Phenformin-associated Metabolic Acidosis

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SUMMARY

We report 18 consecutive phenformin-treated diabetic patients admitted to this Medical Service acutely ill with metabolic acidosis. Lactic acidosis was anticipated, and documented, in all. Also, however, though most of the patients had only weakly positive, or even negative, serum reactions with the nitroprusside reagent, all were found to have coexisting ketoacidosis, plasma 3-hydroxybutyrate averaging 7.1 mmol/L. ± 3.9 (S.D.). This finding suggests that treatment of these patients should include insulin, and often also glucose, because most do not have marked hyperglycemia and some have hypoglycemia.

The lactic acidosis in the nine patients who survived was, on average, less severe than in the nine who died, but the difference was not statistically significant. Survival correlated closely with the absence of shock on arrival.

Only eight patients had an identifiable acute illness *other than* the metabolic acidosis. The other 10 patients had no discernible cause for the acute illness apart from their treatment with phenformin. This finding raises serious doubts about whether phenformin should be used to treat patients with diabetes. DIABETES 25:292-96, April, 1976.

It is now generally acknowledged that phenformin-treated diabetics may develop lactic acidosis when seriously ill of other causes.[1] Acidosis is usually attributed in these cases to the intercurrent illness, the effect of the drug being regarded merely as an aggravating factor (reviewed in references 1 and 2). However, a recent report by Cohen et al. clearly indicates that phenformin, when its blood concentration is inordinately high, either because of overdosage or renal failure, can itself cause an acute illness characterized by lactic acidosis.[3]

The present report reviews the findings in 18 consecutive phenformin-treated patients who were admitted to this medical service with acute metabolic acidosis. Ten of these patients had no identifiable illness other than the acidosis. An important purpose of this communication is to call attention to the observation that, whereas lactic acidosis was anticipated in these cases and documented in all, the concentration of plasma 3-hydroxybutyrate was also elevated above normal in all of them. That is, ketoacidosis, often unsuspected, coexisted with the lactic acidosis in every instance. This finding fits with the ketogenic action of phenformin on the isolated perfused rat liver found in this laboratory (Hoberman, H.D., and Carnicero, H., unpublished observations).

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Accepted for publication January 13, 1976.

PATIENTS AND METHODS

The 18 patients (five men and 13 women), of average age 71.6 years (range 45-88 years), were all the recognized phenformin-treated diabetics admitted to this medical service with acute metabolic acidosis during a 25-month period (during which 120 diabetics with *recognized ketoacidosis* were admitted).

Arterial blood pH, gas tensions, and plasma lactate and 3-hydroxybutyrate were measured as described elsewhere.[4] Plasma HCO_3^- was calculated from the Henderson-Hasselbalch equation with the use of a pK′ of 6.10 and a CO_2 solubility factor of 0.03. Lactate and 3-hydroxybutyrate were usually measured in pretreatment specimens of arterial blood plasma; measurements made in venous plasma or after treatment was started are so identified. In seven normal nonfasting subjects, venous plasma lactate averaged 1.2 mmol/L. ± 0.2 (1 S.D.), and 3-hydroxybutyrate averaged 0.3 mmol/L. ± 0.1 (1 S.D.) in forenoon specimens. Other biochemical measurements were made by standard AutoAnalyzer methods. Undiluted serum was tested for "ketones" (i.e., acetoacetate and acetone) with Acetest tablets (Ames, Elkhart, Ind.), and the results were recorded as negative or slightly, moderately, or strongly positive. Statistical calculations were made by standard methods,[5] and mean values are reported ± 1 S.D. The significance of differences was estimated by *t* and chi-square tests.

RESULTS

Clinical features (table 1). Lactic acidosis was usually suspected early because of the history of phenformin use and the findings of hyperpnea, low serum CO_2 content, or blood pH, and a serum Acetest reaction that was not strongly positive. Seven patients died within 6-60 hours after admission despite vigorous treatment for shock and metabolic acidosis. Two patients who survived the acute episode died 6-10 days later, one of complications of cardiorespiratory resuscitation (no. 7). Nine of the 18 patients left the hospital feeling well.

Only one survivor had shock (no. 13), but five of the seven who did not survive the acute episode had shock either on admission or shortly thereafter (and a sixth, no. 2, had acute pulmonary edema). Three of those five had a presumptive cause of circulatory collapse other than the severe acidemia: hypoglycemia (no. 1), E. coli bacteremia (no. 3), and gastrointestinal bleeding (no. 12). No such disorders were found, however, in the other two patients who had shock on entry and died early (nos. 8 and 11), and the postmortem examination in no. 8 was not more informative.

Laboratory findings (table 1). Initial serum glucose concentration was below 50 mg./dl. in five patients, and most of the others had modest hyperglycemia. All patients had elevated concentrations of serum urea N on entry, but six of the nine survivors later, during convalescence, had values < 20 mg./dl.

Initial (or early) plasma lactate was between 7.2 and 36.7 mmol/L. The reaction of serum with the sodium nitroprusside reagent was at least moderately positive in only five of the 18 patients (nos. 4, 5, 7, 8, and 17), and they had elevated plasma 3-hydroxybutyrate. In the other 13 cases, the serum Acetest reaction was either negative or only weakly positive, so that coexisting ketoacidosis had been thought absent or minimal. However, these 13 also had elevated plasma 3-hydroxybutyrate (average 6.1 mmol/L. ± 3.6), and one with a negative serum Acetest reaction had a plasma 3-hydroxybutyrate of 12.9 mmol/L. (no. 12).

Treatment and outcome. Almost all the patients were given intravenous solutions of $NaHCO_3$ soon after the metabolic disorder was diagnosed. In those with shock, when that did not raise blood pressure (as it usually did not), solutions of plasma (or albumin) and sometimes vasopressor drugs were given. Bacteremia (in no. 3) and hemorrhage (in no. 12) were treated appropriately.

Three of the five patients with at least moderately

TABLE 1

Clinical and laboratory findings in eighteen patients with phenformin-associated lactic acidosis

Case no.	Arterial blood			Plasma*		Serum		Shock	Outcome‡	Other clinical features
	pH	PCO_2 mm. Hg	HCO_3^- mmol/L.	lactate mmol/L.	3-hydroxybutyrate mmol/L.	glucose mg./dl.	urea N mg./dl.	Nitroprusside reaction†			
1	6.87	34	6.0	17.5 (h)	4.6	25	92	negative	+	D	Hemiplegia
2	6.97	19	4.2	20.7	7.3	415	41	slight	0	D	Acute pulmonary edema
3	6.62	44	4.4	36.7 (v)	3.1	204	57	negative	+	D	E. coli septicemia
4	6.98	20	4.6	7.2 (h)	11.8	507	25	strong	0	L	—
5	7.34	27	14.3	11.7 (v)	4.0	188	31	moderate	0	L	Paroxysmal arterial fibrillation *without* cardiac failure
6	6.83	14	2.3	21.4	9.8	242	42	slight	0	L	—
7	7.13	20	6.5	7.6	13.0	139	63	moderate	0	D (6 days)	—
8	6.65	11	1.1	24.9 (h)	7.3	143	30	moderate	+	D	—
9	6.70	10	1.2	26.5	5.8	61	37	negative	0	L	Bladder obstruction due to prostatism
10	7.19	24	9.4	27.1 (v)	3.1	42	30	negative	0	L	—
11	6.78	24	3.4	25.3	5.8	152	61	slight	+	D	—
12	7.03	10	2.5	13.5	12.9	178	91	negative	+	D	Acute gastrointestinal hemorrhage
13	7.00	17	4.0	13.2 (h)	10.8	45	58	slight	+	L	Acute myocardial infarct
14	7.22	36	14.4	12.6 (v)	2.1	18	57	negative	0	L	Mild chronic congestive cardiac failure
15	6.82	19	3.0	16.8 (v)	8.6	0	82	negative	+	D (10 days)	Presumed acute tubular necrosis
16	6.94	15	3.1	16.1	2.1	58	34	negative	0	L	—
17	7.27	21	9.2	10.8 (v)	12.3	1,050	54	moderate	0	L	—
18	7.10	15	4.4	18.0 (v)	2.8	206	39	negative	0	D	—

*Pretreatment arterial plasma except for specimens identified by (v) = venous, or (h) = obtained within an hour after starting treatment.
†In undiluted serum. ‡L = survived; D = died, within 6-60 hours of admission except in the two cases identified otherwise.

positive serum Acetest reactions (nos. 4, 7, and 17) were initially diagnosed as having combined keto- and lactic acidosis, and hence given insulin early; two of them also had marked hyperglycemia. Seven other patients were given insulin hours after entry, when its usefulness could not be determined.

The patient with urinary bladder obstruction (no. 9) diuresed after catheterization, and then tolerated i.v. administration of 1,320 mmols $NaHCO_3$ during a six-hour period. Another patient, hemodialyzed several times because of oliguria thought secondary to acute tubular necrosis (no. 15), died after ten days. Three patients (nos. 11, 13, and 18) underwent peritoneal dialysis for 15-25 hours after they had remained or become hypotensive despite intravenous fluid administration and, in two of those cases, after the development of pulmonary edema; only patient no. 13 survived.

The clinical and laboratory features listed in table 2 were compared in the nine survivors, and in the seven patients who died within 60 hours of arrival (inclusion of the data of patient nos. 7 and 15, who died later, did not alter the interpretations). The mean blood pH and plasma HCO_3^- were lower, and mean plasma lactate higher, in those who died than in the survivors, but neither those nor any of the other differences in table 2 were statistically significant. There was, however, a striking difference in the presence of shock on arrival: only one of the nine survivors had shock, whereas five of the seven who died early had shock on entry or within an hour. Put differently, of the 10 patients without early shock, eight survived. In contrast, of the six patients with shock on arrival, only one (no. 13, with an acute myocardial infarction) survived ($P = 0.024$ by chi-square test).

TABLE 2

Laboratory findings in survivors and nonsurvivors with phenformin-associated lactic acidosis*

	Survivors	Nonsurvivors†
Number	nine	seven
Age (yr.)	70.9 ± 12.2	71.0 ± 10.8
Arterial blood pH	7.00 (± 50.4 nM/L.) [6.83 – 7.31]	6.83 (± 61.4 nM/L.) [6.68 – 7.06]
Plasma bicarbonate (mmol/L.)	6.9 ± 5.1	3.7 ± 1.6
Plasma lactate (mmol/L.)	16.3 ± 7.1	22.4 ± 7.6
Plasma 3-hydroxybutyrate (mmol/L.)	6.9 ± 4.3	6.3 ± 3.4

*Values are given as the mean ± S.D. Mean blood pH was calculated from mean arterial blood "H+ concentration"; the bracketed blood pH values refer to the −1 S.D. to +1 S.D. range.

†See text for definition.

DISCUSSION

The findings in these 18 consecutive patients with phenformin-associated lactic acidosis highlight three points. First, the prognosis was grim for patients with shock on arrival, whether or not there was a treatable nonmetabolic cause of shock. Second, all patients had coexisting ketosis, often unsuspected, which may warrant treating such patients with insulin. Third, 10 patients had no identifiable cause for the acute illness apart from their treatment with phenformin.

The effects of phenformin on intermediary metabolism are not fully understood and, because this subject has recently been reviewed by others,[6-9] will not be detailed here. It is generally agreed that phenformin inhibits formation of glucose from lactate and pyruvate,[6,7,10] which presumably accounts for the drug's hypoglycemic action. While several studies have shown increased blood lactate after administration of phenformin,[6,8] the basis for this effect is disputed. Lloyd et al.[7] inferred that this was due mainly to decreased hepatic uptake of lactate; Searle and Siperstein[8] attributed the hyperlactatemia mainly to decreased extrahepatic oxidation of lactate; and Hoberman and Carnicero (unpublished observations) found increased hepatic output of lactate when rat liver was perfused with phenformin and pyruvate. Experimental conditions differed in the foregoing studies, but each provides "an explanation" for the lactic acidosis that may follow phenformin administration. With respect to ketogenesis, Toews et al.[10] and Hoberman and Carnicero (unpublished observations) found increased output of "ketones," predominantly 3-hydroxybutyrate, after infusing phenformin into isolated perfused livers of fasted rats. Although starvation may have been a factor in some of our patients' ketosis, the foregoing experimental findings suggest that their coexisting keto- and lactic acidosis likely resulted mainly from specific biochemical effects of phenformin.

We lack precise information about how phenformin is metabolized, excreted, or bound to plasma proteins and whether it is dialyzable. It is apparently altered in the liver to an inert metabolite that, with the unchanged drug, is excreted in the urine.[11] We do not know how to inhibit the drug's action or speed its excretion or metabolic conversion, so treatment of pa-

tients with phenformin-associated lactic acidosis is limited to recognizing and treating coexisting life-threatening disorders and to treating acidemia.

Pathogenesis. Phenformin-treated diabetics have slightly but significantly higher blood lactate than either normal individuals or diet-treated diabetics.[12] However, serious lactic acidosis in patients taking phenformin has usually been ascribed mainly to intercurrent acute illnesses.[2] Thus, the pathogenesis is usually pictured to be as follows: a phenformin-treated patient develops an intercurrent *serious* acute illness (e.g., myocardial infarction or sepsis) that itself causes lactic acidosis; that "serious illness" also lowers cardiac output, which decreases renal function, thereby impairing excretion of phenformin, increasing its concentration, and aggravating the lactic acidosis.[1] This could have been the sequence in eight patients (nos. 1, 2, 3, 5, 9, 12, 13, and 15). However, a few recently reported cases indicate that phenformin, when present in high concentration, can itself cause severe lactic acidosis.[3,13-15] Therefore, and because 10 of our 18 patients (including six survivors and two nonsurvivors who were autopsied, nos. 7 and 8) had no identifiable "serious acute illness" other than the metabolic disturbance, an alternative pathogenetic sequence should be considered: a phenformin-treated diabetic develops a *mild* intercurrent illness (e.g., increased glucosuria or gastroenteritis) that can cause dehydration; renal function thereby decreases, with retention of phenformin, causing lactic acidosis; the acidemia impairs cardiac function,[16] further worsening renal function and resulting in a vicious cycle of increasing lactic acidosis and eventually shock.

Underlying decreased renal function has been asserted to be a predisposing factor in some other reported cases.[2,9] However, six of our nine survivors had serum urea N concentrations < 20 mg./dl. after they recovered. Indeed, in five of those six patients (excepting no. 9, who had bladder obstruction), nitrogen retention during the acute illness may have been *secondary* to the acute metabolic disturbance or to dehydration, as in ketoacidosis or nonketotic hyperglycemic coma.

Ketosis. In many other reported cases of phenformin-associated lactic acidosis, unmeasured anions in plasma have exceeded lactate by as much as 15 mmol/L., suggesting the presence of ketoacidosis as well as lactic acidosis.[1] The sodium nitroprusside reagent is sensitive mainly to acetoacetate, less so to acetone, and not at all to 3-hydroxybutyrate.[17] Therefore, because this reaction has often been negative or only weakly positive in these cases, 3-hydroxybutyrate has been suspected to be the other predominant undetected anion.[1] This suspicion was confirmed by our finding that plasma 3-hydroxybutyrate was elevated in all cases. Although plasma acetoacetate was not quantitated, the usually only weakly positive serum Acetest reactions suggest that acetoacetate was generally not elevated proportionately to 3-hydroxybutyrate. Why the ketosis was presumably manifested mainly as elevated 3-hydroxybutyrate is not understood but does fit the observation that phenformin infused into isolated rat livers increases mainly the production of 3-hydroxybutyrate rather than acetoacetate.[6,10] It would be an oversimplification to interpret this as being due to shifting of the acetoacetate $\rightleftharpoons$ 3-hydroxybutyrate reaction toward the right caused by the lactic acidosis.[18] That effect is thermodynamically improbable because the midpoint potential of the 3-hydroxybutyrate/acetoacetate system is relatively electronegative compared with the lactate/pyruvate system.[19] Hence, rather than lactate's tending to reduce acetoacetate, 3-hydroxybutyrate should tend to reduce pyruvate to lactate.

The frequent presence of moderate ketosis in these patients suggests that early treatment with insulin might be useful, as suggested by Assan et al.[9] and, for other reasons, by Dembo et al.[1] Even if giving insulin should serve only to interrupt ketogenesis (or perhaps also to increase peripheral utilization of ketone bodies[20]), acidemia should lessen more rapidly. Because plasma glucose is usually only mildly elevated (and often low), most patients should also be given glucose solutions i.v. before or while being given insulin.

Outcome. Survival correlated closely with the absence of shock on arrival and not with biochemical measurements or manner of treatment, which was similar in most cases (*v.i.*). Five patients died because of unsuccessfully treated (though recognized) underlying acute illnesses (nos. 1, 2, 3, 12, and 15), and two deaths (of nos. 7 and 18) were related to complications of treating the acute episode. It seems likely that the other two deaths (of nos. 8 and 11) were due to the metabolic disturbance itself.

Treatment. Ideally, management of this disorder should include measures to inhibit the action of phenformin, and speed its excretion and metabolic disposition. Because we did not know how this could be accomplished, treatment was ordinarily limited to recognizing and treating underlying acute illnesses and shock and administering $NaHCO_3$ to mitigate acidemia. Although insulin was not used regularly in these patients, we would now recommend its early

administration, usually with glucose, as discussed earlier and as suggested by others.[1,21] The amounts of $NaHCO_3$ given ranged from as little as 44 mmols in one patient with recognized ketosis and blood pH 7.27 (no. 17), who was also given insulin early, to as much as 1,320 mmols during a six-hour period in a patient with blood pH 6.70 (no. 9), who diuresed after catheterization for acute urinary retention.

Sodium bicarbonate administration is based on the assumption that severe acidemia per se is harmful, especially to cardiac function.[16] However, some dehydrated patients do not tolerate i.v. administration of large amounts of Na^+-containing fluids, because acute pulmonary edema (as in patients 13 and 18) or hyperosmolarity (as in no. 11) can be precipitated. Moreover, abrupt reversal of acidemia with $NaHCO_3$ has other risks: hypokalemia can be induced, which might be dangerous in patients receiving digitalis; it may inhibit hyperventilation;[22] and it can decrease dissociation of O_2 from oxyhemoglobin, causing tissue hypoxia, thereby worsening lactic acidosis.[23] Therefore, the advantages and disadvantages of treating this disorder with $NaHCO_3$ deserve further study, preferably in animal models. Meanwhile, we do administer $NaHCO_3$ to patients with severe phenformin-associated lactic acidosis, trying to avoid large, abrupt increases of blood volume or pH. If volume overload occurs, a diuretic should be given; if urinary output remains low and further administration of $NaHCO_3$ seems warranted, dialysis is indicated. If phenformin were know to be dialyzable, hemodialysis would naturally be a rational treatment.

Treatment of phenformin-associated lactic acidosis is often unsuccessful. Since our findings suggest that this disorder can occur in the absence of other acute life-threatening illnesses, and because patients treated with phenformin are often the elderly, who have other disorders that may limit their ability to compensate for physiologic disturbances, the best "treatment" for this disorder would simply seem to be to avoid using this drug.

ACKNOWLEDGMENTS

We thank many dedicated house officers on this Medical Service who skillfully cared for these patients and helped obtain some of the data.

This work was supported by USPHS grant CA-03651 from the National Cancer Institute.

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