Phenformin and lactic acidosis

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Summary

Thirty-eight patients who presented with diabetes and a changed state of consciousness satisfied the criteria for lactic acidosis. Sixteen patients were non-ketotic, and 15 of these were receiving phenformin on admission. In all but one of these 15 patients, however, additional renal or cardiovascular abnormalities, or both, could be identified, which supported a multifactorial aetiology for lactic acidosis. Advanced age and cardiovascular and renal disease are absolute contraindications to the use of phenformin in diabetics.

Introduction

The association of lactic acidosis and phenformin treatment in diabetic patients has been recorded,^{1,2} but the relative roles of phenformin and various diseases in the induction of the lactic acidosis are unclear.^{3,4} The routine screening for lactic acidosis of all diabetic patients with altered consciousness admitted to a large general hospital lent itself to an analysis of the relative importance of various aetiological factors.

Patients and methods

Diabetic patients admitted to the Royal Adelaide Hospital with altered consciousness (excluding hypoglycaemia) were routinely assessed before treatment. Serum electrolytes, urea, glucose (SMA 6-60), and osmolality were measured. Arterial (or occasionally resting venous) pH and blood lactate were measured, lactate by the method of Marbach and Weil⁵ (normal ≤ 1.5 mmol/l (13.5 mg/100 ml)). Serum ketones were estimated by the method of Watkins and Fitzgerald⁶ using Ketostix (Ames). Ketosis was defined as the presence of serum ketones at a dilution of 1/12 or more. Lactic acidosis was defined, according to Oliva's criteria, as a lactic value of 2 mmol/l (18 mg/100 ml) or more and arterial pH less than 7.37.

Over two years we identified 38 diabetics with lactic acidosis. The figure illustrates lactate levels in these patients, who were divided into two groups according to the presence or absence of ketosis.

Non-ketotic lactic acidosis—The 16 non-ketotic patients (table I) had a mean age of 69 years. Hypoglycaemic treatment had consisted of phenformin in 15, sulphonylurea drugs (invariably in conjunction with phenformin) in seven, and insulin in three (in two of whom phenformin was also being given). Duration of phenformin treatment was under one month in five, one month to one year in three, and one to 10 years in seven. Mean lactate was 16.0 mmol/l (144 mg/100 ml) (range 3.3-33.3 mmol/l (30-300 mg/100 ml)). In the presence of shock or peripheral circulatory failure levels both of lactate (19.6 v

11.4 mmol/l (177 v 103 mg/100 ml)) and serum osmolality (328 v 316 mmol/kg) tended to be slightly but not significantly higher. Hypertension or ischaemic heart disease was identified in 14 patients (88%) and evidence of pre-existing chronic renal disease in eight (50%). Ten patients (mean age 71 years) died.

Ketotic lactic acidosis—Twenty-two patients (table II) with a mean age of 41 years had ketosis. Hypoglycaemic treatment had consisted of insulin in 10 patients, phenformin in five, sulphonylureas in five, and nothing in five. Mean lactate was 4.8 mmol/l (43 mg/100 ml) (range 2.3-25.0 mmol/l (21-225 mg/100 ml)) and was higher (mean 6.8 mmol/l (61 mg/100 ml)) in patients with clinical shock than in those without (mean 3.2 mmol/l (29 mg/100 ml)), although this did not reach significance. Serum osmolality was significantly higher in the shocked group (337 v 314 mmol/kg; $P=0.001$). In the 10 patients aged 40 and over the mean lactate ($\pm$ SE of mean) in those on phenformin (mean age 58 years) was 9.7 ± 1.7 mmol/l (87 ± 15 mg/100 ml) compared with 3.5 ± 0.2 mmol/l (32 ± 2 mg/100 ml) in those not on phenformin (mean age 54 years) ($P=0.01$). Four patients (mean age 58 years) died.

Discussion

Ketotic and non-ketotic lactic acidosis have been considered separately as Watkins *et al*⁷ found that the criteria of Oliva¹ for lactic acidosis were met in 50% of their cases of ketoacidosis; our 22 patients with ketotic lactic acidosis represented 29% of the total cases of ketoacidosis seen.

Lactate levels in the two groups were strikingly different (see fig). With one exception (case 36) lactate values in the ketotic group were 9.0 mmol/l (81 mg/100 ml) or less whereas (with four exceptions: cases 13-16) lactate values in the non-ketotic group were over 9.0 mmol/l (81 mg/100 ml). In cases 13 and 16 there was a major component of respiratory acidosis and in cases 14 and 15 the lactate level was insufficient to explain the large anion gap of 30 and 36 mmol/l respectively. These latter cases may represent the phenomenon⁸ whereby hyper-

Plasma lactate in ketotic and non-ketotic lactic acidosis. ● = Patients receiving phenformin. ○ = Patients not receiving phenformin.

Conversion: SI to traditional units—1 mmol/l $\approx$ 9 mg/100 ml.

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lactataemia, by inhibiting conversion of β -hydroxybutyrate to acetoacetate, may obscure the presence of ketoacidosis when acetoacetate measurement (Ketostix) is used for diagnosis. As β -hydroxybutyrate was not measured we could not estimate the prevalence of this phenomenon in this series. Nevertheless, the data on the two groups suggest that non-ketotic or "true" lactic acidosis might better be defined by a lactate level of over 9.0 mmol/l (81 mg/100 ml) with arterial pH under 7.2, rather

than lactate levels over 2 mmol/l (18 mg/100 ml) as suggested by Oliva.¹

The striking finding in the non-ketotic group was the high prevalence of phenformin administration. For comparison, prescribing patterns in the hospitals largely responsible for initiating treatment were reviewed and phenformin was found to account for 27% of oral hypoglycaemic drug use.

The role of phenformin in the genesis of lactic acidosis has

TABLE I—Data on patients with non-ketotic lactic acidosis

Case No	Age and sex	Insulin	Sulphonylureas (type†/mg)	Phenformin (mg)	Plasma lactate (mmol/l)	Arterial pH	Renal disorder	Other disorders and drugs	Clinical shock	Serum osmolality (mmol/kg)
1*	49 M	Lente 20 U	T/1500	100	15.0	6.97	Diabetic nephrosclerosis (necropsy)	Hypertension, methyl dopa, chronic bronchitis	—	297
2*	72 F			150	11.7	6.88			—	334
3*	71 F			200	25.4	6.70		Hypertension, cardiac failure, frusemide, digoxin, history of myocardial infarction	+	324
4*	66 F	T/1500	T/1500	100	12.8	6.82	Diabetic nephrosclerosis (necropsy)	Hypertension, methyl dopa, cerebrovascular disease	+	352
5	86 F			50	24.4	6.84	Blood ure (16 mmol/l) after recovery	Hypertensive/ischaemic L ventricular failure; controlled on thiazide	+	320
6*	81 F			100	20.0	7.04		Hypertension, L ventricular failure, digoxin and frusemide	—	320
7	62 M	PZI 48 U	T/1500	300	17.8	6.80	Blood urea previously (12 mmol/l) Chronic pyelonephritis necropsy	Ischaemic heart disease	—	327
8	80 F		T/2000	100	25.0	6.98		Ischaemic heart disease	+	310
9*	90 F			75	33.3	6.90		Hypertension	+	341
10*	71 M	Soluble 60 U	T/1500	100	17.3	6.98		Acute myocardial infarction: 2 previous episodes, hypertension and L ventricular failure, Clonidine and digoxin	+	322
11	53 M			75-150	22.0	6.91	Nephrectomy for tuberculosis, blood urea remained 13 mmol/l	Ischaemic heart disease, peripheral vascular disease	+	334
12*	69 F			100	12.2	7.10	Urinary tract infection	Ischaemic-hypertensive heart disease, digoxin	+	318
13	46 F	PZI 48 U	T/1500	100	4.2	7.31	Diabetic nephrosclerosis BUN 9.0 mmol/l	Hypertension, chronic bronchitis	—	297
14*	74 F		C/250	100	5.2	7.04		Hypertension, ventricular failure, digoxin, frusemide, Peripheral vascular disease, gangrene	—	323
15	70 M		T/1500	150	5.6	6.90		Cholelithiasis, pulmonary tuberculosis, rifampicin and ethambutol	—	316
16*	62 M	Soluble 60 U			3.7	7.25	Chronic renal failure	Hypertension, methyl dopa, chronic bronchitis, emphysema	+	329

*Patient died. †T = Tolbutamide. C = Chlorpropamide. Conversion: SI to traditional units—Lactate: 1 mmol/l $\approx$ 9 mg/100 ml. Urea: 1 mmol/l $\approx$ 6 mg/100 ml. BUN (blood urea nitrogen): 1 mmol/l $\approx$ 2.8 mg/100 ml. Osmolality: 1 mmol/kg $\approx$ 1 mosmol/kg.

TABLE II—Data on patients with ketotic lactic acidosis

Case No	Age and sex	Insulin	Sulphonylureas (type†/mg)	Phenformin (mg)	Plasma lactate (mmol/l)	Arterial pH	Plasma ketones	Renal disorder	Other disorders and drugs	Clinical shock	Serum osmolality (mmol/kg)
17	17 M	Semilente 84 U			8.9	7.14	1/9	Persisting raised blood urea (8.5 mmol/l)	Psychopathic	+	314
18	36 F	Semilente 56 U			2.9	7.24	1/4			—	317
19	25 F	Lente 40 U			3.1	7.09	1/12	Acute renal failure	Septicaemia, alcoholic liver disease	—	314
20*	53 F				2.4	7.30	1/3			+	345
21	60 M	Soluble 40 U	T/2000		5.5	6.97	1/8	Persisting raised blood urea (10 mmol/l)	Pneumonia	+	323
22	52 M				2.7	7.00	1/18		Peripheral vascular disease	+	342
23	63 F				3.0	7.32	1/10		Peripheral vascular disease	—	327
24	13 F	Semilente 76 U	C/375		2.4	7.18	1/4			—	314
25	32 F	Lente 32 U			5.4	6.94	1/4			—	307
26	42 F				4.1	7.21	1/5			—	315
27	15 M				2.4	6.98	1/8			—	296
28	34 F	Semilente 90 U			3.8	6.82	1/4		Hyperthyroid	+	364
29	36 F				Lente 64 U	2.3	7.19			1/8	
30	27 M				2.8	7.04	1/4			—	326
31	35 M	PZI 44 U			2.6	7.09	1/4			—	316
32	18 M				Lente 64 U	4.0	7.17			1/4	
33	25 F	Soluble 72 U			2.7	6.82	1/10	Diabetic glomerulosclerosis		+	354
34*	52 M		G/7.5	100	3.1	7.28	1/8		Hypertension, L ventricular failure, ischaemic heart disease	+	357
35	63 F			75	9.0	7.26	1/2	Persisting raised blood urea (11.5 mmol/l), papillary necrosis	Septicaemia	+	304
36*	56 M			150	25.0	6.72	1/4	Chronic renal failure	Hypertension, ischaemic heart disease, digoxin, clonidine, history of myocardial infarction	+	344
37*	69 M		G/10	50	6.6	7.05	1/2	Blood urea persistently (11.0 mmol/l)	Ischaemic heart disease, Prindolol, cyclopenthiiazide	+	329
38	52 F		T/2000	75	5.0	7.00	1/2		Ischaemic heart disease	+	328

*Patient died. †T = Tolbutamide. C = Chlorpropamide. G = Glibenclamide.

been extensively discussed.^{1 2 4 9} Clearly overdosage may play a part, but Sadow³ thought that in therapeutic doses the role of phenformin is only incidental. In our study there was no selection bias in favour of phenformin-treated patients and the large proportion of such patients among those with non-ketotic lactic acidosis strongly suggests an important role for the drug. Furthermore, of these 15 patients on phenformin seven had either started the drug or received a dose increase within the month before presentation, a finding similar to that of Cohen *et al.*²

Nevertheless, clearly there was often associated disease. All non-ketotic patients were azotaemic on presentation, but the presence of underlying renal disease could only be suggested if serum urea or creatinine was raised before presentation, remained raised after recovery, or if necropsy evidence of chronic renal disease was obtained. One or more of these criteria were satisfied in eight (50%) cases, a prevalence in keeping with the review of Cohen *et al.*²

In only one patient (case 10) was recent myocardial infarction identified, though in a further six cases previously confirmed myocardial infarction or chronic ischaemic heart disease was noted. Eleven patients (69%) had previously diagnosed hypertensive heart disease, of whom six were receiving treatment for left ventricular failure. No patient had evidence of alcoholism or clinical or biochemical evidence of liver disease.

Our findings do not support a significant role for tissue under-perfusion, as reflected by peripheral circulatory failure or severe dehydration, in the genesis of the hyperlactataemia. Furthermore, 10 patients with hyperosmolar coma seen concurrently during the study, some with severe hypotension, all had lactate levels under 3.0 mmol/l (27 mg/100 ml).

The mechanism whereby these various factors might predispose to lactic acidosis is not clear. The presence of even a minor degree of cardiac failure might cause congestion and diminished perfusion of the liver, which normally has a large capacity for lactate clearance and possibly plays a central part in the aetiology of lactic acidosis, as suggested by Berry.¹⁰ Impairment of renal function may be relevant to clearance of phenformin itself, but information on this point is lacking.

Management of lactic acidosis was by conventional means except in five patients, who underwent additional peritoneal dialysis.¹¹ A detailed appraisal of this form of treatment is being prepared.¹²

The other major biguanide drug, metformin, had only rarely been prescribed in the population studied and no case of lactic acidosis was associated with it. Even in France, however, where it is used more extensively reports of associated lactic acidosis have been only sporadic.^{13 14}

With the revised diagnostic criteria proposed above, lactic acidosis in diabetic patients is seen to be a syndrome of high mortality (63%) that occurs almost exclusively in the setting of cardiovascular or renal insufficiency, or both, in patients receiving phenformin. We suggest that in addition to the contraindication of coexistent hepatic disease phenformin should not be prescribed for patients with any evidence of impaired renal function, hypertension, ischaemic heart disease, or cardiac failure, and that serum creatinine should be estimated periodically in patients receiving phenformin. Particular caution is indicated in patients over the age of 60, possibly because of the age-related incidence of these risk factors.

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Comparison between ibuterol hydrochloride and terbutaline in asthma

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Summary

The bronchodilating effect, circulatory effects, and subjective side effects of ibuterol hydrochloride, the di-isobutyric acid ester of terbutaline, at two dose levels (2 and 4 mg) were compared with those of 5 mg terbutaline sulphate in a double-blind cross-over study on 12 patients with asthma. Both drugs were given by mouth. The 2-mg dose of ibuterol had the same bronchodilating effect during the first three hours as 5 mg terbutaline.

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The 4-mg dose, however, produced a significantly greater increase in the peak expiratory flow rate between the 30th and 120th minutes than terbutaline. No significant changes in heart rate or pulse amplitude were noted, and there was no difference in the incidence of subjective side effects between ibuterol at either dose level and terbutaline.

Introduction

The development of drugs acting selectively on β_2 -receptors¹ greatly advanced the treatment of obstructive lung diseases. They have a preferential action on the bronchial tree, thus causing fewer circulatory side effects in relation to their effects on the bronchial constriction. The best known of these drugs are salbutamol and terbutaline.^{2 3} Their molecular configuration protects them against two inactivating enzymes in the body, catechol-O-methyltransferase and monoamine oxidase,⁴ which ensures a prolonged effect after administration by mouth.

Ibuterol hydrochloride, a diester of terbutaline,⁵ is relatively