flow and glomerular filtration are not affected but marked salt and water retention occurs. Sedation is common but the hypotensive effect is quite distinct from this. Alpha adrenergic stimulation is shown by the initial pressor response to injection. This can be prevented by phentolamine. Chronic alpha adrenergic effects are seen in the tendency to excess cutaneous vasoconstriction in cold weather and the precipitation of Raynaud's phenomenon. Catecholamine depletion does not occur. The production of saliva and gastric secretion may be reduced.

Between 1968 and 1972 an extensive clinical trial of Clonidine was carried out at the Cardio Vascular Clinic at Sydney Hospital. Patients were elected on the basis of having severe disease, poorly controlled by other medication. They therefore present more serious and resistant disease than is seen in usual clinical practice.

The severity of disease was graded as follows:

Grade 1 (mild): B.P. consistently less than 170/100, fundi normal or grade 1, normal E.C.G., cardiac size and renal function.

Grade 2 (moderate): B.P. greater than 170/110, fundus grade 2 early left ventricular hypertrophy on E.C.G. or chest x-ray, normal renal function.

Grade 3 (severe): Fundus grade 3, marked left ventricular hypertrophy on E.C.G. and chest x-ray, abnormal renal function.

Grade 4 (malignant): Papilloedema.

One hundred and fifty three patients completed the trial (i.e. completed a minimum of six months treatment or were resistant and had intolerable side effect). The severity gradings show that most patients had severe disease and 12% had or had had malignant hypertension. Sixty per cent had abnormal E.C.G.'s % impaired renal function, % symptomatic coronary disease and % had had cerebrovascular accident. The average age was 46 years and the average known duration of hypertension five years.

All patients were treated with a thiazide diuretic. Clonidine was commenced at 0.075 mgms twice daily, increasing weekly or fortnightly. The average effective dose was 0.5 mgm/day, patients with impaired renal function and malignant hypertension required higher doses.

1. Good—B.P. less than 160/100 standing and lying.
2. Fair—Reduction of 20.0 mm systolic and 10.0 mm diastolic on lowest pre-treatment readings.
3. Poor—No useful reduction in B.P.
4. Side effect failure—Side effect intolerable or preventing adequate dosage.

The results were that 47% had a good result with Clonidine and a diuretic and a further 17% had good control when Clonidine was added to other medication, making a total of 64%. Eighty two per cent of 18 patients having Clonidine as initial treatment had a good result. The result was related to the severity of the hypertension, 78% of patients with Grade 1 and 2 having good control, 63% in grade 3 and 30% in grade 4. Fifty five per cent of patients with renal hypertension and 58% of patients with renal failure had a good result.

In the good control group the average of the standing and supine pressures was 143/95 and the average duration of treatment was eighteen months.

Additive effects were demonstrated with methyldopa, guanethedine, debrisoquine and diazoxide. Seven patients with extreme hypertension resistant to all other medications were treated with Clonidine and a beta blocker. Good control was obtained in 2 and fair in 4.

Crossover techniques were not attempted. However, 71 patients had an inadequate result with methyldopa and 68% had a good result with Clonidine.

Clonidine was used intravenously in the treatment of hypertensive emergency and being effective in some cases resistant to diazoxide. Gross hypotension did not occur. The present technique is to inject phentolamine 5.0 mgm then Clonidine 0.15 or 0.3 mgm.

Fifteen patients did not respond to Clonidine and none has since been well controlled by other drugs.

There were no deaths due to Clonidine. Two patients died of cerebral haemorrhage and two suddenly, presumably of coronary disease.

Twenty one patients with pre-existing cerebo-vascular disease were treated. There were no recurrences and all with acute symptoms improved. There were four new cerebrovascular episodes in patients with inadequate control.

Fifty per cent of 29 patients with angina were improved. Six new coronary events developed, 2 sudden deaths, 1 myocardial infarction and 3 new cases of angina.

Side effects were common, namely sedation, dryness of the mouth, constipation, Raynaud's phenomenon and withdrawal effects. Sedation was the most troublesome and caused treatment failure in 10%. Tolerance to sedation developed in many patients, usually within a few weeks. Most patients slept longer but some had sleep disturbance with early waking.

Dry mouth was sometimes objectionable but nasal blockage did not occur. Mild Raynaud's phenomenon developed in two patients.

Withdrawal symptoms developed in two patients within forty eight hours of ceasing Clonidine and consisted of agitation, headache, sweating and tachycardia, responding rapidly to resumption of Clonidine. The hypotensive effect of Clonidine was of short duration and pressures usually returned to pre-treatment levels within forty eight hours of ceasing treatment. Clonidine treated patients tolerated anaesthesia well. However, it was found necessary to give the last dose of Clonidine within four to six hours of anaesthesia to prevent hypertension.

Depression did not occur as a result of Clonidine therapy. Eleven endogenous and 14 iatrogenic depressives were treated, all of the latter recovering on Clonidine. Only one depressive episode occurred, in a patient who had two previous courses of E.C.T. and who has since continued Clonidine for a further year.

Eleven patients were treated with Clonidine and a tricyclic anti-depressant, good blood pressure control

Cardio Vascular Clinic, Sydney Hospital, Sydney, Australia.

was obtained in 10. Clonidine did not prevent an acute rise in blood pressure in 4 patients when either methyldopa or guanethedine were used with a tricyclic.

Impotence and failure of ejaculation were not seen. Six patients impotent while taking methyldopa recovered on Clonidine.

Toxic effects did not occur. Renal function either improved or did not change except in four patients in renal failure.

DISCUSSION

The results obtained in this study indicate that Clonidine is a potent antihypertensive drug, effective in all grades of severity and suitable for use as a first line drug. It presents a desirable type of blood pressure control and in addition, side effects, though frequent, are easily identified and rapidly reversible.

The main advantage of Clonidine is the absence of postural hypotension when used alone though it will potentiate the postural effects of the sympathetic blockers. For this reason it appears the drug of choice in patients with ischemic cerebro-vascular disease. It is well tolerated by patients with coronary disease and the figures though small could be interpreted as indicating lessened mortality from this cause.

It is valuable in the treatment of hypertensive crisis and we now use it as the drug of first choice reserving diazoxide for those resistant to it.

The co-existence of hypertension and depression presents major therapeutic problems. Clonidine would appear to be very helpful in this situation because it does not cause hypertension when used with tricyclics and has not so far caused depression.

A comparison with methlydopa appears inevitable. Both drugs are of roughly equivalent potency about 2/3 of patients being responsive. However, though side effects appear to be more common with clonidine, the fatigue and dry mouth due to Clonidine are much more benign than the depression and impotence due to methyldopa and for this reason, Clonidine is to be preferred as first line therapy.

The beta adrenergic blocking drugs have now been shown to be of value in the treatment of hypertension as well as angina and arrhythmias. The nature of the hypotensive effect has not been established but the following mechanisms have been suggested.

1. A central depressant effect. The incidence of fatigue, depression dreaming is consistent with this. However, there is great variation in the cerebral concentration of the various drugs which does not correlate with their anti hypertensive effect.
2. Reduction in cardiac output. This may account for the anti hypertensive effect being unacceptable to some patients because postural hypotension is uncommon.
3. Reduction in renin production.

A small run in trial of propranolol in the treatment of severe hypertension has been carried out by Dr. Stokes in the Cardio Vascular Clinic. Twenty nine patients with severe hypertension were treated with the following result. Half had good control of blood pressure sustained for several months. Postural hypotension did not occur and treatment was well tolerated. The response to treatment was rapid and there was good correlation between acute and long term responsiveness. There appears to be an association between responsiveness and elevated plasma renin levels and with successful treatment, plasma renin tended to fall.

On the basis of these results and more extensive but uncontrolled clinical studies the present status of beta blocking drugs in the treatment of hypertension may be stated as follows:

1. Between 30% and 40% of unselected hypertensive patients will have a good result with beta blockers.
2. The response is unpredictable and patients appear to respond either very well or not at all.
3. There is significant incidence of side effect including fatigue, nightmares, vomiting, epigastric pain, diarrhoea, aggravation of obstructive airways disease, sore eyes. An insufficient number has been treated to make any comment about the incidence of depression.

Therefore beta blockers are regarded as second line antihypertensive drugs particularly indicated under the following circumstances:

1. In hypertensive patients in whom the primary presentation is with angina.
2. In patients resistant to Clonidine and methyldopa especially with severe or malignant hypertension, prior to commencing sympathetic blockers.
3. If conventional therapy results in postural hypotension and the patient is resistant to clonidine.

Clonidine and the beta blockers represent a major advance and will further reduce the incidence of hypertensive morbidity and mortality.

However, it is already clear that in the treated hypertensive, sudden cardiac death is now the major cause of mortality and such evidence as is available suggests that antihypertensive treatment does not significantly affect this. Therefore, in the long term large scale studies of Clonidine, beta blockers and such other drugs as may become available it will be particularly important to assess the impact of the drugs on sudden cardiac death.

More importantly, hypertension is increasingly detected in younger age groups and in these particularly, the management of those metabolic factors thought to accelerate coronary disease would appear to be of equal importance to the management of hypertension.