Diabetologia 9, 43—46 (1973)

The Relation between Phenformin Therapy and Lactic Acidosis

R.D. Cohen, J.D. Ward*, A.J.S. Brain, C.R. Murray, T.M. Savege and R.A. Iles
The Medical and Anaesthetic Units, The London Hospital, London, England

Received: August 11, 1972, accepted: October 29, 1972

Summary. Two cases of lactic acidosis are described in which the time sequence of events made it certain that phenformin was the precipitating cause. In one patient the condition arose because of self administration of an overdose; in the other, phenformin had been administered to a patient on maintenance dialysis. After recovery, and in the absence of phenformin therapy the second patient was able to clear an intravenous lactate load at a rate similar to that observed in other patients on chronic dialysis. — A review of the literature re-emphasizes the possible danger of phenformin in the presence of diminished renal or hepatic function, which should be shown to be normal before starting the drug and assessed periodically during therapy.

Key words: Phenformin, lactic acidosis, renal failure.

Phenformin has frequently been proposed as a cause of lactic acidosis (reviewed by Oliva, 1970). However, in most of the reported cases other factors, such as diabetes, liver disease, ethanol intake and hypotension have been present which might themselves have been responsible for the lactic acidosis (Sadow, 1969). We describe here the clinical course and biochemical studies in two patients in whom, because of the time relations involved, there could be no reasonable doubt that Phenformin administration precipitated lactic acidosis.

Methods

Lactate and pyruvate were measured in Case 1 by an Autoanalyser adaptation of the enzymic method of Hohorst (1962). In Case 2 lactate, pyruvate, 3-hydroxybutyrate and succinate were simultaneously estimated by the gas chromatographic method of Barnett *et al.* (1968). Values for whole blood by this method in resting normal subjects are: — lactate 0.95 ± SD 0.33 mmol/kg, pyruvate 0.09 ± SD 0.03 mmol/kg, L/P 10.28 ± SD 2.54, 3-hydroxybutyrate 0.035 ± SD 0.01 mmol/kg, succinate < 0.008 mmol/kg. The removal of a lactate load was studied by measurements on arterial blood samples taken at 5, 10, 15, 20, 30 and 40 min after the end of an infusion of sodium L-lactate (1.3 mmol/kg) over a period of 20 min. The base-line level of lactate was subtracted from each of the post infusion values; the decline of the increments above basal level with time did not differ obviously from a single exponential, and this type of curve was fitted to the results by computer using the method of least squares.

pH and pCO_2 were measured by standard methods using 'Radiometer' buffers of nominal pH 6.84 and 7.38.

Case Reports

Case I

This man, aged 36 years, had been placed on maintenance haemodialysis because of renal failure due to chronic glomerulonephritis. By 3 months after the start of dialysis he had developed a severe symmetrical sensorimotor neuropathy, which was not improved by increasing the duration of dialysis. In view of the development of abnormal glucose tolerance (fasting blood sugar 88 mgm/100 ml, at 30 min after 50 g oral glucose 202 mgm/100 ml, at 60 min 181 mgm/100 ml and at 90 min. 183 mgm/100 ml) over the period of dialysis he had been started on Phenformin, 50 mg b.d., in the hope that improved peripheral glucose uptake might ameliorate the neuropathy. Immediately before commencement of Phenformin plasma urea was 90 mg/100 ml, Na 126, K 4.6, bicarbonate 24, Cl. 82 mEq/1. After 8 days of treatment, during which period he had received a total of 650 mg Phenformin and had been dialysed for 42 h, he began to vomit and a few hours later was observed to have marked tachypnoea. The pulse was 120/min, blood pressure 150/100 and the skin was warm and well perfused. A diagnosis of lactic acidosis was made, and treatment with sodium bicarbonate and haemodialysis (Kiil dialyser) commenced. The principal investigations before and during treatment are summarised in Table 1. All symptoms improved markedly over the first eight hours of treatment and he made an uneventful recovery, the plasma lactate falling rapidly. Hyperventilation as judged by the arterial pCO_2 persisted for some eighteen hours after the arterial pH had returned to normal. A total of 1.156 mEq of sodium bicarbonate was administered over the first twenty-four hours of treatment, by which time the blood base deficit had been more than restored. Blood pressure remained at its initial level throughout. Other investigations at the time of diagnosis were as follows: — arterial pO_2 — 96 mmHg, plasma urea 105 mg/100 ml, Na 134, K 5.0, bicarbonate 12 and chloride 88 mEq/1, blood sugar 77 mg/100 ml, E.C.G. — no evidence of infarction, blood culture sterile. There had been no ingestion of alcohol before the start of the acidosis.

Case II

A previously healthy 17 year old boy ingested 30 — 40 slow-release Phenformin capsules (1500—2000 mg) at 6 p.m. on the day before admission. He went to bed, apparently well, at 2 a.m., but the following morning was unrousable. On admission at 8.30 a.m. he was unconscious, with extreme hyperventilation. The blood pressure was 160/70 with warm non-cyanosed extremities. He had

* *Present adress:* The Royal Infirmary, Sheffield S6 3 DA, U.K.

a convulsive episode, for which he was given paraldehyde 10 ml. Gastric lavage was performed without obvious recovery of drug. Salicylates and barbiturates were not detectable in the plasma. The principal investigations are shown in Table 2. In addition, the initial blood sugar was 58 mg/100 ml, arterial pO_2 was 92 mmHg, plasma urea, 39 mgm/100 ml, Na 138, K 4.7, Cl 102 and bicarbonate 8.5 mEq/l. Lactic acidosis was diagnosed at this stage on the basis of the acidosis and large anion gap (32.2 mEq/l). Treatment with intravenous bicarbonate and glucose was commenced and after 4–5 h the arterial pH had returned to normal. Violent hyperventilation persisted, however, and was presumably responsible for a rapid rise of rectal temperature to 39.4° C. Because of the increasing pyrexia and the fear that the respiratory effort might itself increase the lactate load he was paralysed with diallyl bisnortoxiferine (Alloferin) seven hours after admission and intermittent positive pressure respiration (IPPR) commenced, gradually allowing the pCO_2 to rise towards normal. The C.S.F. pH shortly after the start of IPPR was 7.25, and the C.S.F. pressure 200 mm water. A total of 1150 mEq bicarbonate was given in a period of 20 h, without significant positive fluid balance. In spite of a satisfactory fall in blood lactate and correction of the arterial pH and base deficit, consciousness was not restored. There was no recurrence of acidosis, but despite mannitol infusion and other measures the C.S.F. pressure continued to rise. Death occurred on the fourth day after admission. Autopsy showed marked cerebral oedema, possibly attributable to hypoglycaemia in the hours before admission.

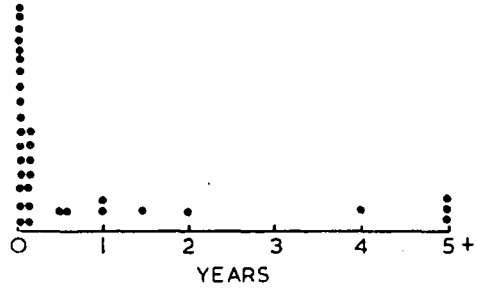
Lactate load studies

These were performed in Case I after recovery and in three other patients maintained satisfactorily on chronic haemodialysis who agreed to act as controls. The studies were carried out immediately before a routine dialysis, after the patients had rested for approximately one hour. Samples were withdrawn from the arteriovenous shunt used for dialysis. Basal lactate levels were 0.47 mmol/kg blood in Case I and ranged from 0.54–1.49 in the controls. Immediately after the end of infusion increments in blood lactate of 1.29–3.70 mmol/kg were observed. The half-time of the single exponential decay of the increments was 6.65 min in Case 1 and 6.88, 14.47 and 9.08 min in the controls. Case 1 thus had the shortest half-time in the series, though it was clearly not significantly different from the controls.

Discussion

In the cases described in this report the close relationship of the time of first administration of Phenformin to the onset of lactic acidosis, together with the absence of arterial oxygen desaturation, hypotension or peripheral vasoconstriction leaves little doubt that Phenformin was directly responsible for the lactic acidosis. It has been pointed out (Sadow, 1969; Oliva, 1970) that in most of the recorded cases of Phenformin-associated lactic acidosis there had been factors present in addition to Phenformin which could have caused lactic acidosis. Thus, of 52 cases from the literature taking ordinary doses of Phenformin the following conditions previously suggested as associated with lactic acidosis in the absence of Phenformin were also present: — diabetes mellitus (in 51 cases), diminished renal function or organic renal disease (in at least 36 cases), hypotension (or dehydration) (in 24 cases at least), infection [13], cirrhosis [4] and ethanol ingestion [4].

In spite of these reservations, analysis of the recorded cases *taken together* does make it seem likely that Phenformin contributes to or precipitates this condition. Fig. 1 shows the time intervals between the start of Phenformin therapy (or an increase in dose) and the onset of lactic acidosis. Instances in which massive overdoses (Davidson *et al.*, 1966; Bingle *et al.*, 1970; Strauss & Sullivan, 1970) have been taken are omitted; also excluded are a number of instances in which actual estimations of blood lactate were not made. Fig. 1 demonstrates that in 24 out of 34 patients on



The interval between the start of Phenformin therapy (or, in 6 cases, increase in dose) and the onset of lactic acidosis. Each point refers to a single patient

whom sufficient information is available lactic acidosis occurred within two months of the start of therapeutic doses; in 17 patients the onset was within 2 weeks. If lactic acidosis had resulted purely from long-standing conditions such as cirrhosis or diabetes, such an early concentration of incidence would not have been expected.

The mechanism by which Phenformin might cause lactic acidosis is uncertain. The evidence for stimulation of lactate production on the one hand, and inhibition of lactate uptake on the other has recently been reviewed by Oliva (1970) and Woods (1971). The role of the liver and kidney require special comment. These two organs are the major ones responsible for the removal of circulating lactate; they are also responsible for the excretion or metabolism of Phenformin (Hall, Ramachander & Glassman, 1968). It is, therefore, not surprising that, with few exceptions, renal or hepatic disease has been present in cases of lactic acidosis associated with Phenformin; in these instances usually either (a) shock has been present or (b) ethanol, a known cause of lactic acidosis, has been consumed or (c) a gross overdose of Phenformin has been taken. Only in one instance out of the 56 recorded cases of Phenformin-associated lactic acidosis was the blood urea indicated as being within normal limits and no evidence given of any other relevant factors. The precise role of defective renal function is often difficult to assess, since in lactic acidosis not initially associated with hypotension and clinically poor tissue perfusion, these signs often supervene after some hours, together

Table 1

Hours post admission	0	4	6	8	10	12	15	23	30	37	48	72	96
Arterial blood													
pH	7.20	7.23	7.38	7.4	7.4	7.36	7.42	7.45	7.49	7.53	7.57	7.48	7.50
PCO_2 mm/Hg	28	24.5	19	26	26	27	31.5	25.5	37.5	35	47	40	36
Base excess mEq/1	−16	−16	−12	−7.3	−7.5	−9.5	−3.5	−4.5	+5	+7	+9	+5.5	+4
Lactate mmol/kg		28.4		21.2		11.5		6.0	4.2				
Pyruvate mmol/kg				0.3		0.31		0.23	0.23				
L/P				71		37		26	18				
Cumulative Bicarbonate given mEq		500				900		1150					

Table 2

Hours post Admission	0	1.25	1.75	2.75	4.5	7.58	9.75	13.25	19.75	23.75	26.75	31.75	52.0
Arterial blood													
pH	7.08	7.26	7.35	7.35	7.43	7.54	7.46	7.51	7.44	7.54	7.44		7.4
pCO_2 mm/Hg	21.5	31	27.5	26	29	17.5	25	30	40	29	43		
Base Excess mEq/1	−23	−12	−9.5	−10	−4	−5	−4	+2	+3	+3	+4		
Lactate mmol/kg		15.8	16.8		16.1	20.0		12.0		8.9		5.1	
Pyruvate mmol/kg		0.37	0.53		0.44	0.62		0.45		0.35		0.21	
L/P		42.3	31.7		36.8	32.2		29.11		25.5		24.3	
3-hydroxy-butyrate mmol/kg		1.03	1.35		1.98	1.72		0.63		1.01		0.27	
Succinate mmol/kg		0.004	0.004					0.003		0.005		0.003	
CSF													
pH							7.25				7.26		7.29
Lactate mmol/1							10.95				8.68		3.2
Pyruvate mmol/1							0.121						0.04
L/P							90.2						77.2
3-hydroxy-butyrate							4.15						0.16
Cumulative bicarbonate given mEq					440				1150				

with azotaemia. Since death has resulted in 30 out of 52 recorded cases of lactic acidosis associated with therapeutic doses of Phenformin, it seems advisable, as emphasised by Oliva (1970) and McGregor *et al.* (1972) not to administer Phenformin in the presence of defective renal or hepatic function. It is suggested that the integrity of these organs should be specifically assessed before starting this drug. It may be necessary to monitor plasma urea or creatinine at regular intervals in patients taking Phenformin since the development of comparatively minor renal impairment due to pyelonephritis, glomerulosclerosis or other cause could reduce the excretion of Phenformin and precipitate lactic acidosis.

It is implicit in these arguments that the precipitation of lactic acidosis is a dose (or body fluid concentration) dependent effect. This concept is supported in animals by the observation that the inhibition of gluconeogenesis from lactate in the isolated perfused rat or guinea pig liver is dose dependent (Altschuld & Kruger, 1968; Woods, 1971) and by the development of lactic acidosis in Case II of this paper in whom renal function was normal. In Case I the capacity to remove a lactate load after recovery was at least as good as in a control series of patients maintained on chronic dialysis; this suggests that there was no permanent hepatic inability, either hereditary or acquired, to remove lactate, and that Phenformin resulted in lactic acidosis because of accumulation of the drug due to inadequate removal by routine dialysis.

Acknowledgement. We are grateful to Mrs. J.M. Strunin for the lactate and pyruvate estimations in Case 1.

References

1. Altschuld, R.A., Kruger, F.A.: Inhibition of hepatic gluconeogenesis in guinea pig by Phenformin. Ann. N.Y. Acad. Scienc. **148**, 612–622 (1968).
2. Barnett, D., Cohen, R.D., Tassopoulos, C.N., Turtle, J.R., Dmitriadou, A. Fraser, T.R.: A method for estimation of Krebs cycle and related intermediates in animal tissues by gas chromatography. Analyt. Biochem. **26**, 68–84 (1968).
3. Bingle, J.P., Storey, G.W., Winter, J.M.: Fatal self-poisoning with Phenformin. Brit. med. J. **1970, III**, 752.
4. Davidson, M.B., Bozarth, W.R., Challoner, D.R., Goodner, C.I.: Phenformin, hypoglycaemia and lactic acidosis. New Engl. J. Med. **275**, 886–888 (1966).
5. Hall, H., Ramachander, G., Glassman, J.M.: Tissue distribution and excretion of Phenformin in normal and diabetic animals. Ann. N.Y. Acad. Sci. **148**, 601–611 (1968).
6. Hohorst, H.J.: In Methods of Enzymatic Analysis (Ed. by A.U. Bergmeyer) pp. 266–270. New York: Academic Press 1962.
7. MacGregor, G.A., Poole Wilson, P.A., Jones, N.F.: Phenformin and lactic acidosis. Lancet **1972 I**, 69–71.
8. Oliva, P.B.: Lactic acidosis. Amer. J. Med. **48**, 209–225 (1970).
9. Sadow, H.S.: This question of lactic acidosis. Postgrad. Med. **45**, May Suppl., p. 30–35 (1969).
10. Strauss, F.G. Sullivan, M.A.: Phenformin intoxication resulting in lactic acidosis. J. Hopkins Med. J. **128**, 278–281 (1970).
11. Woods, H.F.: Some aspects of lactic acidosis. Brit. J. Hosp. Med. **11**, 668–676 (1971).
12. Woods, H.F.: D. Phil. Thesis. University of Oxford (1970).

R.D. Cohen, M.D.
Reader in Medicine
The London Hospital Medical Unit
Whitechapel London E1 1BB
England