Our figures show, in common with all other surveys, an increased proportion of child deaths in the category under 1 year and a diminishing proportion over this age. Also, from a study of the time of the year and the relative proportions of sudden death, we find that, on top of the known annual variation in the time of these acute deaths (Bowden and French, 1951; Stowens, 1957), the proportion of sudden deaths, as well as the absolute numbers, is also much higher in this period.

The apparent variation in site of death during the week and week-end could be a reflection of the patient-doctor relationships at different times of the week—that is, in a number of cases, when I have been able to discuss the child's death later, it seems that the parents knew that the child was ill. They did not realize that it was severely ill, and thought that they would wait until the doctor was back or on duty again on Monday before calling him in, or taking the child to the surgery. It would seem likely that this increased death rate at home at the week-ends is a reflection of this attitude of parents to the medical profession. Parents have also stated that they have known that their own doctor was not on duty at the week-end, and that one of the partners would be called in, and for that reason they had delayed calling in a doctor.

The feature, however, which is probably of even more importance is that an almost similar number of deaths occur during the week-days as at the week-end, which suggests that, even if the doctors had been called to the children, in a large number of instances the death could not certainly have been prevented. On the other hand, we know of many instances in which, but for the prompt intubation and aspiration in the reception rooms of the hospital, children would have died from tracheobronchitis.

Summary

A study was made of 249 children over the age of 7 days who died in Sheffield during the years 1949 to 1956. During these seven years the number of deaths from disease with symptoms of less than 48 hours' duration appeared to remain constant, and possibly increased relative to other diseases.

The proportion of rapid deaths from disease of longer standing appeared to remain constant up to the age of a year. Over that age rapid death became less common.

Death face-down in a pillow showed no particular age distribution.

Of the deaths 120 occurred at home, 13 in an ambulance, and 116 in hospital.

Rapid deaths appeared to be both absolutely and relatively more common in the winter than in the summer months of the year.

While the total number of deaths varied little on different days of the week, there appeared to be a greater tendency for deaths to occur at home at the week-end, and in ambulance or hospital on a week-day.

REFERENCES

- Banks, A. L. (1958). *Monthly Bull. Minist. Hlth*, **17**, 182.
 Boucher, C. A. (1958). *Proc. roy. Soc. Med.*, **51**, 395.
 Bowden, K., and French, E. L. (1951). *Med. J. Aust.*, **1**, 925.
Brit. med. J., 1957, **1**, 1411.
 — 1958, **2**, 684.
 Emery, J. L., and Crowley, E. M. (1956). *Brit. med. J.*, **2**, 1518.
 Stowens, D. (1957). *A.M.A. J. Dis. Child.*, **94**, 674.
 Swinscow, D. (1951). *Brit. med. J.*, **2**, 1004.

DIURETIC EFFECT OF HYDROFLUMETHIAZIDE

BY

J. H. JONES, M.B., M.R.C.P.

Registrar in Clinical Pathology

AND

J. VERRIER JONES, B.M., M.R.C.P.

Lately Senior House Officer in Medicine

Queen Elizabeth Hospital, Birmingham

Following the synthesis of chlorothiazide, a benzothiadiazine derivative, various studies, including those of Ford *et al.* (1957) and Bayliss *et al.* (1958), showed that it was the most effective compound yet produced in the search for non-mercurial and non-carbonic-anhydrase-inhibiting oral diuretic agents.

Hydroflumethiazide (6-trifluoromethyl-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide) is a new benzothiadiazine derivative. This paper reports the response of 21 oedematous patients treated with this drug, and also the effect of a single dose of hydroflumethiazide on the pattern of urinary excretion in five non-oedematous males.

Preliminary studies (Kobinger and Lund, 1958; Holbooth *et al.*, 1958; Sele, 1958) have shown that hydroflumethiazide is an effective oral diuretic and is between 15 and 20 times more active than chlorothiazide in comparable dosage. The present studies confirm this diuretic effect and in addition show that hydroflumethiazide does not significantly inhibit carbonic anhydrase.

Method

Twenty-one consecutive patients with oedema were treated with hydroflumethiazide. The patients were observed for a minimum of three days before hydroflumethiazide was given, except for five cases whose clinical condition did not justify delay. With three exceptions the duration of hospital treatment was between three and four weeks. Half the patients had received various diuretics, and all except three of the cases of heart failure (cases 7, 11, and 12) had been digitalized before admission. Throughout their stay in hospital patients received a low-sodium diet (15 mEq daily). Potassium supplements were not given as a routine. Hydroflumethiazide was given in a dose of 100 or 200 mg. at 6 a.m. and 12 noon on four consecutive days per week. Patients were weighed daily, and 24-hour urine collections were made from midnight to midnight. Weekly blood counts were performed, and serum electrolytes were measured at least once a week. In nine patients urine electrolytes were measured daily.

In the study of the effect of a single dose of hydroflumethiazide the subjects were five adult male convalescent patients who had never been oedematous. On the control day urine was collected under liquid paraffin every two hours for the first 12 hours, and the urine passed in the last 12 hours was collected and studied as a single specimen for each patient. The volume and sodium, potassium, and chloride content of each specimen were measured, and on the specimens

passed during the first 12 hours the pH, titratable acidity, and bicarbonate content were also estimated immediately after collection. A similar procedure was followed on a subsequent day after 400 mg. of hydroflumethiazide had been given at 8 a.m. On the control and test days the food and fluid intake of each patient were matched.

Standard chemical methods were used for estimations. Sodium and potassium were measured by flame photometry, chloride by mercuric-nitrate titration (Schales and Schales, 1941). The pH of the urine was estimated with the glass electrode pH meter. The carbon dioxide was measured manometrically and the urine bicarbonate was derived from the carbonic-acid-bicarbonate curve according to pH (Peters and Van Slyke, 1932). The titratable acidity was measured by titration of the urine with standard NaOH to a pH of 7.4, measured with the glass electrode.

Results of Clinical Trial

Twenty patients with congestive cardiac failure and one with the nephrotic syndrome were treated with hydroflumethiazide. The cases are summarized and classified according to their aetiology in the accompanying Table. In 16 of the patients with congestive cardiac failure there was a satisfactory response. These patients became free of oedema, and there was no recurrence when they were fully ambulant before discharge. This response did not bear any relation to the underlying cause of the heart failure.

The patient with the nephrotic syndrome (Case 21) had developed oedema while receiving 200 mg. of

cortisone daily. She responded well to hydroflumethiazide, and was free of oedema on discharge, having been maintained on the same dose of cortisone throughout her stay in hospital.

During this study four of the patients who had severe heart failure died. The details of these cases are as follows.

Case 4.—A patient with aortic stenosis and incompetence in severe low-output failure who showed no response to hydroflumethiazide.

Case 13.—A patient with hypertensive heart disease and recurrent attacks of congestive cardiac failure. Her initial response to hydroflumethiazide was moderate, and after the addition of 2 ml. of thimerin on alternate days she showed an improved diuresis. Nevertheless, some oedema persisted until her death.

Case 16.—A patient with cor pulmonale secondary to pulmonary fibrosis. She failed to respond to hydroflumethiazide. Thimerin, 2 ml. on alternate days, was added, and after the first injection she showed a slight diuresis. Further injections were without effect, and oedema persisted until she died.

Case 19.—A patient with a syphilitic aortic aneurysm which had recently ruptured into the pulmonary artery. After an initial good response he died in irreversible high-output failure.

In the nine patients in whom urinary electrolytes were measured daily, it was found that the maximum sodium and chloride excretion coincided with the maximum water diuresis, which was usually on the second day of the first course. Sodium excretion on the day of maximum response ranged from 60 to 300 mEq in 24 hours, and at first the loss of sodium tended to be slightly greater than the loss of chloride. As the oedema decreased and the sodium excretion fell, the diuretic produced in some cases a disproportionately greater chloride excretion. In none of the 21 cases was any significant change in serum-sodium level noted. Most cases developed some hypochloroemia, with serum-chloride figures of 90 to 95 mEq per litre.

The amount of potassium lost in the urine was extremely variable. In most cases hydroflumethiazide produced some increase in potassium excretion, which was more pronounced when the sodium diuresis had declined.

The average potassium loss on days on which hydroflumethiazide was not given was 33 mEq daily. This compares with the average excretion of 34 mEq of potassium daily during the first course of hydroflumethiazide and with 42 mEq daily during the final course before discharge. The greatest increase in the potassium excretion was seen in Case 17, whose average potassium loss without hydroflumethiazide was 44 mEq daily, and this rose to an average of 70 mEq daily during treatment.

A fall in potassium levels below normal was noted in 16 cases. The greatest differences between the initial and the final serum-potassium level was 1.3 mEq and the average fall was 0.6 mEq.

The only serum-potassium level below 3 mEq per litre was found on one occasion in Case 9, when it was 2.8 mEq per litre; but two days later this had risen to 3.4 mEq per litre. This case, and three others with serum-potassium levels between 3.1 and 3.4 mEq per litre, were the only patients with a serum-potassium below 3.5 mEq per litre after the last course of hydroflumethiazide. All these patients had previously received

Analysis of Cases

Diagnosis	Case	Age	Hydroflumethiazide mg. per Day (4 Days per Week)	Loss of Weight		Comment
				lb.	kg.	
Rheumatic heart disease	1	78	200	13	5.9	Free of oedema on discharge
	2	51	200	18	8.2	" " "
	3	53	200	8	3.6	" " "
	4	42	200	0	0	Died. See text
	5	60	200	6	2.7	Free of oedema on discharge
	6	58	400	4	1.8	" " "
	7	70	400	6	2.7	" " "
	8	37	400	11	5.0	" " "
	9	43	400	20	9.1	" " "
Hypertensive heart disease	10	76	200	7	3.2	Free of oedema on discharge
	11	60	400	3	1.4	" " "
	12	57	400	8	3.6	" " "
	13	72	400	5	2.3	Died. See text
Cor pulmonale	14	68	400	6	2.7	Also had carcinoma of prostate. Gained 5 lb. (2.3 kg.) on stilboestrol while continuing hydroflumethiazide
	15	53	400	40	18.1	Free of oedema on discharge
	16	56	400	0	0	Died. See text
Ischaemic heart disease	17	59	200	7	3.2	Free of oedema on discharge
Thyrotoxic heart disease	18	72	200	6	2.7	Free of oedema on discharge
Syphilitic aortitis	19	38	400	16	7.3	Died. See text
Congenital heart disease	20	25	200	9	4.0	Free of oedema on discharge
Nephrotic syndrome	21	42	400	12	5.4	Free of oedema on discharge

FIG. 1.—Comparison of average urine volume and sodium, potassium, and chloride excretion in five subjects over 24 hours on control day and after administration of 400 mg. of hydroflumethiazide.

FIG. 2.—Comparison of average pH, titratable acidity, and bicarbonate excretion in five subjects over 12 hours on control day and after administration of 400 mg. of hydroflumethiazide.

diuretics and had some degree of hypokalaemia on admission. No symptoms attributable to hypokalaemia were observed.

No side-effects were observed during treatment with hydroflumethiazide, and weekly blood counts showed no significant changes.

Response to Single Dose of Hydroflumethiazide

The effect of 400 mg. of hydroflumethiazide on the urine volume and sodium, potassium and chloride excretion is shown in Fig. 1, which compares the average excretion on the control day and the test day in five subjects. While the maximum effect of the drug is seen during the first eight hours, the urine volume and sodium and chloride excretion continued to be greater throughout the 24 hours of the test day. The potassium excretion, however, was less during the last twelve hours of the test day than on the control day. The excretion of chloride was slightly greater than that of sodium.

The sodium excretion on the test day was 2.1 times greater than on the control day, and at its maximum was 4.1 times greater. The potassium excretion was 1.2 times greater over the control day than over the test day, and was 1.8 times as great at its maximum.

The effect of hydroflumethiazide as a carbonic-anhydrase inhibitor was investigated by measuring the alteration in urinary pH titratable acidity, and bicarbonate excretion for twelve hours after the test dose. Fig. 2 illustrates the findings, and shows that there is no increase in the urinary pH or bicarbonate excretion, and no fall in the titratable acidity. There is thus no evidence to suggest that hydroflumethiazide significantly inhibits carbonic anhydrase activity.

Discussion

It has been shown in these studies that hydroflumethiazide in doses of 200 or 400 mg. daily is an effective oral diuretic. While no direct comparison has been made, the results suggest that on a weight-for-weight basis hydroflumethiazide is very much more active than chlorothiazide.

Studies of the diuretic effect of chlorothiazide (Ford *et al.*, 1957; Matheson and Morgan, 1958) have shown two modes of action. Like the mercurial diuretics, its primary action is to increase the excretion of chloride. In addition it resembles acetazolamide in inhibiting carbonic anhydrase and thus increasing bicarbonate excretion. It has been suggested (Slater and Nabarro, 1958; Matheson and Morgan, 1958) that the inhibition of carbonic anhydrase may be partly responsible for the hypokalaemia which sometimes complicates treatment with chlorothiazide.

Hydroflumethiazide resembles chlorothiazide and the mercurial diuretics in that it produces an almost equimolar loss of sodium and chloride. Unlike chlorothiazide or acetazolamide, however, it produces no increase in the pH of the urine or in bicarbonate excretion and no fall in hydrogen-ion excretion estimated from the titratable acidity. It therefore appears that hydroflumethiazide does not significantly inhibit carbonic anhydrase, although, like chlorothiazide, it contains the free SO_2NH_2 group in its molecule, to which this action is attributed (Mann and Keilin, 1940). These findings are confirmed by the laboratory observation that it is 100 times less active than chlorothiazide and over 5,000 times less active than

acetazolamide in this respect (W. F. J. Cuthbertson, personal communication, 1959).

Our results show that hydroflumethiazide produces some increase in potassium output in association with the greatly increased excretion of chloride. However, as hydroflumethiazide does not significantly inhibit carbonic anhydrase the additional loss of potassium through this action should not occur. This may help to reduce the likelihood of potassium depletion and the necessity for potassium supplements during treatment with drugs of the benzothiadiazine group.

Summary

A trial of a new non-mercurial oral diuretic, hydroflumethiazide, is reported. Seventeen out of twenty-one oedematous patients responded well to doses of 200 or 400 mg. daily. Two patients showed no response, and in two others an initial response was not maintained; these four patients ultimately died.

No toxic effects attributable to hydroflumethiazide were seen in any patients.

A study of the response to a single dose showed a marked increase in sodium and chloride excretion with no increase in bicarbonate loss. It therefore appears that hydroflumethiazide does not significantly inhibit carbonic anhydrase.

While some increased potassium excretion has been demonstrated, absence of significant carbonic-anhydrase inhibition might be expected to reduce the degree of potassium depletion.

We wish to thank Dr. Oscar Brenner for his interest and for allowing us to study patients under his care; Dr. J. N. Marshall Chalmers and Mr. Garfield Thomas for facilities and advice; Miss I. Florence for some of the urine electrolyte estimations; and Glaxo Laboratories, Ltd., for supplying the hydroflumethiazide ("NaClex").

REFERENCES

- Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F. (1958). *Lancet*, **1**, 120.
- Ford, R. V., Moyer, J. H., and Spurr, C. L. (1957). *A.M.A. Arch. intern. Med.*, **100**, 582.
- Hobolth, N., Thomsen, K., From Hansen, P., Hågensen, N. R., and Oresnik, J. (1958). *Ugeskr. Læg.*, **120**, 1585.
- Kobinger, W., and Lund, F. (1958). *Ibid.*, **120**, 1583.
- Mann, T., and Keilin, D. (1940). *Nature*, **146**, 164.
- Matheson, N. A., and Morgan, T. N. (1958). *Lancet*, **1**, 1195.
- Peters, J. P., and Van Slyke, D. D. (1932). *Quantitative Clinical Chemistry*, vol. 2. Baillière, Tindall and Cox, London.
- Schales, O., and Schales, S. S. (1941). *J. biol. Chem.*, **140**, 879.
- Sele, V. (1958). *Ugeskr. Læg.*, **120**, 1592.
- Slater, J. D. H., and Nabarro, J. D. N. (1958). *Lancet*, **1**, 124.

A new 204-bed hospital, designed to be "noiseless and odourless," was opened earlier this year in California as an addition to the Fresno Community Hospital. The 500-ton air-conditioning plant installed in the new buildings permits a difference in air pressure in corridors, rooms, and bathrooms, thus preventing the escape of odours from one to the other. To reduce noise, nylon carpets have been fitted in the halls and corridors, and acoustical ceilings and special vinyl-plastic-covered walls in the public areas. Other features are an all-electric kitchen from which food is served to patients in seven minutes, a pneumatic tube system for messages and small packages, and a central dictating system which enables doctors to dictate their notes by telephone from any part of the hospital. (*News Bulletin*, August, 1959, International Hospital Federation.)