TREATMENT OF HYPERTENSION BY ORAL METHONIUM COMPOUNDS

BY

A. J. M. CAMPBELL, M.B., F.R.F.P.S.

Medical Registrar, Royal Alexandra Infirmary, Paisley

J. GIBSON GRAHAM, M.D., F.R.F.P.S.

*Senior Physician, Royal Alexandra Infirmary, Paisley ;**Associate Physician, Western Infirmary, Glasgow*

AND

R. D. H. MAXWELL, M.B., Ch.B., B.Sc.

May and Baker, Ltd.

For almost two years we have used methonium compounds in the treatment of hypertension, and during this time have examined their action upon nearly 100 patients, of whom a fair cross-section have been followed up and observed in detail.

Hexamethonium, pentamethonium, and hexamethylene bis-dimethylethyl ammonium ("M. & B. 1863") in bromide, chloride, iodide, and tartrate salts have been used. Our chief aim has been to establish, where possible, control of the hypertension and relief of symptoms mainly by the oral dosage of one of these compounds.

Since the original clinical investigations of the effect of pentamethonium and hexamethonium upon the cardiovascular system (Arnold and Rosenheim, 1949; Arnold, Goetz, and Rosenheim, 1949), a series of reports have appeared upon their therapeutic application. Smirk and Alstad (1951), giving these drugs chiefly parenterally, have described the precise control of pressure which is obtainable. Saville (1950), Turner (1950), and Mackey and Shaw (1951b), together with Campbell and Robertson (1950), have, with oral administration, obtained a reasonable depression of the blood pressure of many of their cases, accompanied by a clinical improvement comparable at times to that seen when the drug is given parenterally. The action is much less constant and less apparent when assessed by the effect upon the pressure, and Locket, Swann, and Grieve (1951) have recorded that in their series there was little effect upon the pressure of out-patients.

We have treated hypertensive patients with methonium compounds when their response to dietary limitation and sedation was unsatisfactory, and by careful examination have excluded patients with hypertension of remedial origin. Renal disease was not regarded as a contraindication, and several cases of chronic nephritis with hypertension and severe symptoms were treated.

It is known that most patients with hypertension may be maintained symptom-free by severe dietary restriction and sedation in hospital, but it is equally recognized that often when these patients return home or to work there follows a reversal of improvement both in symptoms and in blood pressure. In the absence of any treatment of the underlying cause of the hypertension there is every indication for an out-patient therapeutic measure which would enable these patients to be maintained in reasonably good health, with an arrest of progress of their symptoms and signs.

We gave methonium compounds intravenously, intramuscularly, subcutaneously, and orally, and tended to use parenteral routes for investigation and the oral route for treatment. Latterly we employed combined oral and subcutaneous administration when the pressure response to oral administration was unsatisfactory. Parenteral dosage consisted in the cautious administration of 10–15 mg. of hexamethonium bromide initially, with increase in quantity and frequency until up to 300 mg. in divided doses was given daily. Oral dosage begins with a single tablet, followed by a progressive increase in frequency and quantity to a maximum of 12–16 tablets a day. Tablets of comparable methonium content were used—that is, a 250-mg. tablet of hexamethonium bromide, which is equivalent to a 350-mg. tablet of the bitartrate and to 125 mg. of M. & B. 1863 bromide.

At no time was more than 4 g. of hexamethonium bromide given daily, as activity is not proportional to dosage beyond this level, other than a possible local effect upon the bowel. Clinical results are tabulated in three groups.

1. Essential Hypertension

This group comprised most of our cases, their ages ranging from 29 to 67 years. All had a diastolic pressure above 115 mm. Hg. Of these patients 35 who could conveniently attend for regular examination were observed at short intervals for a period of 4–18 months, the average duration of treatment being 12 months. Hexamethonium was used in 25 and M. & B. 1863 in 10, in both bromide and bitartrate salts.

In every case methonium treatment was preceded by at least 14 days' rest in bed, with sedation and dietary limitation. Cases were selected for treatment only when the response was either disappointing or absent.

Effect upon Signs and Symptoms

The incidence of the signs and symptoms of 16 male and 19 female patients with essential hypertension are reproduced in Table I.

Results are expressed by the classification of Wagener and Keith (1939), which is a clinical assessment and is also of some prognostic value.

TABLE I

Symptoms	Incidence	Signs	Incidence
Headache	29	Cardiac enlargement	10
Lassitude	24	Left ventricular preponderance	16
Vertigo	13	Orthopnoea	8
Dyspnoea	26	Cardiac asthma	1
Palpitation	10	Congestive cardiac failure	3
Precordial discomfort	9	Albuminuria	2
Angina pectoris	3	Previous cerebral vascular disorders	6
Encephalopathy	6	Fundal changes:	
Mental deterioration	8	Grade I	8
		Grade II	20
		Grade III	3
		Grade IV	4

TABLE II.—Number in Each Group by the Classification of Wagener and Keith Before and After Treatment

Group	Before Treatment	After Treatment
I	—	1
II	2	23
III	29	10
IV	4	1

Table II shows the change in grading after treatment—that is, a marked reduction in symptoms and signs. Clinical improvement was obtained in 23 out of 35 cases, with results

similar to those recorded by Smirk and Alstad (1951). Most striking was the relief of headache, and this could be obtained in some patients with a dosage too low to influence systemic blood pressure. Regression of papilloedema, when present, and organization of exudates and haemorrhages were noted. Dyspnoea was markedly reduced, and over a period of months reduction in size of the heart was seen when enlargement was present before treatment. The most remarkable effect was the return of most of these patients to a state of normal activity, either to work or to domestic duties. There were a number of failures. Two young adults with a symptomless hypertension were treated prophylactically without producing a fall in pressure. One patient developed a hypertensive encephalopathy during treatment, and in another two cases there was a possible extension of a recent cerebral thrombosis. One patient with severe headaches and a previous cerebral thrombosis had no relief of headache despite a satisfactory fall in pressure.

Effect upon the Blood Pressure

The assessment of the long-term effect of hexamethonium on the blood pressure is difficult. We found that in many

FIG. 1.—Typical response of blood pressure to M. & B. 1863.

cases it is possible to produce by oral and by parenteral administration of the methonium compounds a fall much greater than is seen during rest in bed alone, and this fall bears no relation to that obtainable during profound sedation such as the sodium amyltal test. When these drugs were used parenterally it was possible to obtain low levels of pressure, as Smirk and Alstad (1951) have described. Treatment was mainly by the oral route, which differs from parenteral administration in that the response is much slower, single doses producing a much less definite effect. It is generally necessary to administer the drugs for several days, during which time a fall in the pressure is observed in favourable cases, either beginning immediately or after several days, suggesting a cumulative effect. During this initial period of treatment one-third of the patients had diastolic pressures of under 100 mm. In a further one-third the effect upon the pressure, while considerable, was not so pronounced, and in the remaining one-third the systolic and diastolic pressures fell less than 20 mm. The fall was generally greater in the systolic than in the diastolic pressure. An increase of dosage does not produce any greater response, but the addition of parenteral administration was usually effective in producing lower pressure levels.

The maximum effect is found about the seventh to fourteenth day of treatment. A typical response is recorded in Fig. 1.

The blood pressures of out-patients show an initial progressive rise, and the drug loses some of the original effective-

ness during the first weeks of treatment. Subsequently tolerance does not appear to increase for a period of one to two months, and this not in all patients. Tolerance developed more rapidly to M. & B. 1863 than to the other compounds. Withdrawal of treatment for a period of a few weeks or less is usually followed by some loss of this tolerance, and resumption must be cautious. While tolerance to pentamethonium and hexamethonium was interchangeable, this did not always apply to tolerance developed to M. & B. 1863 and hexamethonium. Locket, Swann, and Grieve (1951) have attributed much of the effect upon pressure to the high concomitant dosage of bromide. In six cases we substituted for hexamethonium bromide similar tablets of potassium bromide with the same bromide ion content, and found a steady rise in pressure and recurrence of symptoms identical with results obtained by drug withdrawal. Further, hexamethonium bitartrate was found to be as effective therapeutically as hexamethonium bromide.

Fig. 2 shows the effect of hexamethonium bromide and bitartrate upon the blood pressure.

FIG. 2.—Effect of hexamethonium bromide and bitartrate on blood pressure.

2. Chronic Nephritis

Table III records the effect of hexamethonium bromide upon five patients with chronic nephritis with marked hypertension, impairment of renal function, and fundal changes. In each case some reduction of pressure has been possible, with good alleviation of symptoms and signs. Poor renal function in these cases was not a contraindication to treatment. Renal pathology, however, was unaltered, and two of these patients died during treatment—one from cardiac failure and the other from uraemia.

3. Malignant Hypertension

Two young patients with progressive hypertension and grave signs and symptoms were treated, their initial progress having been recorded previously by Campbell and Robertson (1950).

Case 1.—A married woman aged 22 was found in the third month of her pregnancy to have marked hypertension, which was unaltered when pregnancy was terminated at the

TABLE III

Age and Sex	Before Treatment			Treatment with Hexamethonium							
	Initial B.P.	Symptoms	Signs	Renal Function			Average B.P.	Dosage g./day	Symptoms	Signs	
				Alb. (Esbach)	Volhard-Fishberg max.						Blood Urea mg./100 ml.
					Conc.	Dil.					
41 F. ..	275/150	Severe	Severe	2	1018	1012	65	200/125	3.5	Minimal	Moderate
39 M. ..	220/140	"	"	Tr.	1015	1002	35	205/120	3	"	"
22 F. ..	225/165	Minimal	Minimal	1	1010	1002	30	210/135	2	Absent	Minimal
46 M. ..	260/180	Severe	Moderate	1	1010	1010	30	250/150	3	Moderate	Moderate
15 F. ..	230/130	"	Severe	2	1010	1010	130	180/110	2.5	"	"

fifth month owing to a steady rise in pressure, with dimness of vision and increasing headaches. During the subsequent three months in hospital her condition deteriorated, with increasing blood pressure and the appearance of albuminuria, and the prognosis seemed to be very poor. Hexamethonium bromide in an average daily dosage of 2 g. was administered for six weeks, producing a fall in pressure from 220/135 to 140/90, with disappearance of headaches, visual improvement to normal, and regression of fundal changes from grade IV to grade II. During the past year she has been keeping house and leading a full life with no treatment whatsoever. However, during this period her albuminuria has tended to increase and her blood pressure rose steadily, reaching 180/105, so we decided to make a further attempt to modify her blood pressure. Marked sensitivity to hexamethonium was found, and, because of hypertensive vertigo, continuous administration does not appear at present to be advisable. It seems likely that the course of the disease has been modified, and that she has been given a useful extension of life.

Case 2.—This patient was a man aged 30, whose early treatment has previously been described. Subsequent progress was less favourable in that there was no arrest of his progressive renal lesion, but his general condition before death, which occurred eight months after the beginning of treatment, was good enough to permit of his discharge and even return to employment. Death was occasioned by uraemia, and the post-mortem findings were those of malignant hypertension.

Side-effects and Toxicity

The unselective action of the methonium compounds in producing a generalized interruption of the autonomic nervous system entails effects other than upon the blood pressure. Reference to this in the production of constipation and paralytic ileus has been made in the literature, particularly by Campbell and Robertson (1950), Bourne and Hosford (1951), and Mackey and Shaw (1951a), and transient effects upon accommodation and salivation have been described. The side-effects of M. & B. 1863 have not been significantly different in any respect.

No abnormal sensitivity to the initial dosage of methonium compounds orally was encountered, but early in our work two sudden circulatory collapses followed 100 mg. of hexamethonium bromide parenterally as a first dose.

During the earlier part of this investigation two patients developed bromide rashes and one-third of those treated had bromide retention accompanied by drowsiness, fatigue, depression, and muscular weakness. Substitution of the bitartrate of chloride salts resulted in the disappearance of these symptoms with no diminution of therapeutic response, as already recorded by Campbell and Robertson (1951).

Overdosage of one of the methonium compounds produced a circulatory collapse.

A woman aged 59 had a blood pressure of 210/170 when first seen, and this pressure fell to 220/120 after four weeks in bed. She had severe symptoms of hypertension, and treatment with hexamethonium bromide in amounts up to 2 g. a day produced a fall in her pressure to 115/95. She was sent home to attend as an out-patient, and during the next two months the average levels of pressure were 160/100. She was readmitted comatose with a pressure of 55/30, probably due to a gross self-administered overdosage. The response to continuous adrenaline infusion was transient and death ensued in a few hours.

Discussion

Our experience of the clinical application of the methonium compounds in hypertension accords with the early observations reported from this unit (Campbell and Robertson, 1950) and with the observations of Turner (1950), Saville (1950), and Mackey and Shaw (1951b). It has been possible to alleviate or to remove symptoms and to effect a disappearance or marked regression of physical signs, resulting in

reasonable health, compatible in most cases with the patient's return to useful activity and employment. No limitation has been imposed by age or severity of illness.

We are particularly interested to note that our clinical results were very similar to those obtained by Smirk and Alstad (1951), who used a more elaborate method of parenteral administration to obtain continuously lower levels of pressure than we sought. In fact, in our series we found that reduction of pressure to even 140/90 was not always well tolerated by patients who had a long history of hypertension. They complained of listlessness and fatigue.

Previous observations have been in general agreement in regard to the clinical improvements obtainable by oral dosage, but Lockett, Swann, and Grieve (1951) have not reproduced the effects upon the blood pressure described. We have observed that, during treatment, blood pressures are very labile in many patients—downwards in response to erect posture and upwards in response to emotion and anxiety. Paton (1951) has noted the difference between the effect of methonium compounds and sympathectomy, the former blocking both the sympathetic and the parasympathetic components of the autonomic nervous system, so that there is a paralysis of the compensating mechanisms which normally maintain the constancy of the blood pressure; and procedures and drugs affecting the blood pressure will produce an exaggerated response. We have found it necessary to allocate a definite weekly time of attendance at the wards, where pressures are taken regularly by the hospital staff, who are known to the patients, in circumstances providing a reasonable period of observation. Failure to observe these precautions may have led to the disappointing results obtained by some workers, in direct contrast to the pressure records made during the careful and prolonged investigation by Mackey and Shaw (1951b).

Smirk and Alstad (1951) have declared that the optimum therapy in hypertension is the establishment of low levels of pressure; and Platt and Stanbury (1950), in the assessment of sympathectomy, have used as their criterion a fall of 20 mm. in the basal diastolic pressure. We have attempted rather to obtain a moderate but definite reduction over a long period in the blood pressure of these patients compared with their pressure when first seen. White, Dimond, and Williams (1950) have surveyed the morbidity and mortality over a three-year period among 100 patients with hypertension, half of whom had been subjected to sympathectomy. They found a much higher morbidity in the control series, and at the end of three years 16% of the sympathectomized patients were dead, as compared with 58% of the controls. They point out that this is more impressive evidence of the beneficial effect of this therapeutic measure in certain cases than is the usual method of studying the effect on blood pressure alone in cases in which important complications do not exist.

Ellis (1942) has emphasized that hypertension in itself does not constitute in general a serious limitation to life expectation, but, once signs and symptoms develop, a threshold has presumably been exceeded and the prognosis is altered.

From experience with hexamethonium administered orally it seems possible that a rather lower average of pressure, with relief of symptoms and some regression of signs, may enable a proportion of hypertensive patients to return to this asymptomatic category with its more favourable prognosis. Keith, Wagener, and Barker (1938) have examined the life expectation of patients with hypertension grouped in the categories we have used, and find that 30% of group I, 42% of group II, 78% of group III, and 98% of group IV do not survive four years. Most of our patients have fallen within group III, and in up to two years of continuous observations there have been no deaths other than the one occasioned by overdosage.

Summary

Methonium compounds have been in use for up to two years, and the treatment of an unselected group of

35 patients with hypertension and severe symptoms and signs is described. These compounds were used orally with variable results upon the blood pressure, but in 23 of the 35 patients there was a good symptomatic improvement with regression of the signs.

Hexamethonium also produced a symptomatic improvement in five patients with severe chronic nephritis and two with malignant hypertension.

We are grateful to Dr. E. Robertson for his work during the early part of this trial and to other members of the hospital staff for their assistance. Mr. E. J. Baines, of the New Products Division of May & Baker Ltd., kindly made available the supplies of the compounds used.

REFERENCES

- Arnold, P., Goetz, R. H., and Rosenheim, M. L. (1949). *Lancet*, 2, 408.
 — and Rosenheim, M. L. (1949). *Ibid.*, 2, 321.
 Bourne, G., and Hosford, J. (1951). *Ibid.*, 1, 527.
 Campbell, A., and Robertson, E. (1950). *British Medical Journal*, 2, 804.
 — (1951). *Lancet*, 1, 797.
 Ellis, A. (1942). *Ibid.*, 1, 1.
 Keith, N. M., Wagener, H. P., and Barker, N. W. (1938). *Trans. Ass. Amer. Phys.*, 53, 81.
 Locket, S., Swann, P. G., and Grieve, W. S. M. (1951). *British Medical Journal*, 1, 778.
 Mackey, W. A., and Shaw, G. B. (1951a). *Ibid.*, 1, 1205.
 — (1951b). *Ibid.*, 2, 259.
 Paton, W. D. M. (1951). *Ibid.*, 1, 773.
 Platt, R., and Stanbury, S. W. (1950). *Lancet*, 1, 651.
 Saville, S. (1950). *Ibid.*, 2, 358.
 Smirk, F. H., and Alstad, K. S. (1951). *British Medical Journal*, 1, 1217.
 Turner, R. (1950). *Lancet*, 2, 353.
 Wagener, H. P., and Keith, N. M. (1939). *Medicine*, 18, 317.
 White, P. D., Dimond, E. G., and Williams, A. (1950). *J. Amer. med. Ass.*, 143, 1311.

M. & B. 1863, A HOMOLOGUE OF HEXAMETHONIUM, IN TREATMENT OF HYPERTENSION

BY

S. LOCKET, M.B., B.S., M.R.C.P.

Physician-in-Charge, Medical Unit

P. G. SWANN, M.D., M.R.C.P.

Senior Registrar, Medical Unit

W. S. M. GRIEVE, M.Sc., Ph.D., F.R.I.C.

Biochemist

AND

H. P. PLAYER, M.R.C.S., L.R.C.P., D.R.C.O.G.

Late Registrar, Obstetric Unit

Oldchurch Hospital, Romford, Essex

Following work by Paton and Zaimis (1949), Organe, Paton, and Zaimis (1949), and Arnold and Rosenheim (1949), pentamethonium and hexamethonium compounds have been used for the investigation and treatment of hypertension and peptic ulceration (Kay and Smith, 1950, 1951). It has been the experience of some (Freeman, 1950; Locket, Swann, and Grieve, 1951; Banton, 1951) that the oral administration of these in hypertension may fail to produce and maintain a lower blood pressure. Smirk (1950, 1951) and Frankel (1951) have suggested that, therapeutically, hexamethonium bromide should be given subcutaneously, much as insulin is given, the patient being instructed to inject an appropriate dose once or twice daily, or even more frequently.

Bromidism (Rosenheim, 1951; Holt and Litchfield, 1951; Locket *et al.*, 1951; Campbell and Robertson, 1951; Sommerville and Allan, 1951), cerebral thrombosis (Locket *et al.*, 1951; C. F. J. Cropper, 1951, personal communication), coronary thrombosis and death (Hirson

and Kelsall, 1951; Locket *et al.*, 1951) have been recorded with these drugs, and in our opinion injection by the patient himself in doses adequate to produce any fall in blood pressure can be an extremely dangerous procedure.

In a previous paper (Locket *et al.*, 1951) we expressed the view that much of the subjective improvement recorded in these patients was due to sedation, reassurance and its consequent relief of anxiety, and possibly other measures instituted, such as a salt-free diet. We did not feel, in view of the natural history of essential hypertension, that any of the symptomatic improvement could reasonably be attributed to the oral administration of the methonium compounds when used by us. Ayman (1930) pointed out that all methods of treatment of hypertension have in common the "enthusiastic treatment of a worried patient," and to this he attributed most of their success.

Through the good offices of Dr. R. Forgan, Messrs. May and Baker Ltd. have kindly provided us with a supply of hexamethonium bitartrate, and also an analogue of hexamethonium known at the moment as "M. & B. 1863." The chemistry of this new compound and related derivatives is described by Barber and Gaimster (1951) and the pharmacology by Wien and Mason (1951). It was originally issued as the bromide salt, but now as the bitartrate. Experimentally it is two to four times as active as hexamethonium bromide (C6) as a ganglion-blocking agent, and therefore might be expected to work in smaller dosage by mouth, with possibly a more sustained action. The formulae given below show the relation between M. & B. 1863 and C6.

M. & B. 1863

Hexamethonium Bromide

For our trials M. & B. 1863 was issued in tablets of 125 mg. of the bromide or 175 mg. of the bitartrate, for oral use only; it was also available in solution for injection.

Most patients have received the drug by mouth only, but a few have had increasing subcutaneous or intramuscular injections of hexamethonium bromide or M. & B. 1863. After 48 hours these have been given oral M. & B. 1863. The dose of this compound was increased until a fall in blood pressure occurred or side-effects prevented any further increase. Most of our cases received no M. & B. 1863 from midnight to 6 a.m.

This communication is mainly based on a detailed analysis of our results in the treatment of 14 patients, both as in-patients and as out-patients. Since completing this review, however, we have also given M. & B. 1863 to many others, both as in-patients and as out-patients. We do not feel that these later results have differed in any way from those obtained in the 14 recorded cases. In all we have used the drug in more than 40 cases.

These results and conclusions relate to the long-term treatment of hypertension. We have found that a small intravenous dose (5 mg. of M. & B. 1863) will produce a most dramatic amelioration of dyspnoea in pulmonary oedema and "cardiac asthma" due to left ventricular failure in hypertension (not associated with coronary thrombosis). The results in some cases were infinitely better than when