ocular appearances it is essential that electroretinography should be carried out as soon as possible to make or refute the diagnosis of tapetoretinal degeneration. This is the only way of eliminating the considerable period which may elapse before the diagnosis becomes evident on clinical examination, during which time an increasingly severe disturbance of behaviour may occur.

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Hyperlactataemia in Phenformin-treated Diabetics

S. K. VARMA, S. J. HEANEY, W. G. WHYTE, R. S. WALKER

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Summary

Raised fasting blood lactate levels were observed in diabetic patients on phenformin in therapeutic dosage. After an intravenous glucose load this effect was exaggerated and the lactate/pyruvate ratio increased. Withdrawal of the drug led to normal blood lactate levels and a fall in the lactate/pyruvate ratio.

Introduction

Our interest in this field was stimulated by the admission of an elderly diabetic patient who had been treated with phenformin in a dose of 150 mg daily. She was found to have hyperlactataemia and was acidotic. After withdrawal of phenformin, when the patient had recovered and was on dietary treatment alone, an oral glucose tolerance test with 50 g of glucose was carried out. Phenformin was then reintroduced and the dose built up to 150 mg/day. The glucose tolerance test was repeated. Levels of glucose and blood lactate are shown in Table I. Blood sugar levels were satisfactory but lactate levels became high. This seemed to show a relation between the use of phenformin at this dosage level and a fall in blood sugar with a coincident hyperlactataemia.

Law Hospital, Carlisle, Lanarkshire

S. K. VARMA, M.B., B.S., Medical Registrar
 S. J. HEANEY, M.B., CH.B., Medical Registrar
 W. G. WHYTE, M.B., CH.B., F.R.C.P., Consultant Physician
 R. S. WALKER, M.D., F.R.C.P., Consultant Physician

It was therefore decided to investigate the problems further in other patients by using glucose intravenously to avoid any variation in absorption and to produce a high glucose load.

Patients and Methods

Twelve patients attending the diabetic clinic were chosen. Each had had a diabetic glucose tolerance test at the start of treatment. They were reasonably stabilized on phenformin 150 mg/day and a daily diet containing 150 g of carbohydrate. Treatment with phenformin and the duration of diabetes varied from a few months to several years (Table II). Routine blood sugar levels one-and-a-half to two hours after a meal on their last three attendances at the clinic were less than 180 mg/100 ml. There was no evidence of significant renal or liver disease and they were having no other drugs. The patients were admitted to hospital and following an overnight fast venous blood samples were collected (with minimal constriction) before, and 5, 15, 30, 60, and 120 minutes after giving glucose (25 g in 50% solution, intravenously). In Cases 9 to 12 a further intravenous glucose tolerance test was carried out after phenformin had been withdrawn for at least a week and while the patients were on a diet containing 150 g of carbohydrate.

In each sample true glucose was estimated, and lactate and pyruvate were measured by the Sigma (1965) method, the blood samples having been deproteinized immediately.

Results

The results are given in Tables III and IV. In the 12 patients on phenformin the average fasting lactate level was 15.4 (range

TABLE I—Oral Glucose Tolerance Test in Elderly Diabetic

	Glucose mg/100 ml						Lactate mg/100 ml					
	Fasting	Minutes					Fasting	Minutes				
		30	60	90	120	150		30	60	90	120	150
Phenformin 150 mg/day	98	162	168	92	48	38	23.2	25.0	28.4	27.5	23.2	19.4
Diet alone	100	192	198	176	163	148	6.02	6.45	6.9	7.9	8.8	8.2

TABLE II—Details of Patients in Series

Case No.:	1	2	3	4	5	6	7	8	9	10	11	12
Sex	F.	F.	F.	F.	F.	F.	F.	M.	M.	F.	F.	F.
Age	59	58	60	74	40	62	58	40	60	33	63	57
Duration of diabetes (years) ..	5	7	10	4½	3½	3½	8	4	5	5	9	8
Phenformin therapy (years) ..	4	15/12	3	4	2	1	4	3	15/12	2/12	8/12	4

TABLE III—Intravenous Glucose Tolerance Test in Patients on Phenformin 150 mg/day

	Glucose mg/100 ml						Lactate mg/100 ml						Pyruvate mg/100 ml					
Case No.	F.	Minutes					F.	Minutes					F.	Minutes				
		5	15	30	60	120		5	15	30	60	120		5	15	30	60	120
1	123	244	244	231	213	193	20.6	21.7	20.4	18.6	16.0	17.4	1.06	1.01	0.91	0.88	1.06	—
2	95	108	151	136	112	140	21.8	22.9	23.9	24.2	23.0	19.0	0.88	1.07	1.10	1.10	1.23	—
3	109	244	332	176	139	170	29.5	32.3	37.3	32.3	36.2	37.2	0.98	0.91	1.07	1.07	0.52	—
4	241	430	365	350	321	288	14.0	13.8	15.5	16.5	18.1	19.3	0.72	1.04	0.88	1.09	0.82	0.88
5	220	390	364	312	290	243	9.7	9.4	11.9	13.0	12.3	13.0	0.60	0.57	0.66	0.85	0.60	0.69
6	61	210	—	94	42	45	15.7	19.0	—	20.7	19.8	22.5	0.85	1.01	—	1.91	1.03	1.01
7	221	396	258	174	119	122	11.7	12.3	14.1	14.3	21.0	12.4	0.50	0.54	0.96	0.57	0.85	0.44
8	202	282	268	226	105	136	11.6	11.5	17.5	15.2	17.3	12.7	0.63	0.66	0.69	0.76	0.88	—

TABLE IV—Intravenous Glucose Tolerance Test in Patients on Phenformin 150 mg/day (A) and after Withdrawal (B)

Case No.	Glucose mg/100 ml						Lactate mg/100 ml						Pyruvate mg/100 ml					
	F.	Minutes					F.	Minutes					F.	Minutes				
		5	15	30	60	120		5	15	30	60	120		5	15	30	60	120
9 { A B	120	227	203	203	185	176	10.9	10.5	11.6	11.5	13.2	9.7	0.25	0.50	0.38	0.38	0.25	0.41
	227	436	400	357	347	316	6.9	4.6	6.6	8.5	5.3	8.5	0.32	0.44	0.28	0.44	0.42	0.44
10 { A B	112	286	235	209	176	120	10.2	12.4	11.9	10.5	16.7	16.7	0.66	0.69	0.72	0.82	0.72	0.82
	187	403	357	336	281	220	6.1	5.5	7.6	5.9	5.8	8.9	0.54	0.60	0.54	0.57	0.50	0.32
11 { A B	104	413	229	194	187	131	16.1	18.0	21.6	19.4	24.5	26.5	0.78	1.04	1.01	0.96	0.98	1.5
	129	283	271	246	208	170	6.8	6.7	5.1	4.7	5.8	5.2	0.47	0.47	0.35	0.41	0.24	0.38
12 { A B	126	356	338	300	238	100	17.0	—	15.9	15.1	17.3	18.5	0.93	—	0.79	0.79	1.04	0.79
	113	267	240	229	196	167	6.3	5.8	6.7	5.5	7.3	7.5	0.44	0.54	0.47	0.41	0.57	0.47

9.7 to 29.5) mg/100 ml. After intravenous glucose there was a rise in lactate levels, highest at 60 minutes, when the average level was 19.6 mg. Pyruvate levels did not rise correspondingly. In the four patients who had phenformin withdrawn there was no significant rise in lactate or pyruvate levels following the intravenous glucose tolerance test and the average fasting lactate was 6.5 (range 6.1 to 6.9) mg/100 ml.

Biochemical Considerations.—Lactic acid accumulates in the tissues and blood either in proportion to the pyruvate levels or in excess of this (Huckabee, 1958). This latter condition occurs either in the presence of inadequate peripheral tissue perfusion or when the mitochondrial redox state is modified by alcohol, infection, or other factors, one of which is an appropriate concentration of phenformin (Tranquada *et al.*, 1966). In the normal patient venous levels of lactate are in the range 4.0 to 11.5 mg/100 ml, with a lactate/pyruvate ratio varying from 9.3 to 13.4 (Tranquada *et al.*, 1966). "Excess lactate" is recognized by an increase in this ratio. In our unpublished normal series the lactate levels were in the range of 4.0 to 9.5 mg/100 ml, with a lactate/pyruvate ratio of 8 to 12.

Discussion

There is evidence that in the treatment of diabetics with phenformin, lactic acidosis occurs (Walker *et al.*, 1960; Danowski, 1963; Proctor and Stowers, 1967; Johnson and Waterhouse, 1968; Oliva, 1969), though this has been denied and attributed to other coincidental disease (Sadow, 1969). The absence of other factors such as alcohol, tissue hypoxia, and hepatic or renal disease in our patients and the resumption of normal blood lactate levels in those in whom the drug was withdrawn point to a specific effect of phenformin. These normal lactate levels occurred in spite of inferior diabetic control. The patients who were on 150 mg of phenformin daily

were selected because they were among the few patients in the clinic to whom a dose in excess of 100 mg of the drug was given. It may be significant that though all were maturity-onset diabetics (non-insulin-dependent) there is a fairly wide range of lactate levels and lactate/pyruvate ratios. The work thus confirms the in-vitro studies of Steiner and Williams (1958), Williamson *et al.* (1963), and Schafer (1964). It shows that phenformin alone can be associated with "excess lactate" according to Huckabee's (1958, 1961) concept. The lactate/pyruvate ratio shows a mean of 22 over the whole series, while it is 13 in the four control cases, confirming the consistent lactate excess.

While these 12 patients were symptom-free, it would seem reasonable to regard them as subjects in whom one of the known additional stimuli might readily provoke lactic acidosis.

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