HAEMODYNAMIC EFFECTS OF HYPOTENSIVE DRUGS AND CONSEQUENT DANGERS IN THEIR USE*

B. GOLDBERG, M.D. (RAND), M.R.C.P. (LOND.) and I. R. YUDAKEN, M.B. (RAND), M.R.C.P. (EDIN.)

In recent years a considerable number of drugs have been used in the treatment of hypertension. Their efficacy in reducing the blood pressure varies with the drug or combination of drugs used and from patient to patient. Their ultimate effect on prognosis is not known but in a proportion of patients considerable subjective relief is obtained during treatment and in some an improvement in existing cardiac and vascular disease ensues. However, the lowering of blood pressure may be accompanied by profound readjustments in the circulation through different organs or parts of the body, which in some instances may result not only in unpleasant and harmful but even lethal side effects. A knowledge of the circulatory changes that do occur with these drugs may permit one therefore to anticipate and so perhaps avoid harm resulting from their use.

In this paper some of the haemodynamic effects of the ganglion-blocking agents, of reserpine, and of hydralazine, are presented and discussed with particular reference to the heart and the renal and cerebral circulations. Difficulties encountered in their use are illustrated with case reports, and some of the factors which should be considered in the choice of drugs in the treatment of hypertensive patients are indicated.

Ganglion-Blocking Agents

This group consists of hexamethonium, pentapyrrolodinium (pentolinium, Ansolysen) and mecamylamine (Mevasine) as well as several others. Their action in reducing the blood pressure results from their effect in blocking transmission of impulses through autonomic (sympathetic) ganglia. As far as is known, differences observed between the hypotensive effects of these drugs are in the main due to the rate and completeness of their absorption and excretion and their duration of action. It has been suggested, however, that the hypotension produced by mecamylamine may also be a result of a central cerebral and direct cardiac effect.[1]

When administered parenterally to hypertensive subjects they cause a fall in blood pressure which is usually accompanied by a decrease in cardiac output or, in patients with cardiac failure, by an increase; total peripheral resistance is unchanged or reduced.[2-4] In dogs, ventricular work and coronary blood flow decrease.[5] The decrease in cardiac output results from a reduction in venomotor tone with an increase in the capacity of the venous reservoir.[7] Venous return is reduced and the cardiac output falls. With the reduction in mean arterial pressure and hence coronary filling pressure the coronary blood flow is decreased. Renal blood flow and glomerular filtration rate fall but tend to return within a short while towards control levels even though the blood pressure remains lowered; renal vascular resistance usually increases.[3,6,8,9] These changes may be due to a reduction in cardiac output and a shift of blood away from the splanchnic area to the periphery, where vasodilatation occurs. In both normal and hypertensive individuals with no known cerebrovascular disease there may be no change in cerebral blood flow with moderate falls of blood pressure, or with more marked hypotension the blood flow may be reduced.[10-12] The decrease in cerebral blood flow has been considered to be a passive one, resulting from the decrease in blood pressure rather than from any direct effect on the cerebral arteries.

Smith and Hoobler found that during maintenance therapy with pentolinium a decrease in cardiac output without any significant alteration in total peripheral resistance occurred,[4] although during treatment with a combination of pentolinium

* A paper presented at the South African Medical Congress, Durban, September 1957.

and reserpine no consistent alteration in cardiac outptu was noted.[13] The reduction in blood pressure occurring during treatment has been attributed to this change in

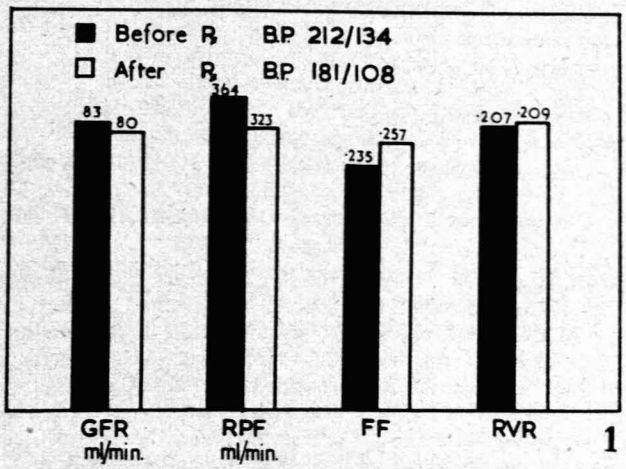

Fig. 1. The effects of treatment with a combination of oral reserpine and mecamylamine on the renal circulation of a hypertensive patient. GFR=glomerular filtration rate. RPF=renal plasma flow. FF=filtration fraction (GFR/RPF). RVR=renal vascular resistance (ratio mean blood pressure/renal blood flow). Numbers on top of columns are absolute values.

cardiac output rather than to any alteration in the peripheral resistance. Maintenance therapy with hexamethonium or a combination of ganglion-blocking drug and reserpine does not result in any marked changes in the renal circulation of recumbent hypertensive patients (Fig. 1) except for a decrease in renal vascular resistance and a slight reduction in glomerular filtration rate.[13,14]

Based on these observations one might expect that renal insufficiency may occur or, when previously present, be aggravated by treatment with a ganglion-blocking drug. That this is so is supported by reports of the development of increasing and fatal uraemia during treatment.[15,16] However, provided renal functional impairment is not too severe and a gradual reduction in blood pressure is achieved, with care these drugs can be used.[13,17,18]

Similarly in the presence of cerebrovascular disease a reduction in blood pressure may be accompanied by undesirable side-effects due to cerebral ischaemia, as illustrated in the following case report:

A 68-year-old man was readmitted to hospital 10 weeks after a previous admission for myocardial infarction. He had had a cerebral thrombosis 18 months previously. On the day of admission he took for the first time some pentolinium pills which had been prescribed for hypertension. An hour or two later he felt faint and collapsed, and on recovering consciousness found his right side to be paralyzed. Examination showed a hemiparesis, blood pressure was 160/90 mm. Hg, and his pupils were widely dilated. During the next few hours the blood pressure gradually rose and eventually averaged 208/123 mm. Hg. Parallel with the rise in blood pressure there was a progressive recovery from the hemiparesis.

Although cardiac output and ventricular work are reduced by ganglion-blocking drugs the coronary blood flow also decreases. This reduction, if proportionately greater than the decrease in ventricular work, may result in myocardial ischaemia.

A 42-year-old man had been observed during a 3-year period during which his blood pressure averaged 210/136 mm. Hg. Because of the development of retinal and electrocardiographic changes he was started on oral reserpine and pentolinium in hospital, and was discharged with an average blood pressure in the recumbent position of about 165/113 mm. Hg. During the next 3 months it became necessary to increase the thrice-a-day dose of pentolinium from 75 mg. to 140 mg. and later to 180 mg. because of the development of tolerance to the drug. When an attempt was then made to increase each dose by a further 20 mg. he developed faintness due to postural hypotension and substernal pain on excretion.

Fig. 2 illustrates ischaemic electrocardiographic changes after the intravenous injection of hexamethonium in a hypertensive patient.

Hydralazine

Hydralazine (Apresoline, 1-hydrazinophthalazine) has been shown to be an effective hypotensive agent acting, both centrally on the brain (possibly the hypothalamus) and peripherally on the arterioles so as to produce vasodilatation and thereby the blood pressure.[15] The injection of hydralazine produces a sympathomimetic effect on the heart, with an increase in heart rate, stroke volume and cardiac output. Vasodilatation occurs, particularly in the splanchnic area and the total peripheral resistance decreases.[19,20] The

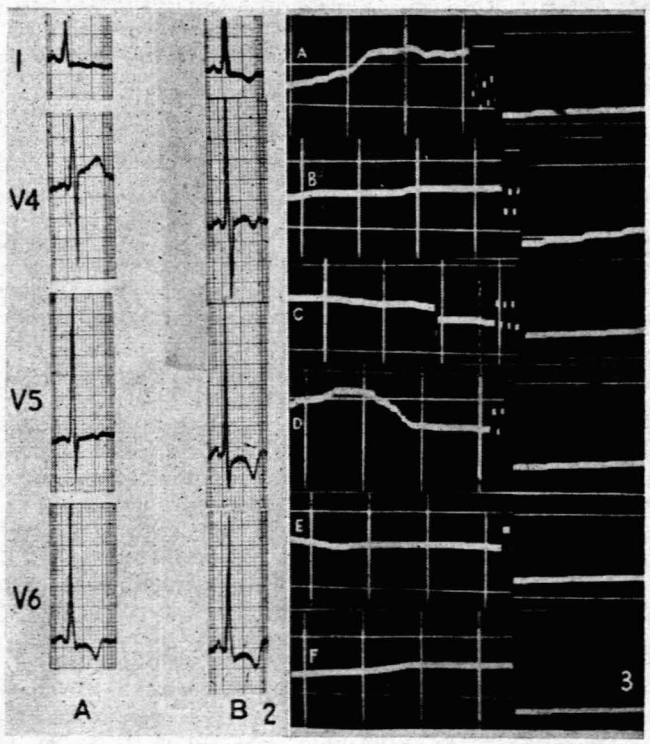

Fig. 2. The effect of intravenous hexamethonium on the electrocardiogram of a hypertensive subject. A: Before injection. B: 20 minutes after injection.

Fig. 3. The effect of intramuscular hydralazine on the digital pulse volume and blood flow of a hypertensive subject. A: Basal. B, C, D, E and F: 15, 30, 45, 60 and 70 minutes after injection. The recordings on the left are at slow paper speed and show a small pulse wave which does not increase after injection. The recordings on the right at fast speed show no significant alteration in the digital blood flow (measured by the steepness of the slope of the curve/unit time).

renal blood flow increases but the glomerular filtration rate is unchanged and the filtration fraction consequently falls.[6,19,21] The digital blood flow may increase or not alter[20,21] (Fig. 3). The cerebral blood flow remains constant in spite of the decrease in blood pressure and the cerebral vascular resistance decreases.[22]

During maintenance therapy with hydralazine the mean resting renal plasma flow is usually not altered significantly, although in individual patients a moderate increase has been noted. Moreover, after a period of treatment oral administration of hydralazine fails to increase the flow significantly, indicating the development of tolerance to the drug.[23]

The effect of hydralazine in increasing ventricular work may be manifest clinically as coronary insufficiency or cardiac failure.

A 50-year-old man had a thoraco-lumbar splanchnicectomy in 1949 because of malignant hypertension. Two years later his blood pressure was about 250/150 mm. Hg and he had symptoms and signs of cardiac failure. He was treated with digitalis, diuretics and for a while with hexamethonium; cardiac failure improved and the blood pressure was reduced moderately. In April 1952 hydralazine was given. On taking 50 mg. *t.i.d.* he experienced for the first time pain in his jaw. On reducing to 25 mg. *t.i.d.* this pain was not felt, but symptoms of cardiac failure returned, with breathlessness and oedema of the legs. This was controlled again with diuretics and hydralazine was stopped for a week. When it was resumed in a dose of 50 mg. *t.i.d.* he had anginal pain about 45 minutes after the second and also the third dose. Hydralazine was again stopped for one day. On resumption pain occurred in the chest, jaw and arms, with palpitations. Thereafter the dose was reduced to 25 mg. *t.i.d.* with no angina but also no significant change in the blood pressure. Hypotensive treatment was stopped for 4 months but when hydralazine was started again angina recurred. Subsequently he was treated with reserpine and hydralazine with a good effect on blood pressure but with the development of severe mental depression.

Reserpine

The mode of action of the rauwolfia alkaloids, of which reserpine is one, appears to be a centrally mediated (possibly hypothalamic) depression of sympathetic nervous activity with resulting peripheral vasodilatation and consequent reduction in blood pressure.[24]

In acute experiments on dogs and in hypertensive patients the intravenous administration of reserpine causes no consistent effect on cardiac output and the fall in blood pressure has been shown to be due to a decrease in peripheral resistance. Similarly no consistent alteration in the glomerular filtration rate or renal blood flow has been observed.[24]

During maintenance therapy with reserpine alone or a combination of reserpine and pentolinium no significant change occurs in the renal plasma flow or glomerular filtration rate. The renal vascular resistance decreases.[9,13,24]

We have observed no deleterious effects due to haemodynamic changes in patients treated with reserpine alone.

Combination of Drugs

Since many patients are treated with combinations of the various hypotensive drugs it is of importance to know whether the action of one is modified by simultaneous treatment with another. It has been shown that pre-treatment with reserpine does not prevent the acute renal haemodynamic changes produced by hexamethonium.[9] Similarly, the effects on renal haemodynamics of maintenance therapy with a combination of reserpine and pentolinium[13] are similar to those reported during treatment with hexamethonium alone.[14] The increase in the heart rate following the administration of hydralazine is prevented if reserpine is also given.[25] It is possible that the action of the ganglion-blocking agents on the cardiac output may be antagonistic to the opposite effect of hydralazine, although hexamethonium does not inhibit the renal vasodilating action of hydralazine.[26] In Table I are summarized the various haemodynamic alterations produced by the individual drugs.

TABLE I. SUMMARY OF THE EFFECTS OF GANGLION BLOCKING DRUGS, HYDRALAZINE AND RESERPINE ON THE CARDIAC OUTPUT AND RENAL AND CEREBRAL CIRCULATIONS

	Ganglion Blockers	*Hydralazine*	*Reserpine*
Cardiac output	−	+	O
Renal blood flow	$\frac{-}{O}$	$\frac{+}{O}$	O
Glomerular filtration rate	$\frac{-}{O}$	O	O
Cerebral blood flow	−	$?\frac{-}{O}$	? O

+ = increase. − = decrease. O = no change. ? = effect doubtful.

DISCUSSION

The heart, kidneys and brain are the important organs which may suffer harm from the haemodynamic changes that occur during treatment with hypotensive agents. The patient who will suffer and the part which will be affected will depend upon the particular drug used and the presence and severity of accompanying vascular disease.

A reduction in blood pressure resulting from the use of ganglion blockers may result in a decreased cerebral blood flow. When cerebro-vascular disease is present, not in the form of hypertensive encephalopathy, but in the form of associated organic cerebral arterial disease, this reduction in blood flow may result in general or local cerebral ischaemia and anoxia. While we have not observed cerebral ischaemia during treatment with hydralazine or reserpine we have seen syncope follow a single injection of hydralazine. In the elderly atherosclerotic hypertensive patient it is likely that a sudden, marked reduction in systemic blood pressure, produced by any means, will result in cerebral ischaemia and its sequelae. It follows, therefore, that in this type of patient hypotensive treatment should be instituted cautiously and only when the disease itself is of sufficient severity to warrant treatment. The aim of therapy is to produce a moderate and gradual lowering of the blood pressure, avoiding sudden sharp reductions. Thereby one may alleviate the symptoms, and perhaps prevent the progression, of the generalized hypertensive vascular disease. The gradual and moderate reduction in pressure that is desirable is characteristic of the action of reserpine, which is the drug of choice in these cases. Treatment with reserpine alone, however, is not always adequate, and then the addition of hydralazine in gradually increasing doses may be effective. Moreover, the postural hypotension which occurs during maintenance treatment with the ganglion-blocking agents is not a problem with reserpine and hydralazine.

In the presence of severe progressive renal functional impairment it is unlikely that the reduction in blood pressure will prevent the usual fatal outcome. However there is little doubt that associated hypertension worsens the prog-

nosis of renal disease, either directly by its effect on the kidneys, or secondarily by the production of cardiac failure. It is important, therefore, in these instances to try and reduce the blood pressure and so retard these changes. When renal disease, although advanced, is static or only slowly progressive it may be possible by treatment to alleviate symptoms due to hypertension and perhaps improve prognosis. Theoretically the drug of choice under these circumstances should be hydralazine, by virtue of its effect in increasing blood flow. We have observed in an occasional individual with severe but only slowly progressive renal insufficiency an apparent improvement in renal function as evidenced by a gradual decrease in the blood urea over a period of months. However, this is unusual and, because it has been shown that hydralazine does not significantly affect renal blood flow during maintenance therapy, the most that can be hoped for in the majority of these cases is that by reducing the blood pressure the incidence of other fatal consequences of hypertension, particularly cerebral haemorrhage and cardiac failure, will be lessened. While hydralazine is the drug of choice when renal disease is severe, it has been shown that the ganglion-blocking agents can be used with care and combined with hydralazine and reserpine in the treatment of these cases. As with patients with cerebro-vascular disease the aim of treatment is to produce a gradual decrease in blood pressure. However, as the ganglion-blocking agents are excreted in the urine, cumulative effects of these drugs may occur unless increments in dosage are small and made slowly. If this is not done, acute hypotension may result, with rapid worsening of renal function due to a decrease in the glomerular filtration rate. In general it is safe to use the ganglion-blocking agents if the blood urea is less than 70 mg.% provided caution is exercised and renal function is checked fairly frequently, particularly by the blood urea. The aim of treatment is to reduce the blood pressure to a level which is not associated with increasing uraemia. If the blood urea does rise it is wiser to allow the pressure to increase slightly by a reduction in the dose or by temporarily stopping the administration of the drug.

We have illustrated the development of angina during treatment with pentolinium; but this is unusual and in the majority of instances the ganglion-blocking agents are the drugs of choice in the treatment of hypertension with associated myocardial or coronary-artery disease. Often symptoms of cardiac failure are improved, as in angina. This results from the decrease in cardiac work. Hydralazine, on the other hand, may increase the severity of the symptoms of coronary insufficiency, or in some instances, as shown, produce them for the first time. It is best to avoid its use in patients with cardiac involvement or to combine it with reserpine or a ganglion-blocking drug if treatment is inadequate without it. The antagonistic effect of reserpine on the tachycardia, and of the ganglion-blocking agents on the increase in cardiac output, produced by hydralazine may prevent or reduce the incidence of side-effects.

No attempt has been made here to discuss the other toxic effects of the hypotensive drugs. Treatment may be difficult because of the parasympathetic blockade resulting from the use of ganglion blockers with consequent genito-urinary, gastro-intestinal and visual disturbances. With hydralazine the production of the drug rash, fever, blood dyscrasia or a collagen-like disease may interfere with treatment. When reserpine is used, in addition to the lesser toxic effects marked mental depression may be produced which may make it necessary to stop the drug. The efficacy of the various drugs in their hypotensive action, and the ease with which control of blood pressure is achieved with a particular drug in in-patients and out-patients has not been discussed. Only the haemodynamic effects have been presented and, although not common, in some patients these changes result in unpleasant symptoms and even harm. It is hoped, however, that a knowledge of the factors discussed will make the treatment of hypertension in the individual patient safer and control easier.

SUMMARY

The haemodynamic effects of a group of hypotensive drugs are discussed with special reference to their effects on the heart and the renal and cerebral circulations. The effects observed in hypertensive subjects of the ganglion-blocking agents and reserpine on the kidney and of hydralazine on the heart are presented and compared. Reference is also made to their effects on the cerebral circulation.

On the basis of these findings possible dangers in the use of these agents in the treatment of hypertension are pointed out and illustrated with case reports. Indications and contra-indications for the use of particular drugs or combinations of drugs in individual patients are discussed.

We are indebted to Dr. M. M. Suzman for permission to study patients under his care and to Prof. H. B. Stein, Department of Clinical Pathology, for providing laboratory facilities.

REFERENCES

1. Bennett, G., Tyler, C. and Zaimis, E. (1957): Lancet, **2**, 201.
2. Werko, L., Frisk, A. R., Wade, G. and Eliasch, H. (1951): *Ibid.*, **2**, 470.
3. Freis, E. D., Rose, J. C., Partenope, E. A., Higgins, T. F., Kelley, R. T., Shnaper, H. W. and Johnson, R. L. (1953): J. Clin. Invest., **32**, 1285.
4. Smith, J. R. and Hoobler, S. W. (1956): Circulation, **14**, 1061.
5. Crumpton, C. W., Rowe, G. G., O'Brien, G. and Murphy, Q. R. (1954): Circulat. Res., **2**, 79.
6. Mackinnon, J. (1952): Lancet, **2**, 12.
7. Freis, E. D. and Rose, J. C. (1957): Amer. J. Med., **22**, 175.
8. Mills, L. C. and Moyer, J. H. (1953): Amer. J. Med. Sci., **226**, 1.
9. Goldberg, B. (1957): Lancet, **1**, 74.
10. Moyer, J. H., Morris, G. and Smith, C. P. (1954): J. Clin. Invest., **33**, 1081.
11. Moyer, J. H., Snyder, M. and Miller, S. I. (1954): Amer. J. Med. Sci., **228**, 563.
12. Stone, H. H., McKrell, T. N. and Wechler, R. L. (1955): Anaesthesiology **16**, 168.
13. McDonald, L. and Goldberg, B. (1957): Lancet, **1**, 77.
14. Ford, R. V., Moyer, J. H. and Spurr, C. I. (1953): J. Clin. Invest., **32**, 1133.
15. Schroeder, H. A. (1952): Arch. Intern. Med., **89**, 523.
16. Carter, A. B. and Payne, R. W. (1956): Lancet, **2**, 537.
17. Abrahams, D. G. and Wilson, C. (1957), *Ibid.*, **1**, 68.
18. Moyer, J. H., Snyder, H. B., Johnson, I., Mills, L. C. and Miller, S. I. (1953): Amer. J. Med. Sci., **225**, 379.
19. Wilkinson, E. L., Backman, H. and Hecht, H. H. (1952): J. Clin. Invest., **31**, 872.
20. Zion, M. M., Goldberg, B., Gear, J. H. and Whidborne, J. (1953): S. Afr. J. Clin. Sci., **4**, 275.
21. Redisch, W., Wertheimer, L., Delisle, C. and Steele, J. M. (1954): Circulation, **9**, 68.
22. Hafkenschiel, J. H. and Lindauer, M. A. (1953): *Ibid.*, **7**, 52.
23. Vanderkolk, K., Dontas, A. S. and Hoobler, S. W. (1954): Amer. Heart J., **48**, 95.
24. Moyer, J. H. (1954): Ann. N.Y. Acad. Sci., **59**, 82.
25. Winsor, T. (1954): *Ibid.*, **59**, 61.
26. Moyer, J. H. (1953): Arch. Intern. Med., **91**, 419.