CASE REPORT

The anti-diabetic action of guanethidine

K. K. GUPTA*

M.D. Agra

County Hospital, Lincoln

A CASE was recently reported where stoppage of guanethidine treatment of hypertension in a diabetic patient resulted in a marked increase in insulin requirements and blood sugar levels (Gupta & Lillicrap, 1968). This patient had been previously receiving 20 mg guanethidine daily for 4 months for control of hypertension. An additional 24 units of soluble insulin were needed daily after guanethidine was discontinued. This raised the possibility of a significant anti-diabetic action of guanethidine. This communication describes results of a trial designed to evaluate it.

Material and methods

This study was done on three maturity onset type diabetics (Table 1). These were admitted to hospital, two for cataract extraction and one for the initiation

of dieting for obesity. All these had hypertension. There was no significant complication in any case.

All of them had been in the ward for a week on ordinary diet (no calorie restriction) before the study was commenced and no change was made during it.

Guanethidine was started in a dose of 20-30 mg daily and the dose was increased to 50-90 mg over the next few days. No side effects of guanethidine were observed. No attempt was made to push guanethidine to limits of tolerance, or to secure evidence of definite sympathetic blockade, since the aim was only to find out if guanethidine in moderate dosage has a significant anti-diabetic effect. Glucose tolerance tests were performed according to the recommendation of the British Diabetic Association (FitzGerald & Keen, 1964). After a 12-hr overnight

TABLE 1

No.	Age and sex	Disease	BP (mmHg)	Dose of guanethidine (mg/day)	Results of oral glucose tolerance tests (mg/100 ml)			
					Before treatment		After treatment	
I	51, F	Diabetes, obesity, hypertension	220/120	50	13 May 1968	20 May 1968		
					Fasting	110	120	
					$\frac{1}{2}$ hr	187	120	
					1 hr	228	177	
					$1\frac{1}{2}$ hr	228	198	
					2 hr	198	170	
					$2\frac{1}{2}$ hr	173	163	
II	61, F	Diabetes, cataract, obesity, hypertension	180/120	60	30 May 1968	4 June 1968	12 June 1968	
					Fasting	260	131	141
					$\frac{1}{2}$ hr	294	224	177
					1 hr	327	252	232
					$1\frac{1}{2}$ hr	344	302	252
					2 hr	344	278	271
					$2\frac{1}{2}$ hr	315	264	—
III	65, M	Diabetes, cataract	190/100	60 90 between second and third tests	6 June 1968	11 June 1968	20 June 1968	
					Fasting	131	145	106
					$\frac{1}{2}$ hr	224	240	181
					1 hr	302	248	244
					$1\frac{1}{2}$ hr	232	212	184
					2 hr	201	152	138
					$2\frac{1}{2}$ hr	166	134	102

* Present address: Medical Registrar, Atkinson Morley's Hospital, London, S.W.20.

fast 50 g of glucose in 200–500 ml of water was given and capillary blood collected at 0, $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2 and $2\frac{1}{2}$ hr. Samples were analysed for glucose using ferrocyanide method.

Results

The results are shown in Table 1 (page 455).

Discussion

Although oral hypoglycaemics have been in use for more than 12 years there are very few studies of their effect on oral glucose tolerance tests (GTT). Duncan, Baird & Dunlop (1956) found in a group of ten patients treated with 3 g carbutamide daily that the mean fasting blood glucose fell from 247 to 146 mg/100 ml. They commented that this treatment was without effect on glucose tolerance and rate of its absorption.

Case 2 in the present study showed a fall in fasting blood glucose from 260 mg/100 ml before treatment to 131 mg/100 ml after 5 days' treatment with guanethidine. All the three cases showed a significant improvement in oral GTT as shown in Table 1. Englehart & Vecchio (1965) reported results of oral GTT before, and 8–24 months after, administration of tolubutamide in a dose of 1 g daily. The mean blood glucose levels in the treated group were lower than the controls in all except the 120-min samples, where the adjusted values were identical. After guanethidine treatment for 5–7 days the 120-min blood glucose levels showed falls of –28, –66 and –49 mg/100 ml, respectively, with a further increase in the fall to –73 mg in Case 2 and Case 3 after 14 days treatment (Table 1). Herman (1966) using various sulphonylureas in maturity-onset type diabetics reported that eleven out of thirty-two patients showed no improvement in oral GTT; the improvement in GTT was marked in ten cases and moderate in nine cases. The improvement in oral GTT seen in the present study is comparable to the 'moderate response' group of the above series. It is thus clear that the results of the present study suggest a significant anti-diabetic effect of guanethidine, comparable to the existing oral hypoglycaemics.

The mechanism of the anti-diabetic action of guanethidine needs further study. Acute intravenous administration of guanethidine leads to liberation of adrenaline from the sympathetic nerve endings, and

also hyperglycemia (Okun, Wilson & Gelfand, 1964). On the other hand long-term oral treatment with guanethidine produces depletion of tissue stores of catecholamines (the opposite of the acute effect), and a fall in fasting blood glucose levels with improvement in oral GTT as shown by the present study. Woeber, Arky & Braverman (1966) reported reversal of abnormal oral GTT in thyrotoxic patients during guanethidine administration. Porte *et al.* (1966) showed that adrenaline interferes with the secretion of insulin by the pancreas, and Woeber *et al.* (1966) suggested that guanethidine, by reducing the sympathetic tone, could modify the insulin response to an oral glucose load. Thus, study of plasma insulin levels before and during guanethidine administration would be necessary before drawing any conclusions about the mechanism of the anti-diabetic action of guanethidine. It is of some interest to note that guanethidine, being a guanidine derivative, is related to biguanides which are already in use as oral hypoglycaemic agents.

The results of the present study would justify controlled trials to compare the anti-diabetic effect of guanethidine with that of other oral hypoglycaemic drugs.

Acknowledgment

I wish to thank Dr C. A. Lillicrap, Consultant Physician, County Hospital, Lincoln, for permission to study these patients, and to publish this report.

References

- DUNCAN, L.J.P., BAIRD, J.D. & DUNLOP, D.M. (1956) A clinical trial of BZ 55. *Brit. med. J.* **2**, 433.
- ENGELHART, H.T. & VECCHIO, T.J. (1965) The longterm effect of tolubutamide on glucose tolerance in adult asymptomatic diabetics. *Metabolism*, **14**, 885.
- FITZGERALD, M.G. & KEEN, H. (1964) Diagnostic classification of diabetes. *Brit. med. J.* **1**, 1568.
- GUPTA, K.K. & LILICRAP, C.A. (1968) Guanethidine and diabetes. *Brit. med. J.* **2**, 697.
- HERMAN, J.B. (1966) Glucose tolerance in diabetes mellitus during treatment with sulphonylurea hypoglycemic agents. *Israel J. med. Sci.* **2**, 733.
- OKUN, R., WILSON, W.R. & GELFAND, M.D. (1964) The hypoglycemic effect of hypotensive drugs. *J. chron. Dis.* **17**, 31.
- PORTE, D.J., GRABNER, A.L., KUZUYA, T. & WILLIAMS, R.H. (1966) The effect of epinephrine on immunoreactive insulin levels in man. *J. clin. Invest.* **45**, 228.
- WOEBER, K.A., ARKY, R. & BRAVERMAN, L.E. (1966) Reversal by guanethidine of abnormal oral glucose tolerance in thyrotoxicosis. *Lancet*, **i**, 895.