FACULTY PROJECT

Oral diuretics and carbohydrate metabolism

Report from the North-west England Faculty Research Committee of the Royal College of General Practitioners

Recorder, G. H. ANDERSON, M.B., Ch.B., M.R.C.P.(G.)., M.R.C.G.P.
Lancaster

The objectives

The objectives of this study were (1) to examine the effect of oral diuretics on the glucose metabolism, (2) to determine whether any disturbances of glucose metabolism as measured by the glucose tolerance tests of these patients is temporary or permanent and (3) the frequency of such disturbance.

Review of the case histories of those in whom retrospective analysis[6, 9, 13, 14, 15, 16] suggested a diuretic induced diabetes revealed that any prospective study should be conducted over a period of at least a year in the first instance; and that even this period would only reveal a proportion of the numbers which might ultimately become diabetic, as other observers[1, 2, 3] suggest there may be a longer interval between the starting of a diuretic and the onset of resulting diabetes.

Keen and Jarrett[11] have recently re-emphasized the lack of information on these problems and reports of prospective studies[8, 10, 13] have in the main been conducted on one particular diuretic in highly controlled clinic conditions, difficult to reproduce in general practice.[8, 13]

Method

Selection of patients

Any patient who had not previously been given diuretics and was known not to suffer from diabetes mellitus or revealed by the preliminary glucose tolerance test (GTT) to be a frank diabetic was considered suitable for inclusion in the trial. Pregnant patients and those who were unwilling to undergo the necessary investigations were excluded.

Such patients were asked to have a necessary GTT prior to starting treatment, and a further GTT after one year's observation, or sooner in the event of diabetes mellitus being suspected.

The diuretic

A diuretic was administered only when it was part of the normal treatment requirement of each patient and was not specially prescribed for the purpose of this study. The choice of diuretic was left to the discretion of the physician who was asked not to alter his normal prescribing routine. He was asked to record other drugs used simultaneously and particularly to note the prescription of potassium supplements.

The primary disorder for which the diuretic was given was recorded, likewise the presence of co-existing disease which might also require treatment.

*The following College members are participating in the study; J. W. Duff, Shifnal; P. Frank, Manchester; C. Haigh, Wigan; J. Miller, Stockport; R. Moffitt, Lancaster; M. Parker, Crewe; R. Neville, Clitheroe; J. Scott, Bamber Bridge; A Whitewright, Bolton.

The recording

On finding a suitable patient fulfilling the above conditions the recording doctor arranged the initial GTT and then started treatment. A minimum of monthly urine checks (by Clinistix) was charted. This procedure was completed for the whole 12 months and finally a repeat GTT was done. Any changes of therapy throughout this period was recorded.

If glycosuria was discovered, then a GTT was done as soon as possible, and a repeat GTT at not less than a month after stopping the diuretic. Suitably printed recording charts were issued to all the doctors taking part. The recording charts included spaces for noting coincidental disease and drugs, and a history of familial diabetes, large babies and other material which might be considered relevant.

Standards adopted

For the purpose of recruitment to the study the same arbitrary grouping as used by the Bedford observers was adopted.[4, 7]

Capillary blood sugar levels in mg.	—	Normal—less than 120 mg.
100 ml. at 2 hours after 50 gm.	—	Hyperglycaemia 120–199 mg.
Glucose loading.	—	Diabetes mellitus—more than 199 mg.

This classification has the advantage of being well known in this country and at the same time allows study of border-line states as recommended by the World Health Organization.[17]

The standards adopted in interpretating abnormal GTT's are those recommended by the WHO, i.e.:

(1) Fasting capillary blood sugar level over 130 mg per 100 ml with or without glycosuria indicative of 'positive alert finding as to the probability of diabetes'.
(2) Capillary blood sugar level of 140 mg and over per 100 ml blood two hours after 50mg glucose loading indicates diabetes mellitus.

A patient recruited within the hyperglycaemic group would therefore be either border-line state (cap. blood sugar two hours after 50 g glucose—120 to 139 mg/100 ml.) or diabetic (cap. blood sugar two hours after 50 g glucose—140 mgms or higher) by internationally accepted recommendation.

Results

In the present series no case in the hyperglycaemic level was in fact studied.

The results are presented in tables which includes the geographical location of the patient to confirm that such abnormal GTT's as were recorded did not emanate all from the same laboratory. Males are listed before females.

They are not separated according to the diuretic used, as all the diuretics used belong to the same category and there is no evidence that one member of the group is more prone to cause diabetes than any other. All blood sugar levels are capillary blood sugars.

Group I

No abnormality and no alteration in the GTT (*see* table I). Fasting sugar below 120 mg and below 130 mg two hours after 50 g glucose.

Group II

Some changes in second GTT but not to abnormal levels (see table II).

Group III

Changes in fasting levels of second GT to 'alert' level (130 mg) as defined by WHO (*see* table III).

TABLE I

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary disease*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
MALES										
G.H. .. .. Stockport	49	190	68	Hypertension	Nil	Chlorthalidone 50 mg. (Hygroton 50) 1 daily	Pot. chloride 600 mg (Slow K)	—	N.A.D.	No change
H.B. .. Manchester	52	128	66	Oedema and varicose veins	Nil	Hydrochlorothiazide 12·5 mg Pot. chloride 600 mg (Esidrex K) 2 b.d. 1 month Frusemide (Lasix) 80 mg 11 months	Pot. chloride 600 mg (Slow K) 2 daily	Phenylbutazone (Butazolidin) 100 mg t.i.d.	N.A.D.	No change
J.M. .. .. Bolton	63	174	68	Hypertension	Nil	Bendrofluazide (Aprinox) 5 mg daily	Pot. chloride 600 mg (Slow K) 2 daily	Methyl dopa 250 mg (Aldomet) b.d.	N.A.D.	No change
C.R.-F. .. Shifnal	69	143	68½	Hypertension	Angina	Cyclopenthiazide 0·25 mg Pot chloride 600 mg (Navidrex K) 1 daily, 2 months 2 daily, 10 months	—	Trinitrin	N.A.D.	No change
FEMALES										
S.B. .. Lancaster	36	156	63	Hypertension	Nil	Clorexolone (Nefrolan) 10 mg t.i.d.	—	Methoserpidine (Decaserpil) t.i.d.	N.A.D.	No change
E.M. .. .. Stockport	67	133	65	Hypertension	Cholecystitis	Chlorthalidone 50 mg (Hygroton)	Pot. chloride 600 mg (Slow K)	—	N.A.D.	No change
A.W. .. Bolton	67	184	61	Hypertension	Hypothyroidism	Bendrofluazide (Aprinox) 5 mg b.d.	Pot chloride.600 mg (Slow K) 2 alternate days	Thyroxin 0·1 mg t.i.d.	N.A.D.	No change
F.S. .. .. Stockport	69	140	62	Hypertension	Nil	Cyclopenthiazide 0·25 mg Pot. chloride 600 mg. (Navidrex K)	—	—	N.A.D.	No change
J.B. .. .. Bolton	70	170	62	Hypertension	Pernicious anaemia	Bendrofluazide (Aprinox) 5 mg daily, 4 months	—	Guanethidine (Ismelin) 30 mg 3 months; 20 mg 9 months. Cytamen	N.A.D.	No change
E.L. .. .. Bolton	71	120	59	Hypertension	Cardiac failure	Frusemide (Lasix) 40 mg. 1 daily	Pot. chloride 600 mg (Slow K) 2 alternate days	Guenethidine (Ismelin) 40 mg. 4 months Methyl dopa 250 mg (Aldomet) b.d. 8 months	N.A.D.	No change
E.B. .. .. Stockport	72	174	66½	Hypertension	Colitis	Polythiazide 1 mg (Nephril)	Pot. chloride 600 mg (Leo K)	Vitamin B complex	N.A.D.	No change
E.F. .. .. Bolton	73	172	62	Hypertension	Chronic dyspepsia	Bendrofluazide (Aprinox) 5 mg daily	Pot. chloride 600 mg (Slow K) 2 alternate days	Guanethidine (Ismelin) 10 mg 5 months Methyl dopa 250 mg (Aldomet) b.d. 7 months	N.A.D.	No change

TABLE 1 continued

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary disease*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
FEMALES										
R.P. .. .. Shifnal	44	188	62	Hypertension	Nervous dyspepsia	Cyclopenthiazide 0·25 mg Pot. chloride 600 mg (Navidrex K) 1 daily 2 months	—	Prochlorperazine (Stemetil) 5 mg t.d.s. Chlordiazepoxide 5 mg Clidinium bromide 2·5 mg (Libraixn) 6 months	N.A.D.	No change
M.G. .. Manchester	46	143	63½	Oedema	Anaemia	Bendrofluazide (Aprinox) 5 mg 2 daily, 5 months	Pot. chloride 600 mg. (Slow K) 5 months		N.A.D.	No change
V.L. .. .. Manchester	48	141	64	Oedema	Varicose veins	Bendrofluazide 10 mg daily	Pot. chloride 600 mg (Slow K) 1 b.d.		N.A.D.	No change
E.J. .. .. Manchester	54	142	62½	Oedema	Varicose veins	Bendrofluazide (Aprinox) 5 mg daily, 2 months Frusemide (Lasix) 40 mg 2 daily, 10 months	Pot. chloride 600 mg (Slow K) 1 daily		N.A.D.	No change
F.H. .. Shifnal	58	144	63	Hypertension	Coronary artery disease	Cyclopenthiazide 0·25 mg Pot chloride 600 mg (Navidrex K) 1 daily, 5 months	—	Methyl dopa 250 mg (Aldomet) 1–11 daily, 4 months Trinitrin	N.A.D.	No change
M.W. .. Shifnal	60	145	62½	Hypertension	Depression	Cyclopenthiazide 0·25 mg Pot. chloride 600 mg. (Navidrex K) 1 daily	—	Amitriptyline (Tryptizol) 25 mg t.i.d. 9 months	N.A.D.	No change
J.T. .. .. Wigan	73	168	63	Hypertension	Nil	Hydrochlorothiazide 12·5 mg Pot chloride 572 mg Reserpine 0·0625 mg (Salupres) 1 daily	—	Nil	N.A.D.	No change
E.G. .. Bolton	77	165	63	Cardiac failure	Chronic bronchitis	Bendrofluazide (Aprinox) 5 mg 1 daily	Pot chloride 600 mg (Slow K) 2 alternate days	Lanatoside C (Cedilanid) t.d.s. Anti-biotics Bronchidilators	N.A.D.	No change

TABLE II

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary diagnosis*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
MALES										
D.C. .. .. Lancaster	45	172	65	Hypertension	Nil	Clorexolone (Nefrolan) 10 mg daily	—	Methyl dopa (Aldomet) b.d.	Fasting 65 mg	Fasting 90 mg
H.S. .. .. Lancaster	50	206	70	Hypertension	Nil	Clorexolone (Nefrolan) 30 mg. daily 1 month Reserpine 0·15 mg Bendrofluazide 2·5 mg (Abicol) 11 months	—	Phenobarbitone 60 mg. t.d.s.	Fasting 75 mg	Fasting 105 mg
FEMALES										
E.C. .. .. Lancaster	54	178	62	Hypertension	Nil	Frusemide (Lasix) 40 mg daily	—	Methyl dopa (Aldomet) q.i.d. 3 months Guanethidine (Ismelin) 10 mg daily, 9 months	Fasting 65 mg	Fasting 120 mg
M.B. .. .. Lancaster	64	90	61	Hypertension	—	Hydrochlorothiazide 25 mg Pot. chloride 572 mg Reserpine 0·0625 mg (Salupres) b.d.	—	Nil	Fasting 50 mg Bloo d sugar at 1 hour 140 mg	Fasting 60 mg Glycosuria at 1 hour with a blood sugar of 190 mg

TABLE III

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary diagnosis*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
MALES										
N.H. .. .. Lancaster	55	161	67	Hypertension	Peptic ulcer	Hydrochlorothiazide 12·5 mg Pot. chloride 572 mg Reserpine 0.0625 mg (Salupres) b.d.	—	Nil	Fasting 90 mg	Fasting 155 mg

Group IV

Second GTT abnormal to diabetic levels not requiring treatment (*see* table IV).

Group V

Second GTT to gross diabetic levels reversible to normal GTT on stopping the diuretic (*see* table V).

This patient developed glycosuria and other manifest symptoms of diabetes suddenly in her fourth month of treatment. She required 100 mg chlorpropamide daily during her temporary diabetes. Her fasting capillary blood sugar was 200 mg and her blood sugar at two hours after 50 mg glucose loading was 275 mg. One month after stopping her diuretic the GTT returned to normal and her glycosuria has since not returned. There is no history of diabetes in her family.

Three charts could not be completed, one of which showed a diabetic state (capillary blood sugar 193 mg per 100 ml two hours after 50 mg glucose loading) at the end of the observation period, but as no initial GTT was performed it is not proven as a diuretic induced diabetes.

Analysis

Prospective study of 27 patients taking oral diuretics produced three patients with significant diabetic changes in their GTT's compared with the GTT prior to the use of the diuretic. Four other patients showed minor changes, the significance or otherwise of which may well be determined with further observation.

Discussion

The results are neither reassuring nor surprising. Within the limitation of the small numbers involved they conform to the anticipated results based on the retrospective observations on which this project was designed.[1,2]

Administration of potassium, in this series, has not prevented impairment of glucose metabolism. Healy and his co-workers[10] have shown that depletion of total body potassium by diuretics was not accompanied by any evidence of impaired glucose metabolism in their intensively studied cases.[10] This must throw some doubt on accepting Conn's theory[5] that potassium depletion is a major factor in producing diabetes in these cases, though it may be true in the particular cases of hyperaldosteronism with which he was working.

All the diuretics used in this study contain a sulphamoylbenzine grouping and the thiazides are related to diazoxide, the powerful hyper-glycaemic drug.

The evidence confirms that there is a price to pay in using these potent diuretics which is measurable as a percentage of patients who will develop diabetes mellitus. The price may not be quite so high as might at first be thought, as apparently even the elderly can survive assault on their carbohydrate metabolic system provided the offending diuretic is stopped quite soon, but there remains the question whether permanent diabetes is induced if the diuretic is continued over a long period.

If, in this small series alone, three patients developed diabetes at the end of one year's diuretic treatment it follows that a not inconsequential number of iatrogenic diabetes similarly produced has been annually generated since 1957 when thiazides first began to be used freely in this country. Much of our modern information on the incidence of diabetes in this country stems from the Bedford and Birmingham series of observations.[7, 18] The Bedford survey was published in 1964 on work done in 1962, five years after thiazides had been widely used. They quote an incidence of over 30 per cent of cardio-vascular disease with diabetes. It seems probable that in this 30 per cent some unknown proportion had received diuretic therapy and in turn produced a percentage of iatrogenic diabetes. It would be unwise, on the basis of our small series,

TABLE IV

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary diagnosis*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
FEMALES F.L. .. Preston	.. 57	146	65	Hypertension	Nil	Hydrochlorothiazide (Hydrosaluric) 25 mg daily, 3 months Alternate days, 9 months	—	Nil	80 mg 2 hours after glucose loading	140 mg 2 hours after glucose loading

TABLE V

Patient	*Age*	*Weight lbs*	*Height ins*	*Primary diagnosis*	*Secondary diagnosis*	*Diuretic*	*Potass.*	*Other drugs*	*First GTT*	*Second GTT*
FEMALES E.H. Stockport	.. 79	154	64	Cardiac failure	Nil.	Frusemide (Lasix)	—	Pot. chloride 600 mg (Slow K)	N.A.D. *Third GTT* 1month after stopping diuretic N.A.D.	Fasting 200 mg and 275 mg 2 hours after glucose loading

to attempt to calculate what proportion of total diabetes recorded in these epidemiological studies does not represent naturally occurring disease and therefore to some extent avoidable.

Summary

Prospective studies on 27 patients using diuretics revealed two diabetics and one 'alert' (fasting blood sugar of 155 mg/100 ml) in a year's observation. Minor deteriorations are recorded in four other patients.

Acknowledgement

This study has been made possible by a generous grant to the Research Fund of the Royal College of General Practitioners by Hoechst Pharmaceuticals Limited, and this we gratefully acknowledge.

REFERENCES

1. Anderson, G. H. (1966). *Journal of the College of General Practitioners*, **12**, 197.
2. Anderson, G. H. (1967). *Journal of the Royal College of General Practitioners*, **14**, 346.
3. Breckenridge, A. *et al.* (1967). *Lancet*, **I**, 61.
4. Butterfield, W. J. H. (1967). *British Medical Journal*, **4**. 505.
5. Conn, J. W. (1965). *New England Journal of Medicine*, **273**, 1135.
6. Cranston, W. I. *et al.* (1963). *Lancet*, **2**, 966.
7. Sharp, C. L. (1964). *Proceedings of the Royal Society of Medicine*, **57**, 193.
8. Jahnecke, J. (1967). *Deutsche Medizinische Wochenschrift*, **92**, 1270.
9. Jones, I. G. and Pickens, P. T. (1967). *Practitioner*, **199**, 209.
10. Healy, J. J. *et al.* (1970). *British Medical Journal*, **1**, 716.
11. Keen, H. and Jarrett, R. J. (1970). *Update*, **2**, 1013.
12. Leading article (1965). *Lancet*, **2**, 328.
13. Schaefer, H. F. (1964). *Medizinische Welt*, **16**, 1270.
14. Schapiro, A. P. *et al.* (1961). *New England Medical Journal*, **265**, 1028.
15. Toivonen, S. and Mustala, O. (1966). *British Medical Journal*, **1**, 920.
16. Wilkins, R. W. (1959). *Annals of Internal Medicine*, **50**, 1.
17. World Health Organization (1959). Technical Report Series No. 310.
18. College of General Practitioners (1963). *British Medical Journal*, **2**, 655.