COMMUNICATIONS

OCULAR EFFECTS OF METHONIUM COMPOUNDS*

BY

A. J. BARNETT

Clinical Research Unit, Alfred Hospital, Melbourne, Australia

SINCE the demonstration by Paton and Zaimis (1948) of the ganglionic blocking activity of the pentamethonium and hexamethonium compounds, the pharmacological action of these drugs in man has been fairly extensively studied, and trials have been made of their clinical use in arterial hypertension and duodenal ulcer. However, only brief and scattered mention has been made of the ocular changes resulting from their use. Thus, Burt and Graham (1950) stated that after intravenous injection of these compounds the pupils became slightly dilated, but the light reflexes remained brisk, and two subjects experienced transient loss of accommodation. Drucker and others (1950) reported a fall in intra-ocular pressure in two patients who were given 50 mg. pentamethonium iodide intravenously. Campbell and Robertson (1950) noted regression of papilloedema and of other pathological fundus changes in certain cases of severe hypertension treated with hexamethonium bromide.

In the course of an investigation of the activity of these drugs in patients suffering from severe hypertension, the ocular effects noted were considered of sufficient interest to warrant a separate short communication. The observations to be reported fall under two heads:

(a) immediate ocular changes noted during investigations into the relative activity of penta- and hexamethonium bromide given by intramuscular injection,

(b) changes in the ocular fundi seen in patients suffering from severe hypertension treated with pentamethonium bromide over a prolonged period.

I. Ocular Effects of Methonium Compounds given Intramuscularly

(a) OBSERVATIONS IN HYPERTENSIVE PATIENTS.—In seven patients suffering from severe hypertension, intramuscular injections of pentamethonium bromide and hexamethonium bromide (2 mg./kg. body weight in each instance) and distilled water were given on different days. The order of injections was varied from case to case. Observations were made, at intervals of 15 minutes or less, during a control period of at least 30 minutes and for a minimum of 3 hours following the injection, of the pupil size, reaction to light and accommodation, and ability to focus for near vision. The intra-ocular pressure was measured with a Schiötz tonometer; usually

* Received for publication March 13, 1952.

at least two readings were made before the injection and several afterwards. (Concurrently, records were made of the pulse rate, the systolic and diastolic arterial blood pressure, and the gastric acid content in response to a gruel test meal procedure.) The mode of conducting the investigation will be apparent from Fig. 1.

FIG. 1.—Effects in a patient with arterial hypertension on pulse rate, blood pressure, gastric acidity, and certain ocular features produced by intramuscular injection of equal amounts of hexa- and pentamethonium bromide 2 mg./kg. body weight.

G Gruel meal. R to L reaction to light. R to A reaction to accommodation.

The results are summarized in Table I, opposite. It will be noted that, although the response varied from patient to patient, the ocular effects from the intramuscular injection of the penta- and hexa- compounds were similar in each.

The intra-ocular pressure fell in all six cases in which it was recorded, (It was not possible to measure the intra-ocular tension in one patient who was orthopnoeic.) The greatest fall recorded was 16 mm. Hg, the least 4.5 mm., and the average 9.3 mm. The fall was apparent within 30 minutes of the injection and was still present when recording was terminated, in one case as long as 255 minutes after the injection (Table II, overleaf).

The effect on the power of accommodation for near vision, and on the

TABLE I
EFFECTS OF INTRAMUSCULAR INJECTION OF PENTAMETHONIUM
BROMIDE (P.M.B.) AND HEXAMETHONIUM BROMIDE (H.M.B.)

Feature Observed	No. of Cases	Injection of P.M.B. (2 mg./kg.)		Injection of H.M.B. (2 mg./kg.)		Concordant Effect from Injection of P.M.B. and H.M.B.	Discordant Effect from Injection of P.M.B. and H.M.B.			
<i>A. Ocular Effects</i>		Effect Present	Effect Absent	Effect Present	Effect Absent					
Fall in Intra-ocular Pressure	6*	6	0	6	0	6	0			
Cycloplegia	7	3	4	3	4	7	0			
Loss of Reaction to Light ...	7	4	3	4	3	7	0			
Loss of Reaction to Accommodation	7	4	3	4	3	7	0			
<i>B. Non-Ocular Effects</i>		Rise	Fall	No Change	Rise	Fall	No Change			
Pulse Rate	7	4	3	0	4	3	0	7	0	
Blood Pressure {	Systolic	7	0	6	1†	0	7	0	6	1†
	Diastolic	7	0	4	3†	0	6	1†	5	2†
Gastric Acidity	6‡	0	5	1	0	5	1	6	0	

* One patient was orthopnoeic, so it was not possible to measure the intra-ocular pressure.

+ One patient with labile hypertension was normotensive on the day of injection of P.M.B. In another patient the diastolic blood pressure was lower on the day of injection of P.M.B.

‡ One patient was achlorhydric and thus no effect of P.M.B. or H.M.B. on the gastric secretion could be observed.

reaction to light and accommodation, also varied from patient to patient but was not related to the other ganglionic blocking effects of the drugs, for marked reduction in arterial blood pressure and diminution of gastric acidity occurred in certain cases in which these ocular functions were not affected.

The change in pupil size has not been charted as it was not found possible to maintain constant illumination. However, in some cases a slight dilatation of the pupil, sometimes with deviation from its circular outline, was noted.

With the use of hexamethonium bromide in the investigation and treatment of persons suffering from arterial hypertension, the effect of the intramuscular injection of this drug on the pupillary reactions and power of accommodation has since been noted in an additional series of patients (Table III, overleaf). The findings suggest that ocular effects are more likely with a dose of 2 mg./kg. and above, than with one of 1 mg./kg. and below. The numbers of cases observed are however too small for a firm conclusion to be drawn.

(b) OBSERVATIONS IN A PATIENT SUFFERING FROM CHRONIC GLAUCOMA.—As it was considered that the lowering of intra-ocular pressure by drug action might be of value therapeutically, the effect of injecting hexamethonium bromide was observed in a patient suffering from chronic glaucoma.

TABLE II
EFFECT OF INTRAMUSCULAR INJECTION OF PENTAMETHONIUM BROMIDE (P.M.B.) AND HEXAMETHONIUM BROMIDE (H.M.B.) (2 mg./kg.) ON INTRA-OCULAR PRESSURE (mm. Hg)

Patient	Age (yrs)	Sex	P.M.B.				H.M.B.			
			Pre-injection Level	Lowest Recorded (and time after injection)	Last Recorded (and time after injection)	Maximum Fall (Mean 9.1)	Pre-injection Level	Lowest Recorded (and time after injection)	Last Recorded (and time after injection)	Maximum Fall (Mean 9.3)
V. W.	40	F	17	13.5 (60')	13.5 (110')	4.5	18.5	13.5 (155')	14 (255')	5
S. C.	34	F	22	8 (205')	8 (205')	14	19	6 (120')	8 (210')	13
E. P.	54	F	26	10 (80')	10 (80')	16	24	12 (130')	12 (130')	12
V. K. (Fig. 4)	38	M	17.5	11 (60')	13.5 (195')	6.5	17	11 (90')	14 (200')	6
C. D. (Fig. 3)	40	F	20.5	12 (130')	12 (170')	7	19	13 (60')	14 (165')	6
H. F.	42	M	17	10.5 (90')	12 (180')	6.5	17	10 (170')	10 (170')	7

TABLE III
EFFECTS OF INTRAMUSCULAR INJECTION OF HEXAMETHONIUM BROMIDE (H.M.B.)

Dose (mg./kg.)	No. of Cases	Ocular Effects			Non-Ocular Effects				
		Loss of Reaction to Light	Loss of Reaction to Accommodation	Cycloplegia	Fall in Blood Pressure*		Change in Pulse Rate*		
					Systolic	Diastolic	Rise	Fall	No Change
0.5	1	0	0	0	1	1	0	1	0
1	4	1	0	0	4	4	1	1	2
2	13	9	9	4(10+)	13	11	2	1	10
2.5	2	2	2	0(1+)	2	1	0	0	2
3	1	0	0	1	1	1	0	0	1

* Fall in blood pressure of less than 10 mm. Hg or alteration of pulse rate of less than 10 beats per minute was recorded as no change.

† Figures in brackets show number of cases in which test for cycloplegia was made. (In some cases this could not be done because of impaired vision.)

Case Report

H. C., male, aged 72 years, had noted visual disturbance ("stars with tails, crescents, and dashes of light") in his right eye for 12 months. This condition was ameliorated by the use of pilocarpine drops. When he closed his right eye, objects appeared "out of focus". The intra-ocular pressure in the right eye was 50 mm. Hg and in the left eye 33 mm. Blood pressure was 180 mm. Hg systolic, 105 mm. Hg diastolic. An intra-

muscular injection of 65 mg. (1 mg./kg.) of hexamethonium bromide (Fig. 2) was followed by a marked fall in the intra-ocular pressure to 30 mm. Hg in the right eye and to 20 mm. in the left. There was also a marked fall in the blood pressure to 105 mm. Hg systolic, and 80 mm. Hg diastolic.

(c) DISCUSSION.—There is a difference of opinion concerning the nervous control of the formation of the aqueous humour. Because of the observation that a fall in intra-ocular pressure occurred during an infusion of the adrenergic blocking agent "Dibenamine", Christensen and Swan (1949) suggested that the "secretion" of the aqueous humour in man may be controlled by the sympathetic nerves. On the other hand, Davson (1950) has found in rabbits that section of the cervical sympathetic nerve causes a rise in the intra-ocular pressure and that stimulation of the cut end of the nerve causes a fall.

The fall in intra-ocular pressure noted after the intramuscular injection of hexamethonium bromide might result from general vascular effects from reduction in blood pressure, or from local effects on the eye from blockade of either the sympathetic or parasympathetic nerves supplying the organ. In either case it might be due to decreased rate of formation or increased rate of removal. The question of the relation of the fall in intra-ocular pressure to the fall in blood pressure may be answered by comparing the effect on the intra-ocular pressure of the injection of methonium compound in normotensive persons (in whom there is often no great fall in blood pressure) with that in hypertensive persons. The question as to the part played by sympathetic and parasympathetic block may be answered by noting the effect of the injection of a small amount of methonium (not sufficient to produce general vascular effects) into the superior cervical and ciliary ganglia respectively.

Observation of the fall in the intra-ocular pressure after the intramuscular injection of methonium compounds suggests the possibility of their use in the treatment of glaucoma. It should be remembered, however, that in certain patients suffering from hypertension there may be a marked, perhaps embarrassing, fall in blood pressure after the injection. For this reason measures for restoring the blood pressure should be at hand. *Nor*-adrenaline (*NOT* adrenaline) would appear to be the physiological antidote.

FIG. 2.—Effects in a patient with chronic glaucoma and arterial hypertension on pulse rate, blood pressure, and ocular tension produced by intramuscular injection of hexamethonium bromide 1 mg./kg. body weight.

Cycloplegia and loss of reactions to light and accommodation would be expected from synaptic blocking in the ciliary ganglion. The fact that they are present in some cases and not in others is unexplained. The cycloplegia may be a nuisance in treating patients with these drugs, but the inconvenience can be minimized by supplying suitable convex lenses for reading.

As stimulation of the sympathetic nerves causes dilatation of the pupil and stimulation of the parasympathetic nerves causes constriction, the administration of a drug interfering with the activity of both these components of the autonomic nervous system would be expected to produce no great change in pupil size, as is indeed the case.

II. Effects of Continued Administration of Methonium Compounds in Patients suffering from Severe Arterial Hypertension with Retinopathy

(a) OBSERVATIONS.—The effect of continued administration of pentamethonium bromide has been noted in six patients with severe diastolic hypertension and marked retinal changes. All six patients showed haemorrhages and exudates in the ocular fundi and five had papilloedema. Following a trial of the responsiveness to the drug given by intramuscular injection, oral therapy was commenced, the dosage varying from 0.5 to 2.0 g. pentamethonium bromide* at 8-hourly intervals.

The ocular fundi were examined by a physician and by an ophthalmologist before beginning treatment and at intervals thereafter. In certain cases an artist's painting of the ocular fundi was made before and after treatment.

In all six patients there was absorption of soft exudates and haemorrhages, and lessening of papilloedema occurred in the five cases in which this was present. The changes in the ocular fundi were not closely related to the fall in blood pressure. In two of the patients the latter was considered unsatisfactory and the treatment was stopped. However, in both these patients the condition of the fundi had improved during treatment, and in one relapse occurred after its cessation. Treatment with pentamethonium bromide was therefore resumed in both patients with continued improvement in the condition of the fundi in both and a late reduction in the blood pressure in one.

Two patients whose fundi were depicted by an artist before and after treatment are described below.

Case Reports

Case 3, C. D., married female, aged 40 years, admitted to hospital on January 10, 1951, suffering from malignant hypertension. Blood pressure 260/146.

Ocular Fundi.—Slight papilloedema present, more marked on the right side; arteries showed increased light reflex and irregularity of calibre, mainly in small vessels; scattered flame haemorrhages, hard exudates, and a few soft exudates present (Fig. 3a).

Therapy.—Oral treatment with pentamethonium bromide was begun on January 25, 1951. Dosage varied between 0.5 and 1.5 g. 8-hourly.

* "Lytonsium" syrup, May and Baker.

FIG. 3(a).—Case 3, ocular fundi before beginning methonium treatment.

FIG. 3(b).—Case 3, ocular fundi 9 weeks after beginning methonium treatment.

By March 5, 1951, all soft exudates and nearly all haemorrhages had absorbed hard, exudate was somewhat more apparent, and swelling of the disk less (Fig. 3*b*). By May 15, 1951, condition of ocular fundi was further improved; though the disk edges were still a little blurred no actual swelling was seen.

In this patient there was also a definite hypotensive effect from the administration of the pentamethonium bromide. The pressure readings varied, but recordings of the diastolic blood pressure in the region of 100 mm. Hg were common.

Case 4, V. K., male, aged 38 years, admitted to hospital on February 5, 1951, suffering from malignant hypertension. Blood pressure 220/146.

FIG. 4(a).—Case 4, ocular fundi before beginning methonium treatment.

FIG. 4(b).—Case 4, ocular fundi 11 weeks after beginning methonium treatment.

Ocular Fundi.—Appearance on October 19, 1950, shown in Fig. 4(a). Since that time he had spent several weeks rest in bed in a Repatriation Hospital, and, although the fundus picture was not identical with that depicted in the figure, bilateral papilloedema, exudates, and haemorrhages were still present.

Therapy.—Treatment with pentamethonium bromide was begun on February 20, 1951, at first with intramuscular injection of 100 mg. 4-hourly, changing 2 days later to oral therapy (2 g. 8-hourly). This was stopped on February 26 because it failed to produce a significant lowering of blood pressure. However, examination of the ocular fundi on March 5, 1951, showed that there had been some absorption of soft exudates and haemorrhages in each eye. Treatment with pentamethonium bromide was recommenced on March 14, 1951 (2 g. 8-hourly), and the condition of the ocular fundi continued to

improve. By May 8, 1951 (Fig. 4b), papilloedema had diminished, soft exudates had disappeared, and only a few tiny haemorrhages were seen.

Although the hypotensive effect in this patient was at first unsatisfactory, there was a definite reduction in the blood pressure after several weeks' treatment. About May 8, 1951, blood pressure was 150/110 mm. Hg.

(b) DISCUSSION.—It may be thought that the changes described in the ocular fundi might be due not to the drug, but to a natural remission, or to other treatment instituted at the same time as the administration of the methonium compound.

Although the changes described in the ocular fundi in these cases (papilloedema, haemorrhages, exudates) are usually considered of very serious import, indicating that prognosis for life is poor, yet in certain cases natural remission has occurred and hypertensive patients have lived for several years after the detection of papilloedema (Keith and Wagener, 1950).

The subsidence of these changes in all the cases in the series treated with pentamethonium bromide is so contrary to the experience with the disease in patients receiving no specific treatment that one finds it hard to believe that they occurred spontaneously.

It is still possible, of course, that the beneficial changes were due to some factor other than the administration of the drug. Thus Kempner (1949) has described regressive changes in the ocular features of severe hypertension treated by rice diet, and it is common experience that hypertensive patients benefit from simple rest in bed. However, no dietary restrictions were adopted in these patients (except a reduction diet in one patient who was overweight), the period of rest in bed was usually no more than two weeks (during the stage of investigation and in certain cases during intramuscular injection of the drug), and no other special treatment was given apart from that previously taken by the patient. Improvement in the condition of the ocular fundi has continued, since the patients became ambulant and in some cases returned to work.

It would therefore seem highly probable that the beneficial effects described were due to the administration of the pentamethonium bromide. It is not possible to state in what way they are brought about. They are not necessarily related to a fall in blood pressure, as in two cases improvement in the condition of the ocular fundi occurred without any significant hypotensive effect. A similar result has been noted in some patients after sympathectomy (Smithwick, 1944). Increased blood supply to the retina (possibly due to interference with release of "sympathin" accomplished by sympathetic block) is a possible cause of the improvement. It may be that the effects are due not entirely to the methonium ion but also to the associated bromide ion. (High serum bromide levels have occurred in some of the patients.) Further speculation on the mode of action of the methonium compounds in producing beneficial effects in the fundi would not seem profitable at this stage.

Summary

(1) When given by intramuscular injection in a dose of 2 mg./kg. to hypertensive patients, penta- and hexamethonium bromide constantly produced a fall in the intra-ocular pressure. The effect on the reaction to light, reaction to accommodation, and power of accommodation for near vision varied from patient to patient.

(2) In a patient suffering from chronic glaucoma (who also had benign arterial hypertension), the intramuscular injection of hexamethonium bromide in doses of 1 mg./kg. produced a marked fall in intra-ocular pressure (and also a marked fall in blood pressure). The question is raised of the possible value of the methonium drugs in treating glaucoma.

(3) Improvement ensued in the retinal conditions of six patients with severe hypertension and retinopathy treated by continued administration of methonium drugs. It is suggested that this improvement was due to the drugs.

Grateful acknowledgment is made to Dr. J. Ringland Anderson for his stimulating interest in this work, to Dr. W. M. Box (Ophthalmic Surgeon, Alfred Hospital) and Dr. H. H. Johnson (Assistant Ophthalmic Surgeon, Alfred Hospital) for opinions concerning the ocular fundi of the hypertensive patients, and to Dr. H. H. Johnson for recording the intra-ocular pressure in the patient suffering from chronic glaucoma. The paintings of the ocular fundi were made by Miss I. G. Hill. The methonium compounds were generously supplied by Messrs May and Baker Ltd.

REFERENCES

- BURT, C. C., and GRAHAM, A. J. P. (1950). *Brit. med. J.*, **1**, 455.
 CAMPBELL, A., and ROBERTSON, E. (1950). *Ibid.*, **2**, 804.
 CHRISTENSEN, L., and SWAN, K. C. (1949). *Trans. Amer. Acad. Ophthal. Otolaryng.*, **53**, 489.
 DAVSON, H. (1950). *J. Physiol., Lond.*, **111**, 55P.
 DRUCKER, A. P., SADOVE, M. S., and UNNA, K. R. (1950). *Amer. J. Ophthal.*, **33**, 1564.
 KEITH, N. M., and WAGENER, H. P. (1951). *Arch. intern. Med.*, **87**, 25.
 KEMPNER, W. (1949). *Ann. intern. Med.*, **31**, 821.
 PATON, W. D. M., and ZAIMIS, E. J. (1948). *Nature, Lond.*, **162**, 810.
 SMITHWICK, R. H. (1944). *Arch. Surg., Chicago*, **49**, 180.