# Insulin Therapy in Phenformin-Associated Lactic Acidosis

## A Case Report, Biochemical Considerations and Review of the Literature

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SUMMARY

**A patient with phenformin-associated lactic acidosis was treated with insulin and showed marked improvement coincident with the expected onset of action of the insulin administered. Relative insulin deficiency was demonstrated although several phenomena characteristic of phenformin-associated lactic acidosis obscured its reflection in the usual indices. From data presented and a review of the literature the following pathogenesis is proposed for the observed metabolic derangement. A background of relative insulin deficiency would permit enhanced pyruvate (and hence lactate) formation from protein sources. Insulin deficiency would also lead to inhibition of pyruvate dehydrogenase which slows pyruvate removal. Phenformin accumulation (cf impaired renal function) further reduces pyruvate removal by decreasing its conversion to glucose, but in addition alters the redox state. For the lactic acidosis which results, insulin administration may thus constitute specific therapy.** DIABETES *24*:28-35, January, 1975.

The occurrence of severe metabolic acidosis due to lactic acid accumulation in patients with diabetes mellitus in association with phenethylbiguanide (Phenformin, DBI) therapy is a distinct, albeit uncommon clinical entity[1-34] (for review see ref. 35). The role of the drug in the pathogenesis of the disorder remains presumptive, notwithstanding the in vitro evidence for inhibition of gluconeogenesis[36-43] and oxidative phosphorylation.[36,37,44-48] The role of excessive drug accumulation in some cases has been suggested by the greater frequency of lactic acidosis in patients with renal disease,[35] and in cases of overdose.[19,22,24,25] An idiosyncratic reaction to therapeutic levels remains possible.

Because one major effect of the drug is lowering of blood glucose, it might be predicted that clinically significant insulin deficiency might be masked by relatively normal blood glucose concentration. Moreover, such levels of ketone acids as are present might be further underestimated by standard clinical tests, owing to the altered oxidation-reduction (redox) state.[26,50] Though several authors have recommended insulin and dextrose therapy[16,32,49] the possible contributions of relative insulin deficiency to the development and course of phenformin-associated lactic acidosis have not been emphasized.

The present report describes a maturity-onset diabetic patient with phenformin-associated lactic acidosis in whom therapy was successful. In this instance, the suspicion of occult insulin deficiency led to early introduction of insulin therapy. A rationale for such management is described on the basis of the observed response of a number of metabolic and acid-base indices. The biochemical basis of other aspects of the therapy is reviewed.

### CASE REPORT

A fifty-three-year-old mildly obese Caucasian female (SMH No. C-13553) was admitted with a diagnosis of severe metabolic acidosis. Diabetes mellitus had been diagnosed three years earlier and was treated with diet and DBI-TD,* 50 mg. twice daily. Four weeks before the present admission she had been hospitalized for management of acute pulmonary edema on the basis of ischemic heart disease. Fasting blood sugar at that time was 110 mg. per 100 ml. and two hours after a 50 gm. oral glucose load, the blood

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*Phenformin hydrochloride timed disintegration capsules (Arlington).

sugar was 306 mg. per 100 ml. An exacerbation of chronic schizophrenia occurred during that admission. The patient was never reported to be suicidal. The patient was discharged from hospital on the following daily medications: digoxin 0.25 mg., hydrochlorthiazide 50 mg., potassium chloride (Slow-K)* 38 mEq and thoriadazine 400 mg. No oral hypoglycemic agent was prescribed on discharge, but the patient admitted to having resumed the DBI-TD at a dose of 50 mg. three times daily.

Eleven days later she presented with progressive breathlessness, severe cramping, central abdominal pain, vomiting and several loose bowel movements of one day's duration. She denied polyuria, polydipsia and ingestion of "toxins." On physical examination, she was alert but in considerable distress. The blood pressure was 130/70 mm. Hg, pulse 92/min., and the extremities were warm. The rectal temperature was 37.4°C. Respirations were deep, rapid and regular but there was no smell of acetone on her breath. Mucous membranes were dry, skin turgor was moderately reduced. There were crepitant râles at both lung bases, but no detectable cardiomegaly, gallop rhythm, nor jugular venous distension. There was a lenticular opacity on the left side, but no retinopathy was detected. The remainder of the examination was negative. A chest X ray showed bilateral basilar lung infiltrates consistent with pneumonitis, and after several hours, fever developed. There were no identifiable medications or blood in the gastric aspirate. The laboratory findings are summarized in table 1. In addition, the serum creatinine was 1.2 mg. per cent and the serum amylase was not elevated. Blood, sputum, and urine cultures and a urine sediment examination were negative. Alcohol and barbiturates were not detectable in the blood. The serum salicylate level was 6.6 mg. per cent. On admission, the serum ketones† were weakly positive in an undiluted specimen and remained unchanged for eighteen hours. The urine was strongly positive for ketones, but negative for sugar.

Of special note is that during the course of treatment of the profound acidosis the patient required 960 mEq of $NaHCO_3$ to correct the acidemia, but the metabolic abnormality, as inferred clinically by unmeasured anions and confirmed later by specific assay,‡ required a much longer period to be corrected. Intravenous and subcutaneous insulin was administered prior to correction of the metabolic defect. It should be noted that hyperglycemia accompanied the administration of dextrose solutions despite insulin therapy. Since the central venous pressure (CVP) increased to 19 cm $H_2O$ after eight hours, furosemide, additional digoxin, and a course of positive pressure ventilation between hours 9 and 14 were employed. Thereafter the CVP remained below 10 cm $H_2O$. Oxygen therapy (35-40 per cent) was instituted at presentation and continued for twenty-eight hours. Ampicillin (2 gm. per day) was commenced after twelve hours for the pneumonitis. The systolic blood pressure fell to 90-100 mm. Hg between the sixth and twenty-eighth hours. However the patient was lucid during the entire period and her extremities remained warm. Hourly urine outputs averaged 150-200 cc. during the first twenty-four hours with a maximum hourly volume of 270 and minimum of 80 cc. per hour. Her course of recovery is documented in table 1. Fasting blood sugars in the remainder of her hospitalization remained within normal limits and the patient was discharged on a 1500 calorie diet.

Whole blood amino acids are shown in table 2, with values from fasted normal subjects for reference. The marked elevation in the levels of alanine at four hours (giving an alanine/pyruvate ratio of 7.3) was associated with high levels of proline, glycine, lysine, valine, leucine and taurine. Of note is that citrulline and ornithine levels were normal, and arginine levels were subnormal. With therapy, those with elevated concentrations showed a trend toward normalization, but of interest is that aspartic acid and glutamic acid levels rose, and that of arginine fell further. Alanine/pyruvate ratio was 2.3 at thirteen hours and 2.1 at seventeen hours.

As there is no specific sensitive assay available to detect phenformin and its metabolites in blood the diagnosis in this case is based on history and the identification of the tablets by the pharmacist.*

## DISCUSSION

The clinical and biochemical presentations of this patient were typical of those described for phenformin-associated lactic acidosis (see table 3). There was a brief prodrome of prominent gastrointestinal symptoms accompanied by a severe metabolic acidosis. The unmeasured anions were increased in a diabetic patient with minimal detectable ketonemia, absence of renal failure and no evidence of ingestion of other compounds which can cause metabolic acidosis. The diagnosis was confirmed by the initial blood lactate level of 21.6 mM (a greater than twentyfold increase), and pyruvate level of 0.5 mM, producing a lactate/pyruvate ratio of 42.6.

The presenting features and survival of phenformin-associated lactic acidosis in seventy-six published cases are recorded in tables 3 and 4. The following is a review of the pathophysiology and management of this condition with particular emphasis devoted to the role of insulin.

### *The biochemistry of phenformin-associated lactic acidosis*

The exact mechanism whereby phenformin (therapeutically) lowers blood glucose remains controversial.[51] Evidence, mainly from animal models, has been put forward to support inhibition of gluconeogenesis,[36-43] reduced intestinal absorption of glucose[52-55] and increased glucose utilization by muscle and fat.[36,37,44-49] The relative importance of each of these effects in man is not clear. For the discussion to follow it is the fact that phenformin lowers blood glucose that is important, rather than the precise mechanism whereby this is achieved.

The metabolic actions of phenformin, which may

*KCl (Ciba)

†Sodium nitroprusside powder (Acetone Test, Denco).

‡Lactate, pyruvate, $\beta$HB and alanine were assayed on blood perchloric acid filtrates by the standard enzymic spectrophotometric and fluorometric methods and amino acids by automated column chromatography methods cited in ref. 20.

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TABLE 1

The Course of Patient H.E.

| Parameters | Hours after admission | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 4 | 6 | 11 | 13 | 17 | 24 | 28 | 42 | 89 |
| Acid-Base | | | | | | | | | | |
| Arterial pH | 6.87 | 6.93 | 7.15 | 7.49 | 7.50 | 7.56 | 7.58 | 7.48 | 7.42 | 7.45 |
| Arterial $PCO_2$ (mm. Hg) | 20 | 16 | 19 | 35 | 28 | 33 | 48 | 47 | 42 | 37 |
| Serum $CO_2$ Content (mEq/L.) | 4 | 5 | 6 | 25 | 23 | 29 | 40 | 34 | 31 | 24 |
| Unmeasured Anions (mEq/L.)* | 36 | 32 | 40 | 48 | 47 | 35 | 15 | 16 | 12 | 12 |
| Intermediary Metabolism | | | | | | | | | | |
| Blood glucose (mg./100 ml.) | 86 | | 179 | | 230 | 230 | 104 | 124 | | 130 |
| Blood lactate (mM) | | 21.3 | | | 26.6 | 17.3 | | | | |
| Blood pyruvate (mM) | | 0.5 | | | 0.9 | 0.7 | | | | |
| Lactate/pyruvate ratio | | 42.6 | | | 29.5 | 24.7 | | | | |
| Blood $\beta'$-hydroxybutyrate (mM) | | 2.8 | | | 3.04 | 0.92 | | | | |
| Blood alanine (mM) | | 3.66 | | | 2.08 | 1.44 | | | | |
| Plasma immunoreactive insulin ($\mu$U/ml.) | | 1 | 3 | | | | | | | |
| Other | | | | | | | | | | |
| Blood Urea Nitrogen (mg./100 ml.) | 22 | | 25 | 27 | 27 | 29 | 26 | 27 | | 11 |
| Serum Sodium (mEq/L.) | 144 | 143 | 148 | 160 | 160 | 153 | 152 | 146 | 143 | 142 |
| Serum Potassium (mEq/L.) | 4.3 | 4.5 | 4.8 | 4.0 | 3.6 | 4.0 | 4.2 | 4.3 | 3.7 | 4.8 |
| Arterial $PO_2$ (mm. Hg) | 76 | 115 | 66 | 100 | 75 | 64 | 112 | 78 | 93 | 76 |
| Cumulative Therapy | | | | | | | | | | |
| Sodium Bicarbonate (mEq) | | 132 | 506 | 960 | | | | | | |
| Insulin (units)† | | | 20 | 40 | 60 | 90 | 120 | | | |
| Glucose (gm.) | | 55 | 105 | 150 | 200 | 300 | 370 | 400 | | |
| Potassium Chloride (mEq)‡ | | | 30 | 40 | 60 | 100 | 130 | 140 | 180 | 230 |
| Furosemide (mg.) | | 40 | 80 | 240 | | | | | | |
| Digoxin (mg.) | | | | 0.5 | 0.75 | | 1.0 | | 1.25 | 1.75 |

*Unmeasured Anions (Na - (Cl + $CO_2$) = 11 ± 3 mEq/L.)
†Intravenous and subcutaneous.
‡Intravenous and oral

contribute to the biochemical abnormality observed, may be classified as direct and indirect. The direct effects exerted at the level of the hepatocyte are schematized in figure 1. Site 1a represents the inhibition of glucose formation from pyruvate. This would be responsible for intracellular accumulation of pyruvate, and hence of lactate and alanine, ultimately reflected in elevated circulating levels of all three substances. Another consequence of inhibited gluconeogenesis might be lowering the blood glucose levels. Normoglycemia was a presenting feature in the case reported, and in 46 per cent of the cases reviewed the presenting blood sugar was below 100 mg. per 100 ml. (table 3).

At high concentrations, phenformin can inhibit the electron transport system (site 1b, figure 1) producing elevated NADH. This reduces the flow through the tricarboxylic acid (TCA) cycle and pyruvate dehydrogenase (PDH). The NADH:NAD ratio also increases in the cytosol, further augmenting the rise in lactate (increased L:P ratio). In the mitochondria, the altered

TABLE 2

Whole blood amino acid concentrations in patient H.E. and in normal subjects ($\mu$moles/liter)

| | 4 hr. | 13 hr. | 17 hr. | Normal (n=5, S.E.M.) |
|---|---|---|---|---|
| Taurine | 753 | 364 | 348 | 209 ± 30 |
| Aspartic acid | 119 | 142 | 148 | 404 ± 108 |
| Threonine | 168 | 98 | 87 | 163 ± 37 |
| Serine | 150 | 84 | 90 | 168 ± 48 |
| Asparagine | 140 | 86 | — | 107 ± 40 |
| Glutamine | — | 118 | 232 | 704 ± 142 |
| Proline | 1,697 | 1,230 | 1,100 | 154 ± 27 |
| Glutamic acid | 310 | 355 | — | 253 ± 67 |
| Citrulline | 128 | 76 | 72 | 31 ± 6 |
| Glycine | 1,552 | 620 | 507 | 327 ± 58 |
| Alanine | 3,656 | 2,084 | 1,442 | 317 ± 43 |
| Valine | 684 | 339 | 244 | 230 ± 36 |
| Isoleucine | 333 | 152 | — | 82 ± 23 |
| Leucine | 635 | 224 | 213 | 136 ± 28 |
| Tyrosine | 322 | 141 | 97 | 62 ± 6 |
| Phenylalanine | 79 | 49 | 67 | 46 ± 5 |
| Ornithine | 101 | — | 97 | 77 ± 6 |
| Lysine | 941 | 258 | 273 | 203 ± 24 |
| Histidine | 99 | 86 | 136 | 59 ± 9 |
| Arginine | 38 | — | 10 | 64 ± 8 |

TABLE 3

Presenting features of phenformin-associated lactic acidosis from a review of seventy-six cases published in the English language literature [1-34]

| Parameter | Number of patients in whom the parameter was recorded | Frequency | |
|---|---|---|---|
| | | Number (with references) | Per cent |
| Clinical: | | | |
| Altered level of consciousness | 47,*† | 33 (1-4,6-16,18-19-23-26-28,29,32-34) | 70 |
| Gastrointestinal (nausea, vomiting, abdominal pain, diarrhea) | 41* | 34 (2,4-7,9,10,12-19,22-25,26,29,30,32,33) | 83 |
| Hypotension (systolic blood pressure below 100 mm. Hg) | 67 | 26 (3,4,7-10,13,14,18,21,23,25,29-31) | 39 |
| Kussmaul Respiration | 46* | 36 (1,4,6-10,12-16,18-20,22-25,28-30,32,33) | 78 |
| Hypothermia (Rectal temperature below 36.5°C) | 31† | 17 (4,7,10,12,20,22-24,26,32,34) | 55 |
| Extracellular Fluid Volume Contraction (Dehydration and/or a transiently elevated BUN) | 48 | 31 (1,2,4,6,8-10,14-16,18,23,26,30-32,34) | 65 |
| Laboratory: | | | |
| pH 7.32-7.11 | 67 | 22 (5,7,9,13,14,16,19-22,26,31) | 33 |
| pH 7.10 or below | 67 | 44 (1,4,6-8,10,11,14-19,24,25 28,30-34) | 66 |
| Diminished Renal Function (Creatinine greater than 1.4, or BUN greater than 20, or 'Renal Failure') | 68 | 61 (1-5,7-19,23,25,26,29-34) | 90 |
| Plasma ketones weakly positive or negative | 35†† | 34 (1,2,4,6-11,13-18,26,28-30,34) | 97 |
| Unmeasured anions greater than 15 mEq in excess of blood lactate (see test) | 20 | 16 (2,7,9,11,14-17,19,20,24,26,30,32) | 80 |
| Blood glucose: | | | |
| below 100 mg./100 ml. | 69 | 32 (1,4,5,7,9,16,18-22,24,25,31,32) | 46 |
| below 60 mg./100 ml. | 69§,// | 19 (1,5,7,16,18-22,24,31,32) | 28 |
| Leukocytosis (white blood count greater than 12,000/mm$^3$) | 20** | 16 (2,3,8-10,12-15,17,18,23,25,29) | 80 |

*This was implied in 'most' of a further twenty-one cases.[31]
†Phenformin-overdose patients excluded.[19,22,24,25]
‡Lowest reported temperature 26.7°C rectal.[4]
§All overdose patients below 60 mg./100 ml.
//Lowest value 5 mg./100 ml.[1,18]
**Highest value 60,000/mm$^3$.[25]
††One case 'moderate'.[18]

NADH:NAD ratio causes a relative decrease of acetoacetate and increase of β-hydroxybutyrate levels which may be reflected in blood concentrations.[26,50] These effects could occur with usual therapeutic doses of the drug because of diminished renal excretion resulting from either intrinsic renal disease or volume contraction (table 3).

The indirect effects of phenformin in this condition would relate to the "fasted" state induced by the anorexia and gastrointestinal symptoms demonstrated by most patients with this condition (tables 1 and 3). The metabolic consequences of the fasted state, in large measure mediated by fall in insulin levels,[56] include fat mobilization and consequent fatty acid oxidation (and ketogenesis) in the hepatocyte (site 2a, figure 1). The latter leads to inhibition of PDH activity,[57-59] further decreasing pyruvate oxidation via the TCA cycle, thus enhancing pyruvate, lactate and alanine accumulation.

Any factor leading to relative or absolute insulin deficiency, superimposed upon the background of the direct hepatic phenformin effects described, would

TABLE 4

Survival in phenformin-associated lactic acidosis from a review of seventy-six cases published in the English language literature[1-34]

| | Number of Cases (with references) | Frequency of Fraction Surviving No. | Per cent |
|---|---|---|---|
| No insulin therapy | 40 (7-9,11,13-15, 17-19,22,23,25, 31,33) | 19 | 48 |
| Insulin therapy | 26 (1-10,12-14,16, 24,26,27,29,31, 32,34) | 17 | 65 |
| Treatment not stated | 10 (7,20,21,28,30) | 5 | 50 |
| Overall | 71* | 41 | 58 |

*Outcome was not stated in five cases.[7,20]

potentiate the lactic acidosis. Whereas the phenformin-related effects can lead to pyruvate accumulation by decreasing its metabolic removal via the TCA cycle, insulin deficiency would amplify such accumulation through accelerated presentation of pyruvate precursors from peripheral tissues to the liver (site 2b, figure 1). Such precursors take the form of lactate itself, and of amino acids whose conversion to glucose passes via pyruvate. The level of peripheral substrates is regulated by insulin which acts to diminish release of amino acids originating in, for example, muscle protein.[60] In normal subjects, provision of insulin in adequate postabsorptive amounts is sufficient to prevent massive muscle release of amino acids. This is lacking in patients with diabetes mellitus, and may be further exacerbated as an indirect consequence of the phenformin-related gastrointestinal disturbances. Indeed, gastrointestinal upset (nausea and vomiting) is the commonest side-effect of

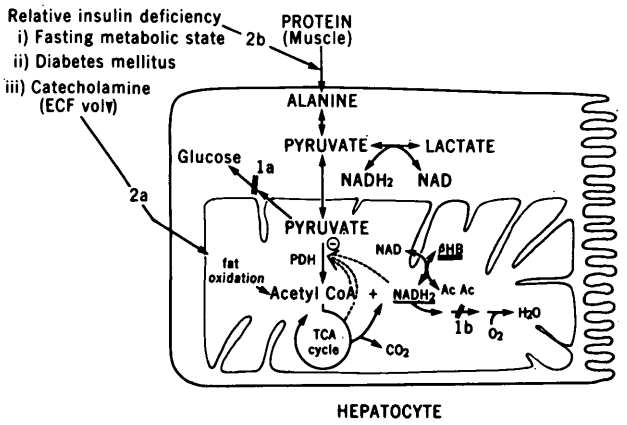


FIGURE 1

phenformin. In the cases reviewed these symptoms were prominent prodromal features in a high percentage and could have contributed to the volume contraction so frequently reported (table 3). Epinephrine and norepinephrine secretion is increased in response to extracellular fluid volume contraction and these catecholamines are capable of inhibiting insulin secretion.

Hence, the inhibition of pyruvate formation by therapeutic insulin administration (with glucose if required) may be specific for at least part of the underlying metabolic abnormality. The decrease in most plasma amino acids observed with therapy in this patient (table 2), associated with improvement in clinical and biochemical parameters, may in part be attributable to an insulin effect. Reduction of muscle proteolysis would be implied by the profound fall in lysine levels (this amino acid is not metabolized by liver) and in levels of the branched-chain amino acids, valine, leucine and isoleucine.[60] It is of interest that both endogenous and exogenous insulin have been demonstrated to decrease the hyperlactatemia induced by large doses of phenformin in dogs.[61]

Relative insulin deficiency was present in our patient as evidenced by the immunoreactive insulin (IRI) value of 3 μU/ml. when the blood glucose value was 179 mg. per 100 ml. However, the hallmarks of insulin deficiency, namely hyperglycemia and a strongly positive nitroprusside reaction for serum ketones, were absent at presentation. Hyperglycemia may not be present because of the hypoglycemic effects of phenformin described above. In addition, the altered β-hydroxybutyrate:acetoacetate ratio consequent on elevated NADH has been shown to obscure the detection of the presence of significant amounts of ketone body in lactic acidosis.[26,50] This is because the nitroprusside test detects ketone bodies present as acetoacetate and acetone, but not as β-hydroxybutyrate. In 97 per cent of reported cases (table 3) and in the present case, the nitroprusside reaction was, at most, weakly positive. However, in 80 per cent of the cases in which they were recorded (table 3), the unmeasured anions exceed the lactate concentration by more than 15 mEq/L. Such findings are consistent with a high incidence of unrecognized but significant ketonemia.

There is an additional pitfall in the clinical use even of total blood ketone body level as a reflection of the rate of ketogenesis. The circulating level of ketone bodies is a function both of rates of production and removal. Since it has recently been shown that the infusion of lactate increases renal clearance of ketone

bodies,[62] increased ketone body excretion would be expected in lactic acidosis. Hence elevated levels of β-hydroxybutyrate in phenformin-associated lactic acidosis[4,13,26] (1.7-4.8 mM, table 1, with normal less than 0.1 mM) might in fact underestimate the rate of ketone body formation. Thus the degree to which ketogenesis contributes to acid production would also be underestimated.

*Therapy of phenformin-associated lactic acidosis*

Phenformin-associated lactic acidosis has a high mortality (table 4). The cornerstone of therapy is correction of acidemia by administration of alkali, usually in massive doses. Sodium bicarbonate is probably the alkali of choice.[33,63] The attendant complications of sodium overload and potassium fluctuations require careful monitoring and appropriate management. It is apparent that therapy directed at the acidemia alone is not sufficient to correct the metabolic derangement. Additional therapy directed towards the latter would be desirable. From the foregoing discussion, insulin therapy might be expected to reverse at least part of the metabolic disorder.

It is suggested that many of the parameters of deranged metabolism measured in the case reported here began reverting to normal, coincident with the expected onset of action of the insulin administered (table 1).

Twenty units of insulin given at time 6 hours were insufficient to reverse the metabolic parameters reflecting insulin deficiency. Relative insulin resistance may have been present at that time (for example, the blood pH was 7.15) or simply more insulin may have been required. However, after 60 units of insulin had been administered, a return towards normal of the unmeasured anions, blood lactate, pyruvate, ketoacids and alanine is noted (table 1). In fact, the continued rise in unmeasured anions in the first eleven hours, during which time the acidosis was fully corrected by the administered sodium bicarbonate, indicates progression of the metabolic parameters independent of the acid-base status. Insulin deficiency was evidenced by the hyperglycemia induced by the small amounts of glucose infused early in the course, and by the increased blood concentrations of β-hydroxybutyrate and the insulin-sensitive amino acids. With insulin therapy the blood ketone bodies, amino acids as well as lactate and pyruvate levels fell toward normal.

Table 4 summarizes the outcome of seventy-six reported cases of phenformin-associated lactic acidosis. The groups receiving insulin and not receiving insulin are not matched and there are limitations to the conclusions which can be drawn. However, it is tentatively suggested that insulin administration enhances survival. The indication for insulin administration was hyperglycemia in most instances, though in some[16,31,32] it was the lactic acidosis per se.

Other modalities of therapy have been proposed. Hemodialysis may be of potential value in enhancing removal of phenformin end products, although there is insufficient evidence to evaluate its efficacy.[3,19,30] Peritoneal dialysis is inefficient in this regard.[8,14] The value of hemodialysis in control of sodium overload during therapy is more definite, though it is usually not required. Hemodialysis also removes the lactate anion, which is not the cause of the metabolic derangement and its presence is not harmful. In fact there are practical advantages in not removing the lactate by dialysis. First, the blood lactate level is directly reflected in the unmeasured anions, which, after the initiation of alkali therapy, provide the most valuable indication of the progress of the underlying metabolic abnormality (table 1). Second, when the metabolic derangement is reversed and lactate metabolism commences, large amounts of endogenous bicarbonate ion are produced. Indeed, an alkaline overshoot sometimes occurs[28] (table 1).

The use of methylene blue as a proton acceptor from NADH has been advocated.[1,10,18,33] Although this might be expected to restore the L:P ratio to normality, it does not remove the block which exists to pyruvate metabolism. Thus its usefulness in therapy of lactic acidosis is confined to those situations where pyruvate metabolism is diminished consequent to a reduced blood pyruvate level. The lactic acidosis which is alcohol induced is such an example.[64] In phenformin-associated lactic acidosis, blood pyruvate levels are increased (table 1).

In summary, it is proposed that the objectives of therapy should be to a) maintain and restore pH in a safe range with the use of alkali, and b) diminish pyruvate load (and augmented ketone body formation if present) with insulin, while waiting for renal excretion of phenformin and metabolites, the presumed cause' of the derangements. Attention is also given to fluid repletion, maintaining tissue perfusion and oxygenation. In this way many self-perpetuating features of the condition are reduced.

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