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CHLOROTHIAZIDE AND HYDROCHLOROTHIAZIDE IN MANAGEMENT OF HYPERTENSION

BY

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The advent of chlorothiazide constituted an important advance in the management of hypertension. It has proved of value as an adjuvant to other hypotensive drugs (Tapia *et al.*, 1957; Heider *et al.*, 1958; Barnett and Marshall, 1958; Freis *et al.*, 1958; Rochelle *et al.*, 1958). In some cases it is effective when used alone (Hollander and Wilkins, 1957; Hall and Owen, 1959).

As a diuretic agent hydrochlorothiazide has been found to be equally active in a dosage between one-tenth and one-twentieth that of chlorothiazide (Richterich, 1958; Ford, 1959; Moyer *et al.*, 1959; Fleming *et al.*, 1959).

In the present communication our clinical findings in the use of these drugs, alone and in combination with other hypotensive agents, are reviewed. A detailed comparative study of the effects of electrolyte and fluid excretion produced by the two drugs, together with observations on their mode of action in lowering blood-pressure, will be presented elsewhere (McQueen and Morrison). However, certain observations on the practical differences between the two drugs are contained in this paper.

Method

Blood-pressures while under treatment were assessed on day tests at the hypertensive clinic, during which six to eight readings in the sitting and standing posture were recorded. The figures quoted are the means of the average blood-pressures in each posture. The basal blood-pressure was recorded by the technique as recommended by Smirk (1957), after a night in hospital following heavy sedation with pentobarbitone. Chlorothiazide (C.) or hydrochlorothiazide (H.C.) was either added to an existing regime consisting of a ganglion-blocking agent or a rauwolfia alkaloid, or a combination of such drugs, or given at the beginning of treatment, with subsequent addition of other drugs. Cases in which C. or H.C. was added to a regime already in operation had in general either somewhat unsatisfactory blood-pressure control—as reflected in the tables illustrating the effects of addition of C. or H.C.—or had satisfactory control only at the cost of undue side-effects. It is advisable on addition of C. or H.C. to reduce the dosage of ganglion-blocking agent often to approximately two-thirds of the original.

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Findings

In a total clinic population of some 400 patients who attended regularly, C. or H.C. has been used in 203 cases either as an adjuvant to the existing regime or, exceptionally, as the sole form of therapy.

In most instances the dosages used were C., 500 mg., and H.C., 50 mg., twice daily. All patients were given potassium chloride as 0.33-g. sugar-coated tablets in a daily dosage of 1 to 2 g. In addition, they were advised to include plenty of fruit or fruit juice in their diet whenever possible. The definitive form of therapy adopted in 203 cases is shown in Table I.

TABLE I.—*Definitive Form of Therapy in* 203 *Patients Receiving Trial of Chlorothiazide or Hydrochlorothiazide*

C. or H.C. plus ganglion-blocking agent ± rauwolfia alkaloid	147
,, ,, ,, ,, rauwolfia alkaloid	26
,, ,, ,, alone	30

Use in Association with Ganglion-blocking Agents

The amount of ganglion-blocking agent required for a satisfactory regime was considerably reduced. Many patients in whom parasympathetic side-effects made the regime excessively uncomfortable were very much improved. When frequent episodes of postural hypotension occurred with a dosage of ganglion-blocking agent adequate to maintain satisfactory levels, addition of C. or H.C. and appropriate reduction of the dosage of the ganglion-blocking drug often enabled fully satisfactory control to be maintained without the occurrence of such episodes. Nine patients out of 119 were eventually able to dispense with ganglion-blocking drugs. The results of those cases in which we have multiple readings at day tests before and after the addition of C. or H.C. to the regime are shown below. Dosage reduction was evident with both quaternary ammonium compounds and the secondary and tertiary amine ganglion-blocking agents (Table II). It should be pointed out that these patients were selected because blood-pressure control in many was unsatisfactory. Blood-pressure levels after addition of C or H.C. were lower than before (Tables III and IV), and

TABLE II.—*Dosage Requirement of Ganglion-blocking Agent for Satisfactory Hypotensive Regime Before and After Addition of C. or H.C. (mg. per 24 Hours)*

	Pentolinium (31 Patients)	Mecamylamine (17 Patients)	Pempidine (14 Patients)	Chlorisondamine (6 Patients)
Before ..	535	41·6	22·4	554
After ..	403·5	28·5	16·1	329
Reduction	24%	31%	28%	41%

TABLE III.—*Pentolinium* (31 *Cases*) *Blood-pressure in mm. Hg*

		Mean of Averages of Day Tests		Mean of Trough Pressure
		Sitting	Standing	Standing
Before addition of C. or H.C.	Systolic	180·3 S.D. 24·0	177·3 S.D. 24·8	156·9 S.D. 27·2
	Diastolic	108·2 S.D. 15·3	107·9 S.D. 17·1	97·4 S.D. 20·4
After addition of C. or H.C.	Systolic	151·9 S.D. 13·0	148·6 S.D. 15·8	129·2 S.D. 19·7
	Diastolic	97·1 S.D. 9·1	97·3 S.D. 10·1	86·4 S.D. 12·5

TABLE IV.—*Mecamylamine* (17 *Cases*). *Blood-pressure in mm. Hg*

		Mean of Averages of Day Tests		Mean of Trough Pressure
		Sitting	Standing	Standing
Before addition of C. or H.C.	Systolic	175·3 S.D. 16·5	177·7 S.D. 20·9	159·6 S.D. 20·4
	Diastolic	105·7 S.D. 7·7	108·7 S.D. 9·8	100·0 S.D. 10·4
After addition of C. or H.C.	Systolic	147·1 S.D. 19·3	142·9 S.D. 20·2	127·7 S.D. 21·0
	Diastolic	92·5 S.D. 14·0	92·2 S.D. 14·9	84·8 S.D. 17·7

therefore the degree of dosage reduction was probably somewhat less than in cases in which blood-pressure levels before and after addition of C. or H.C. were the same.

In Tables III and IV the means of the averages of day tests before and after the addition of C. or H.C. to regimes including pentolinium and mecamylamine illustrate the improved control. Similar changes were observed with pempidine and chlorisondamine.

C. or H.C. Plus a Rauwolfia Alkaloid

In 26 cases C. or H.C. plus a rauwolfia alkaloid proved the most satisfactory regime. Reserpine was most commonly employed, but rescinnamine and canescine were used in some, especially when there appeared to be any special risk from depression. Considerable increase of the hypotensive action was obtained when rauwolfia alkaloids were combined with H.C. or C. Table V shows the effect of the addition of one of the diuretic agents in 13 patients who were receiving a rauwolfia alkaloid alone (as assessed by the average of day tests before and after).

TABLE V.—*Addition of C. or H.C. Agent in* 13 *Cases Where Rauwolfia Alkaloid Was Being Used Alone*

	Mean of Averages of Day Tests		Significance of Difference
	Before Addition	After Addition	
Systolic ..	171·8 S.D. 20·6	146·1 S.D. 19·0	P<0·001
Diastolic ..	106·6 S.D. 13·2	93·6 S.D. 8·4	P<0·001

C. or H.C. Alone

A total of 30 cases have been maintained on C. or H.C. as the sole hypotensive agent. The averages of day test readings on these drugs have been compared with the basal blood-pressure. In Table VI it will be seen that, in 21 of such patients in whom both sets of data are available, the average systolic pressure on treatment fell below the systolic basal level. The diastolic value was the same.

The cases in which satisfactory control was obtained with diuretic agents alone or in conjunction with rauwolfia alkaloids were, in general, of less severity than those in which a ganglion-blocking agent was required.

Two indices are used to demonstrate this difference, the basal blood-pressures and the appearances in the fundus oculi. They are illustrated in Tables VII and VIII.

Table VII is a comparison of the basal blood-pressures. Those who required ganglion-blocking drugs will be seen to have a significantly higher basal blood-pressure. The fundal grading (Keith *et al.*, 1939) also demonstrates the greater severity of those on ganglion-blocking drugs (Table VIII). However, one patient who was treated initially with ganglion-blocking drugs for malignant hypertension is now well maintained on C. alone.

A number of cases with evidence of cerebral or myocardial ischaemia presented for treatment. These require special caution in management with the more powerful hypotensive agents, and control was preferred for many of them by C. or H.C. alone or in combination with a rauwolfia alkaloid. Of the 56 patients on one or other of the above regimes, 27 presented with evidence of cerebral or myocardial ischaemia. The smoother control obtained with the addition of a diuretic to the ganglion-blocking drug greatly benefited those who still required the more powerful agents.

TABLE VI.—*Basal Blood-pressure and Averages of Day Tests in* 21 *Cases Receiving C. or H.C. Alone*

Systolic	Basal B.P. ..	154·8 S.D. 13·8	0·05>P>0·02
	C. or H.C. ..	146·5 S.D. 15.1	
Diastolic	Basal B.P. ..	95·5 S.D. 12·8	Not significant
	C. or H.C. ..	96·0 S.D. 8·8	

TABLE VII.—*Basal Blood-pressures of Patients on Three Regimes*

	C. or H.C.+G.B. Agent	C. or H.C. +Rauwolfia	C. or H.C. Alone
Systolic ..	174·7 S.D. 22·2	150·7 S.D. 20·8	154·8 S.D. 13·8
Diastolic ..	107·4 S.D. 15·9	94·6 S.D. 18·0	95·5 S.D. 12·8

TABLE VIII.—*Fundal Grading of Patients on Various Regimes*

	Grade 1	Grade 2	Grade 3	Grade 4
C. or H.C. alone ..	14	9	6	1
C. or H.C.+rauwolfia	7	14	5	0
C. or H.C.+G.B. agent±rauwolfia	18	68	49	12

Toxic and Unwanted Side-effects

Of 170 patients who received C., 33 (19.4%) had specific complaints following the inception of therapy, while similar troubles were reported by 8 (13.1%) of the 61 patients receiving H.C. They were for the most part transitory, and are detailed in Table IX.

With the exception of one case with an acute sensitivity rash, all toxic effects of H.C. were much less severe. Nine persons stopped C., six with severe nausea and epigastric discomfort, one with severe palpitations, one with a sensitivity rash, and one with severe dysuria. Of those with gastric irritation, five were changed to H.C. with immediate benefit, only one retaining slight epigastric discomfort for a few days. The patient with severe dysuria had no further discomfort after being transferred to H.C.

TABLE IX.—*Toxic and Unwanted Side-effects*

	C.	C.H.
Nausea and epigastric discomfort	19	2
Dysuria	5	2
Skin irritation	3	1
,, sensitivity	1	1
Weakness and lethargy	2	2
Digitalis toxicity	1	
Palpitations	1	
Metabolic acidosis	1	
	33 (19·4%)	8 (13·1%)

Of 19 cases on maintenance digitalis, one female developed hypokalaemia and digitalis toxicity shortly after C. was started. This was controlled only after increasing the dose of potassium chloride to 8 g. daily. A further disadvantage of C., with its particular tendency to induce loss of bicarbonate, was seen in a 42-year-old man in whom renal impairment had resulted in a mild metabolic acidosis. When C. was added, his general condition rapidly deteriorated owing to a severe reduction of his bicarbonate reserve. This was relieved on cessation of C. He was subsequently maintained satisfactorily on a small dose of H.C. Initial weakness and lethargy have been noted on both drugs, a fact well known to occur with mersalyl; this may be due to a combination of acute reduction of plasma volume and electrolyte depletion.

We have no explanation for the puzzling dysuria present during the first week of treatment and common to both drugs.

Two men had well-documented severe hypotension, which occurred on the second day of treatment with H.C. 100 mg. daily by itself. They have since been satisfactorily controlled with H.C. 50 mg. daily.

Discussion

On the basis of the experience now available it is possible to evaluate the place of C. and the newer derivative H.C. in the management of hypertension.

The assessment of hypotensive agents requires an adequate basis for comparisons. Casual blood-pressure readings are notoriously unsatisfactory for this purpose. The state of the fundi has become the traditional method of comparison of groups of hypertensive subjects, but it is highly desirable to have also some standard and reproducible estimate of the pretreatment blood-pressure both as a basis for comparison of cases and as a standard against which to compare the results of treatment. In the present communication use has been made of the basal blood-pressure as a means of adjudging the degree of severity of the cases under observation. Reduction of blood-pressure to or below the basal blood-pressure in the unsedated ambulant patient implies active blood-pressure reduction beyond the range which would be expected from the effects of a placebo.

The assessment of the effect of therapy also has been carried out under standard conditions at the hypertensive clinic, employing a series of six or eight observations documenting the range of diurnal variation as well as the mean. In addition, the effect of posture is expressed by readings in both sitting and standing postures. An important factor limiting dosage in the control of blood-pressure with ganglion-blocking agents is the "trough" blood-pressure, or lowest level to which the blood-pressure falls in the standing posture.

With these methods it can be seen that C. or H.C. alone can produce a fall in blood-pressure to, or even below, the basal blood-pressure, and that in a number of patients (15% approximately of those attending our clinic who have been given a trial with these drugs), this constituted the optimum form of therapy. These patients were characterized by a somewhat lower average basal blood-pressure than those who required in addition, the use of a ganglion-blocking agent. However, they included a considerable number of patients with complicating cerebral or myocardial ischaemia in whom use of the ganglion-blocking agents constituted a greater hazard. A further 13% approximately of the total were adequately controlled on C. or H.C. plus a rauwolfia drug. Again these patients had an average basal blood-pressure which was significantly lower than that of the group requiring a ganglion-blocking agent. This group also included a number of patients with ischaemic complications.

The majority of our patients still required the use of a ganglion-blocking agent, and in these the adjuvant effect of C. or H.C. has been marked, producing improved control associated with reduction in the dose of the ganglion-blocking agent. As a result there has been a valuable decrease in the incidence and severity of parasympathetic side-effects. During restabilization, postural hypotension has occasionally become more apparent, but eventually it is usually less troublesome. This has been particularly advantageous in those patients in whom cerebral or myocardial insufficiency had previously appeared at the depth of the trough. After the readjustment many commented on their increased alertness and well-being—presumably a further benefit of reduced ganglion-blocking dosage.

Harington and Kincaid-Smith (1958) demonstrated that the non-quaternary ganglion-blocking agent mecamylamine was excreted more rapidly in an acid than in an alkaline urine. Pempidine, which is excreted by the same mechanism (Harington and Kincaid-Smith, 1958), is probably similarly affected. The alkalinization of the urine resulting from the carbonic anhydrase inhibitor effect of (particularly) chlorothiazide might therefore have been expected to produce a more marked enhancement of hypotension in cases where these compounds were being used than with quaternary ammonium compounds. However, the degree of dosage reduction compatible with maintenance of equivalent, or better, blood-pressure control, though greater with mecamylamine and pempidine than with pentolinium, was actually less than that found in the case of chlorisondamine, though the number of cases on the latter was small. Other agents were used in numbers too small for results to be significant.

There is no evidence that mild or moderate renal impairment reduces the efficiency of C. or H.C., but caution is necessary if there is an abnormal serum acid-base or electrolyte pattern. Reference to this is made later. Apart from minor alterations of the sodium/potassium ratio in the urine, the only important difference between the two drugs appears to be in the incidence and severity of the toxic and unwanted side-effects. In this respect H.C. appears to be an improvement on C., though both drugs produce similar untoward reactions. Fortunately, most symptoms were transitory: nausea and epigastric discomfort were most commonly encountered, probably the result of local irritation.

Dysuria was met with in both sexes, in some accompanied by a mild ache in the loins. The former symptom was severe enough in one patient on C. to

make him unwilling to continue treatment. Acute retention in association with prostatic hypertrophy occurs with mercurial diuretics, but to date we have not encountered this problem. As it would occur during the initial diuresis, it is safer to give elderly men half the recommended dosage for the first week.

Both drugs have produced typical acute skin sensitivities, and in addition an itch, which tends to remain much longer than other side-effects. Being sulphonamides, caution is necessary in prescribing C. or H.C. for patients with a history of sulphonamide sensitivity.

Of patients who were forced to stop C., six were transferred to H.C., only one reporting continuance of mild symptoms.

On a normal diet excessive depletion of body sodium has not occurred. However, in patients with congestive heart failure a restricted intake of sodium may produce the salt-depletion syndrome. More important is the increased potassium excretion which is common to both drugs. To compensate, we have given supplementary potassium chloride 1–2 g. daily. Potassium lack, in the presence of ischaemic heart disease, may precipitate cardiac arrhythmias. The association of potassium depletion and digitalis toxicity is well established (Lown *et al.*, 1951), and this phenomenon has been reported with C. (Pfeiffer, 1958; Freis, 1959). Particularly close attention to serum potassium levels is necessary in cases of ischaemic heart disease with failure, and one such case of ours required 8 g. of potassium chloride daily before the serum potassium returned to the pre-treatment level. Chronic potassium depletion may also produce renal lesions, mainly tubular and initially reversible (Relman and Schwartz, 1956), but which may later become permanent. Metabolic acidosis is often a concomitant of renal impairment, and the further depletion of bicarbonate reserve induced by C. may be especially disadvantageous under these circumstances (Watson *et al.*, 1958). H.C. may in this context be the safer of the two.

Bone-marrow depression, though recorded, is very rare, and we have not experienced it. Laragh *et al.* (1958) found that C. raised the serum uric acid, and others have reported the occurrence of joint pain, but we did not observe any such episodes in three patients with chronic gout.

Summary

Chlorothiazide and hydrochlorothiazide are important additions to the list of hypotensive drugs, and in this respect seem equally effective in doses of 500 mg. for C. and 50 mg. for H.C. Both drugs enhance the effect of ganglion-blocking agents and diminish their requirement for satisfactory blood-pressure control with consequent diminution in parasympathetic side-effects. The enhancement is obvious with quaternary ammonium compounds as well as with compounds such as mecamylamine and pempidine.

Of 203 patients receiving these drugs, 15% were managed most satisfactorily with C. or H.C. alone; 13% were controlled by a combination with a rauwolfia alkaloid. Though these patients, assessed in terms of the basal blood-pressure as well as fundal grading, were somewhat less severely hypertensive than those requiring ganglion-blocking agents, they nevertheless included a considerable proportion with completing cerebral or myocardial ischaemia, making their management in other ways difficult.

H.C. certainly had less tendency to induce gastro-intestinal and possibly other side-effects. This gives it certain practical advantages over C. Care must be taken to avoid potassium depletion with both drugs.

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COMPARISON OF TRIMETHIDINIUM AND PEMPIDINE IN TREATMENT OF SEVERE HYPERTENSION

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The value of ganglion-blocking agents in the treatment of severe hypertension is well established (Smirk, 1954; Sears *et al.*, 1959), but because of the frequency and severity of the side-effects they produce there is a constant search for effective drugs which can be used reliably by mouth and have a minimum of unwanted side-effects. In this paper we describe our experience with two recently developed ganglion-blocking agents, trimethidinium and pempidine, and have tried to assess some of their advantages and drawbacks.

Chemistry and Pharmacology

Trimethidinium (see formula) is an ionized quaternary ammonium compound (as is pentolinium), differing from pentolinium in that the two groupings on each nitrogen atom are different. Absorption from the gastro-intestinal tract is incomplete but usually fairly constant in any one person; excretion is in the urine.

Pempidine has the formula shown, and is an unionized tertiary amine (mecamylamine is a secondary amine).