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REFERENCES

- Axelrad, B. J., Cates, J. E., Johnson, B. B., and Luetscher, J. A. (1955). *Brit. med. J.*, **1**, 196.
 Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F. (1958). *Lancet*, **1**, 120.
 Beyer, K. H., Baer, J. E., Russo, H. F., and Haimbach, A. S. (1957). *Fed. Proc.*, **16**, 282.
 Chart, J. J., and Shipley, E. S. (1953). *J. clin. Invest.*, **32**, 560.
 Cort, J. H., and Matthews, H. L. (1954). *Lancet*, **1**, 1202.
 Davies, D. W., and Evans, B. (1958). *Brit. med. J.*, **1**, 967.
 de Stevens, G., Werner, L. H., Halamandaris, A., and Ricca, S. (1958). *Experientia (Basel)*, **14**, 463.
 Lesser, G. T., Dunning, M. F., Epstein, F. H., and Berger, E. Y. (1952). *Circulation*, **5**, 85.
 Nordqvist, P., Cramer, G., and Björntorp, P. (1959). *Lancet*, **1**, 271.
 Pitts, R. F., and Sartorius, O. W. (1950). *Pharmacol. Rev.*, **2**, 161.
 Read, A. E., Haslam, R. M., Laidlaw, J., and Sherlock, S. (1958). *Brit. med. J.*, **1**, 963.
 Relman, A. S., and Schwartz, W. B. (1956). *New Engl. J. Med.*, **255**, 195.
 Singer, B., and Wener, J. (1953). *Amer. Heart J.*, **45**, 795.
 Slater, J. D. H., and Nabarro, J. D. N. (1958). *Lancet*, **1**, 124.
 Zuckerman, A. J., and Chazan, A. A. (1958). *Brit. med. J.*, **2**, 1338.

HYDROCHLOROTHIAZIDE, A NEW ORAL DIURETIC

BY

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Chlorothiazide is a potent oral diuretic which is relatively free from toxic effects. Its main disadvantage is that it often causes potassium depletion (Tapia *et al.*, 1957; Bayliss *et al.*, 1958; Slater and Nabarro, 1958; Harington and Kincaid-Smith, 1958). Hydrochlorothiazide, which is a hydrogenated derivative of chlorothiazide, has recently been synthesized (de Stevens *et al.*, 1958) and has been shown to be a more potent diuretic than chlorothiazide on a weight-for-weight basis (Brest and Likoff, 1959; Ford, 1959; Moyer *et al.*, 1959). This study compares the diuretic potency of these two drugs and their effect on electrolyte excretion in normal persons and in patients with congestive heart failure.

Methods

Three normal adults, who were given a diet of constant fluid and sodium chloride content (7 g. in 24 hours), took single doses of hydrochlorothiazide at intervals of one week. The urinary water and electrolyte excretion were measured and expressed as changes from those occurring during a control period of one or two days.

Twenty-one patients with congestive heart failure were also studied. Nine of these had rheumatic heart disease, eight had ischaemic heart disease or hypertension, two had cor pulmonale, one had severe anaemia, and one had constrictive pericarditis. All these patients drank 1 litre of fluid daily and consumed a diet of constant

sodium chloride content (either 0.5 or 3 g. daily). Patients who were critically ill were excluded from the investigation. It was originally planned to give each patient either hydrochlorothiazide or chlorothiazide for three periods of three days separated from one another by a day during which no diuretic was administered. Alternate patients were to be given hydrochlorothiazide or chlorothiazide first; the other drug was to be given during the second three-day period and the first drug administered again during the third period. Thus the effects of six days' treatment with one drug would be available for comparison with the effects of three days' treatment with the other drug in each patient. This programme was completed in 11 patients; five patients deteriorated during the early part of the trial and treatment with mercurial diuretics had to be instituted; and five were treated only with hydrochlorothiazide in order to compare the effects of different doses in the same patient. The daily excretion of water, sodium, potassium, and chloride was measured during the administration of each drug and the results were expressed as changes from the mean daily excretion during the control period of one to five days which preceded each experiment. Treatment with non-diuretic drugs was begun during the control period and usually remained unchanged during the diuretic trial.

Both diuretics were given in equal oral doses at 12-hour intervals. In all patients the dose of chlorothiazide was 1 g. daily; doses of hydrochlorothiazide ranged from 0.1 to 0.4 g. daily.

Chemical Methods.—Sodium and potassium: flame photometry. Chloride: potentiometric titration with silver nitrate (Sanderson, 1952). Ammonia: aeration and titration (Peters and Van Slyke, 1932). Phosphate: colorimetric estimation after combination with molybdc acid (King, 1951). Titratable acid: potentiometric titration of urine to pH 7.40 with N/50 NaOH. Urine pH: glass electrode at room temperature. Bicarbonate: manometric technique of Van Slyke (Van Slyke and Neill, 1924).

FIG. 1.—Increase in 24-hour urine volume of a normal subject (A) after different doses of hydrochlorothiazide and chlorothiazide.

Effects on Normal Subjects

One normal subject (A) took single doses of hydrochlorothiazide or chlorothiazide at weekly intervals. The 24-hour urine volume, which was measured for one or two days before each dose of diuretic, varied between 1,032 and 1,177 ml. The increase in 24-hour urine volume was 453 ml. after 0.025 g. of hydrochlorothiazide, 1,197 ml. after 0.1 g., and 1,737 ml. after 0.2 g. (Fig. 1). After hydrochlorothiazide the diuresis always lasted for longer than 12 hours. After 0.5 g. of chlorothiazide the increase in the 24-hour urine volume was 813 ml. and after 1 g. it was 1,299 ml. The diuresis had ceased and retention of fluid had begun during the second 12-hour period after taking chlorothiazide. A similar effect was also noticed in the two other normal persons (Fig. 2).

In subject A 0.2 g. of hydrochlorothiazide increased sodium and potassium excretion to almost exactly the same extent as 1 g. of chlorothiazide (Fig. 3). The main difference in the pattern of electrolyte excretion was the greater loss of bicarbonate which occurred after chlorothiazide. Subject B responded poorly to chlorothiazide, whereas his response to 0.1 g. of hydrochlorothiazide was almost identical to that of subject A to 0.2 g.

The increased excretion of bicarbonate was associated with a rise in the pH of the urine (see Table). In four of the five subjects on whom both drugs were tested the increase in the pH of the urine was greater after administration of chlorothiazide than it was after hydrochlorothiazide.

Diuretic Effect in Patients with Congestive Heart Failure

Twenty-one patients with heart failure received hydrochlorothiazide in doses ranging from 0.1 to 0.4 g. daily. In five patients the programme for comparison

FIG. 2.—Changes in urine volume of three normal subjects in two successive 12-hour periods after single doses of hydrochlorothiazide or chlorothiazide.

FIG. 3.—Changes in electrolyte excretion of two normal subjects in 24 hours following single doses of hydrochlorothiazide or chlorothiazide.

Effect of Hydrochlorothiazide and Chlorothiazide on Urine pH

Subject	Hydrochlorothiazide Dose (g.)	Chlorothiazide Dose (g.)	Control pH	pH after Drug
A	0.2	1.0	5.40	6.27
A			5.41	7.24
B	0.1	0.5	5.83	7.24
B			6.15	7.42
C	0.1	0.5	5.90	7.04
C			5.54	7.32
D	0.05		5.59	5.16
E	0.05	0.5	5.41	5.59
E			5.42	6.10
F		0.5	6.55	7.32
G	0.1		5.78	5.77
H	0.1	0.5	5.64	6.32
H			5.78	6.52

with chlorothiazide had to be abandoned because of deterioration in the patients' condition during the first few days of the trial. Each of these patients initially received 0.1, 0.2 or 0.4 g. of hydrochlorothiazide daily, but subsequently also failed to respond to chlorothiazide.

Of the 11 patients in whom the comparison of the effect of the two drugs was completed, four received hydrochlorothiazide first and seven chlorothiazide. Seven of the 11 patients responded better to the drug which was given first. Of the four in whom this did not occur, two received chlorothiazide first and two hydrochlorothiazide.

However, taking the results as a whole it is apparent that there is no significant difference between the diuretic effect of the two drugs in the dosage employed (Fig. 4). Only one patient responded very differently to the two drugs. This may have been due to the effect of a venesection which had to be performed on the second day of the trial when she was receiving hydrochlorothiazide and her condition was deteriorating.

FIG. 4.—Average daily changes in water and electrolyte excretion produced by hydrochlorothiazide and chlorothiazide in 11 patients with congestive heart failure. Each patient received each drug for three or six days.

FIG. 5.—Average daily changes in water and electrolyte excretion occurring during first two or three days' diuretic treatment of 21 patients with heart failure. Data refer only to effects of drug which each patient received first.

On the following day her urine volume doubled, and this diuresis continued throughout the second period of the trial, when she was receiving chlorothiazide. By the third three-day period she was almost free from oedema.

Fig. 5 shows the results of the first three days' diuretic treatment in all the patients, together with the results from those patients in whom treatment had to be abandoned after less than three days. This method of comparing the action of the two drugs also fails to demonstrate any significant difference in their effects on water or electrolyte excretion. The only consistent difference between the effects of the two diuretics is the smaller excretion of chloride produced by chlorothiazide, although the sodium excretion is almost identical with that occurring during treatment with hydrochlorothiazide (Figs. 4 and 5). This probably reflects the higher excretion of bicarbonate produced by chlorothiazide; bicarbonate excretion was not measured directly in the patients with heart failure.

Five patients were treated only with hydrochlorothiazide; all had a diuresis. Three became free from oedema in from 11 to 14 days. Two were not completely free from oedema after 12 and 14 days' treatment but had lost 3.3 and 4.5 kg. in weight respectively.

Four of these five patients began treatment with 0.05 g. of hydrochlorothiazide twice daily. In three patients the sodium excretion increased when the dose was doubled two to four days later, but in no patient did an increase to 0.4 g. a day produce any further rise in sodium excretion. Changing the dose of hydrochlorothiazide did not have any consistent effect on potassium excretion.

Toxic Effects

The plasma potassium concentration of 11 patients was measured before and after treatment with hydrochlorothiazide. In nine patients the plasma potassium concentration fell. In three patients who were treated for only three days the changes in potassium concentration were not significant, but in seven patients treated for 10 days or longer the changes in potassium concentration ranged from -0.4 to -3.2 mEq/l. and in five of these patients the reduction was more than 1 mEq/l. The greatest reduction was seen in a female patient treated for $4\frac{1}{2}$ months, during which her plasma potassium concentration fell from 5.1 to 2.9 mEq/l. During the next three weeks it rose again to 4.3 mEq/l., although no potassium supplements had been given during this period. None of the patients had symptoms attributable to potassium depletion.

No consistent change was observed in the plasma sodium concentration after treatment with hydrochlorothiazide. However, the plasma chloride

concentration fell in seven out of eight patients. The reduction in concentration ranged from 3 to 13 mEq/l. after 3 to 17 days' treatment.

No toxic effects on the kidneys were observed. The albuminuria which was usually present in the untreated patients with heart failure diminished as their oedema subsided.

The white cells of the blood were counted and examined before and after treatment with hydrochlorothiazide in eight patients. In one patient the count was unchanged after treatment, in one it had risen slightly, and in the other six it had fallen. In five of these patients the total white count remained above 4,000 per c.mm. and no toxic effects were observed in the granulocytes. This reduction may simply be a reflection of the general improvement in the patients' condition. In one patient the total white count fell from 5,200 to 3,000 per c.mm. after three months' treatment. The granulocyte count was then only 1,500 per c.mm.; no toxic changes were seen in these cells. The total count subsequently rose again without any alteration in treatment.

Only 3 of the 21 patients had symptoms which might possibly be attributed to the drug. They all complained of abdominal distension and flatulence after taking the tablets. Two of these patients had suffered a substantial fall in plasma potassium concentration. No patient complained of nausea, vomiting, or disturbance of the bowel habit during treatment.

Discussion

Hydrochlorothiazide is a potent oral diuretic. In this investigation 0.1 g. of hydrochlorothiazide produced about the same diuretic effect as 1 g. of chlorothiazide in patients with congestive heart failure. Previous estimates of the relative weights of hydrochlorothiazide and chlorothiazide which produce equal sodium diureses in man have ranged from 1:80 (Ford, 1959) to 1:21 (Richterich, 1958) and 1:10 (Moyer *et al.*, 1959). Since at least 10 of our patients with heart failure had been receiving chlorothiazide at home immediately before their admission to hospital the present results may be slightly biased against chlorothiazide. Ford and Moyer *et al.* found that 0.1 g. of hydrochlorothiazide produced almost maximum diuresis in patients with heart failure, and our results confirm the impression that a daily dose of 0.1 to 0.2 g. of the drug produces a maximum diuresis in such patients. It is probable that smaller doses may serve to maintain such patients free from oedema after recovery. Since the action of hydrochlorothiazide is more prolonged than that of chlorothiazide single daily doses of hydrochlorothiazide should prove satisfactory, while chlorothiazide needs to be administered at least twice daily.

The increments in potassium excretion produced by chlorothiazide and hydrochlorothiazide were almost identical, and it seems likely that hydrochlorothiazide will produce potassium depletion as readily as chlorothiazide, and potassium supplements should therefore be given during treatment. Since the amounts of sodium and chloride excreted in the urine after hydrochlorothiazide are almost equimolecular, this drug may produce hypochloreaemic alkalosis in the same way as the mercurial diuretics. It would be interesting to know whether this causes resistance to the new drug and whether the diuresis can be augmented by the

simultaneous administration of ammonium or potassium chloride.

The lack of toxic symptoms observed in this study confirms the findings of the previous workers, who report that the drug occasionally causes nausea.

Milne *et al.* (1958) believe that the decreased excretion of mecamlamine caused by chlorothiazide is due to the alkalinity of the urine excreted during treatment with this diuretic. It may be expected, therefore, that hydrochlorothiazide, which is a weaker inhibitor of carbonic anhydrase and which produces less change in urine pH, will have a smaller effect on the excretion of mecamlamine. However, in preliminary studies Ford found that hydrochlorothiazide had a similar effect to chlorothiazide in potentiating the action of rauwolfia and ganglion-blocking agents in the treatment of hypertension. It therefore seems probable that hydrochlorothiazide has some hypotensive action in hypertensive patients apart from any effect it may have on the excretion of other hypotensive drugs.

Summary

The effects of hydrochlorothiazide on urinary water and electrolyte excretion have been studied in three normal persons and 21 patients with congestive heart failure.

Hydrochlorothiazide is a powerful oral diuretic producing a marked increase in the rate of excretion of sodium and chloride and a smaller increase in potassium excretion. It increases the excretion of bicarbonate to a less extent than chlorothiazide. In most normal subjects and patients with heart failure, 0.1 g. of hydrochlorothiazide produces about the same diuretic response as 1 g. of chlorothiazide. In patients with heart failure maximum diuresis is usually produced by 0.1 to 0.2 g. of hydrochlorothiazide.

Hydrochlorothiazide produced a reduction in plasma potassium concentration in 9 out of 11 patients studied. The plasma chloride concentration was simultaneously lowered. The only toxic symptoms noted were in 3 out of the 21 patients with heart failure who complained of abdominal distension and flatulence while taking the drug.

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REFERENCES

- Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F. (1958). *Lancet*, **1**, 120.
- Brest, A. N., and Likoff, W. (1959). *Amer. J. Cardiol.*, **3**, 144.
- de Stevens, G., Werner, C. H., Halamandaris, A., and Ricca, S. (1958). *Experientia (Basel)*, **14**, 463.
- Ford, R. V. (1959). *Sth. med. J. (Bgham., Ala.)*, **52**, 40.
- Harington, M., and Kincaid-Smith, P. (1958). *Lancet*, **1**, 403.
- King, E. J. (1951). *Micro-analysis in Medical Biochemistry*, 2nd ed., p. 136. Churchill, London.
- Milne, M. D., Scribner, B. H., and Crawford, M. A. (1958). *Amer. J. Med.*, **24**, 709.
- Moyer, J. H., Fuchs, M., Irie, S., and Bodi, T. (1959). *Amer. J. Cardiol.*, **3**, 113.
- Peters, J. P., and Van Slyke, D. D. (1932). *Quantitative Clinical Chemistry*, **2**, 549. Baillière, Tindall and Cox, London.
- Richterich, R. (1958). *Experientia (Basel)*, **14**, 458.
- Sanderson, P. H. (1952). *Biochem. J.*, **52**, 502.
- Slater, J. D. H., and Nabarro, J. D. N. (1958). *Lancet*, **1**, 124.
- Tapia, F. A., Dustan, H. P., Schneckloth, R. A., Corcoran, A. C., and Page, I. H. (1957). *Ibid.*, **2**, 831.
- Van Slyke, D. D., and Neill, J. M. (1924). *J. biol. Chem.*, **61**, 523.