Lactic Acidosis in Diabetics

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SUMMARY

Eleven diabetic patients were admitted to Groote Schuur Hospital during the past year with severe lactic acidosis; 8 patients recovered and 3 died. All were middle-aged or elderly, taking phenformin, and suffering from a complicating disorder including Gram-negative septicaemia, shock, chronic hepatic disease and chronic renal disease. In some the complicating feature was not in itself serious, either a short anaesthetic or an upper respiratory tract infection, or minor alcohol ingestion. The purpose of this article is to draw attention to a serious complication of phenformin therapy in the patient who has any predisposition to the accumulation of lactic acid.

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Coma in a diabetic may have many causes (Table I). With the advent of modern therapeutic regimens, including insulin, antibiotics, adequate potassium and better intravenous fluid therapy, the mortality from ketotic stupor has been reduced from approximately 94% in the early 1930s and 1940s[1] to around 1,5 - 10% in the 1960s.[2-4]

TABLE I. TYPES OF METABOLIC COMA IN DIABETICS*

Hyperglycaemic
Ketotic hyperosmolar
Non-ketotic hyperosmolar
Lactic acidosis
β-OH-butyric acidosis
Normoglycaemic
Acidotic non-ketotic — mixed lactic acidosis and β-OH-butyric acidosis
Hypoglycaemic
Insulin excess
Oral hypoglycaemic drug (sulphonylurea) excess
Miscellaneous causes — e.g. insulinoma, auto-antibodies, congestive cardiac failure, adrenergic β-receptor blockade, renal failure, chronic pancreatitis

* Excluding more general causes of coma such as uraemia, hepatic encephalopathy, cerebrovascular accident, etc.

With this reduction in mortality from ketotic diabetic stupor, attention has recently been focused on a type of coma in diabetics with acidosis but no ketosis. For some time now it has been recognised that diabetic stupor with acidosis may occur, which is not due to keto-acids, drugs or uraemia. The suggested culprits are lactic acid and/or beta-hydroxybutyric acid.

It is the purpose of this article to report on those diabetic patients who presented at Groote Schuur Hospital with acidotic non-ketotic stupor during the period May 1972 to December 1973.

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CASE REPORTS

Patient 1

A 65-year-old, Coloured, obese female, diabetic for many years and controlled on tolbutamide and phenformin (Insoral), was also hypertensive and had been treated for a paranoid illness. Having developed progressive blindness over the previous 3 years, she was admitted for a lens extraction. After the anaesthetic she failed to recover consciousness and remained in a drowsy, confused state. She was incontinent, with mildly acidotic breathing; her pulse rate was 82/min, blood pressure 190/100 and she was mildly dehydrated. The relevant initial biochemical investigations appear in Table II. She was treated with 400 mEq sodium bicarbonate intravenously and 0,45% (half normal) saline alternating with dextrose water with one unit of insulin for every 2.5 g of glucose infused. She made a rapid, uneventful recovery within 24 hours. However, two days later she again became acidotic, with a fall in pH to 7,32 and a base excess of −14; she was again given 400 mEq sodium bicarbonate and recovered within 12 hours. On metformin (Glúcophage) her diabetes has since been well controlled without recurrence of lactic acidosis.

Patient 2

Diabetic since 1966, this female had been treated with 1,5 g tolbutamide and 100 mg phenformin (Insoral T.D.) since the onset of the illness. She was also treated for congestive cardiac failure. During the week before admission she had complained of a progressive cough with the production of greenish-yellow sputum, shortness of breath, loss of appetite and a feeling of general malaise and pyrexia. On admission she was distressed, dyspnoeic and mildly cyanosed, with blood pressure 140/60 and pulse rate 90/min. With clinical and radiographic evidence of bilateral bronchopneumonia, she was treated in a routine manner, and the phenformin and tolbutamide were continued. Four days after admission she became acutely dyspnoeic and acidotic without ketonuria or glycosuria, and biochemical investigation revealed severe lactic acidosis. She was immediately taken off phenformin and forced diuresis was attempted with Lasix and intravenous half normal saline with sodium bicarbonate to correct the metabolic acidosis.

TABLE II. CLINICAL AND INITIAL METABOLIC FEATURES

Patient	Sex	Age (yrs)	Diabetes: Duration (yrs)	Diabetes: Therapy: Drug	Diabetes: Therapy: Daily dose and duration of treatment	Complicating factors	Initial blood or plasma values: Time after onset (days)	Glucose (mg/100 ml)	Osmolality (mOsm/kg) (normal 280 - 295)	pH	Na^+	K^+	Cl^- (mEq/litre)	HCO_3^- (mEq/litre)	BE	Anion gap	Urea (mg/100 ml)	Lactate (mg/100 ml) (normal 6 - 16)	White blood cells/mm^3	Therapy	Outcome
1	F	65	10	Phenformin Chlorpropamide	100 mg yrs 250 mg yrs	Hypertension Gen. anaesthetic	4	176	288	7,36	144	3,8	112	12	−12	24	145	87	12 500	400 mEq $NaHCO_3$ Insulin and glucose	Recovered Metformin
2	F	70	8	Phenformin Tolbutamide	100 mg 8 yrs 1,5 g 8 yrs	CCF, bronchopneumonia Chr. renal disease	7	138	290	7,20	132	5,4	105	6	−22	27	95	151	4 500	600 mEq $NaHCO_3$ Insulin, glucose and Isuprel	Recovered Metformin
3	F	70	10+	Phenformin	100 mg yrs	Septicaemia, shock DIC, enteritis	2	180	306	7,30	135	5,0	90	8	−18	42	100	90	27 000	Heparin, IV fluid 400 mEq $NaHCO_3$	Recovered Acetohexamide
4	F	69	? Yrs	Phenformin Chlorpropamide	100 mg yrs 500 mg yrs	Anaemia, shock ? Septicaemia	3	128	317	6,5	136	6,7	101	11	−16	30	150	115	—	400 mEq HCO_3 Isuprel	Died (irreversible shock)
5	M	74	7	Phenformin Metformin	100 mg 2 yrs 1,5 g 2 yrs	Diarrhoea, GI bleed, shock	4	200	326	6,98	136	5,0	96	—	Unrecordable	—	200	150	19 200	$NaHCO_3$	Died after 5 h
6	M	69	2	Phenformin Metformin and phenformin	100 mg 2 yrs 1,5 g 1 mo.	IHD, renal disease 1 tot whisky	1	174	306	7,09	137	4,3	—	—	Unrecordable	—	86	—	12 600	350 mEq HCO_3	Recovered Metformin
7	M	58	13	Phenformin	100 mg 2 mo.	CCF, shock Chr. renal disease	2	78	303	6,8	131	4,7	89	—	Unrecordable	—	160	—	10 500	1 000 mEq HCO_3 Isuprel, Glucagon, Cortisol	Died after 4 h
8	F	73	8	Phenformin Chlorpropamide	100 mg 1 mo. 500 mg 1 mo.	URT infection	1	290	317	6,8	137	5,8	85	7	−25	51	89	—	32 000	$NaHCO_3$, plasma, corticosteroids	Recovered Glibenclamide
9	F	60	10	Phenformin Chlorpropamide	100 mg yrs 500 mg yrs	Urinary infection, abdominal pain, controlled hypertension	1	372	331	7,14	139	6,1	96	9,5	−27	40	127	131	15 400	250 mEq $NaHCO_3$ Insulin	Recovered Chlorpropamide
10	M	59	1	Phenformin Chlorpropamide	300 mg 1 mo. 500 mg 2 mo.	Cirrhosis, chronic renal disease, GI bleed, shock	14	564	338	6,9	138	6,5	98	9	−24	37	98	35	13 800	Dialysis $NaHCO_3$	Recovered
11	F	66	26	Phenformin Chlorpropamide	100 mg yrs 250 mg yrs	CCF, COAD, bronchopneumonia, chronic renal disease	21	236	321	7,02	135	6,4	—	—	—	—	155	197	9 750	$NaHCO_3$ IV fluids	Recovered

Significant ketonaemia or ketonuria absent in all cases.

She required repeated administration of bicarbonate.

An incorrect serum sodium reading of 160 mEq/litre suggested excessive administration of saline, and attempted correction with hypotonic fluids resulted in hypotension and repeated epileptiform seizures. The diagnosis of water intoxication was made and therapy with Lasix and isopropyl noradrenaline instituted. The patient continued to deteriorate and developed respiratory failure, for which tracheotomy was performed and she was placed on the Bird respirator. After a stormy course in the respiratory unit, she recovered and has since been well controlled on sulphonylurea alone.

Patient 3

A 70-year-old White female was admitted in a collapsed state, having been diabetic for many years with a long history of alternating constipation and diarrhoea. Several days before admission she had coryzal symptoms with fever and a general feeling of malaise and on the day of admission was found lying collapsed on the floor in a pool of diarrhoea, although conscious and able to complain of an inability to move.

Several months before admission she had been assaulted and suffered mild head injury; since then her personality had changed and she required psychotherapy, together with Valium, Mogadon, and Aldomet for mild hypertension.

On admission she was stuporous, markedly dehydrated and pyrexial. She was clinically anaemic and perspiring profusely, with pulse rate 160/min, peripheral pulses impalpable and the skin warm to the touch, despite a blood pressure of 80/60. She was breathing at a rate of 45/min, and had bruises on the legs and purpuric lesions on the anterior abdominal wall compatible with septicaemia. Investigation suggested a Gram-negative septicaemia and disseminated intravascular coagulation. She also had evidence of diabetic peripheral neuropathy and autonomic neuropathy with bladder and bowel dysfunction, deep vein thrombosis and a urinary tract infection which was probably the origin of the septicaemia. The relevant biochemical features are given in Table II.

The marked metabolic acidosis was thought to be due to lactic acid, which may have been related to the combination of shock, septicaemia and the phenformin therapy. She was treated with intravenous fluid, 400 mEq sodium bicarbonate and heparin because of the disseminated intravascular coagulation, but no insulin. She made a gradual and uneventful recovery, the urinary tract infection being found to be due to a *Klebsiella* organism, for which suitable antibiotic therapy was given.

Patient 4

A frail 69-year-old White woman, a known diabetic, had been treated for many years with chlorpropamide and phenformin. For one week before admission she complained of nausea, vomiting and constipation. She was diagnosed as having faecal impaction, and was disimpacted under general anaesthesia. On the day of admission a practitioner noticed her breathing abnormally fast and deeply and that she was comatose. He diagnosed bronchitis and referred her in a shocked state with an unrecordable blood pressure.

The clinical picture was one of gross acidosis and shock without an obvious cause. The relevant biochemical investigations (Table II) showed a pH of less than 6,5 with the remaining acid-base values unrecordable, and she was given 400 mEq sodium bicarbonate and an isoprenaline infusion. The pH rose to 7,14 and the base deficit became measurable at −16. The serum sodium after the administration of sodium bicarbonate rose to 145 and the potassium to 5,2. She was given penicillin, gentamicin and hydrocortisone, but developed an extreme bradycardia while on isoprenaline therapy; her blood pressure became unrecordable; the acidosis was never corrected and she died 12 hours after admission.

Patient 5

A 74-year-old White diabetic male had had an aortic valve replacement many years ago, and having been in congestive cardiac failure for the past 2 years, he required vigorous therapy. He had been treated for his diabetes with phenformin and metformin. Four days before admission a watery diarrhoea was treated with Lomotil but his stools had become black, suggesting melaena.

He was critically ill and severely acidotic with gross anaemia; his pulse was 130/min, and the blood pressure unrecordable. The relevant biochemical investigations are shown in Table II. The patient was terminal, and despite vigorous therapy with intravenous alkali and supportive drugs he died 4 - 5 hours after admission.

Patient 6

A 69-year-old White male, who had been diabetic for approximately 2 years, had been managed on diet and phenformin until a short while previously when he was supposed to have stopped phenformin and started metformin. On the morning of admission he went gardening, having had a tot of whisky first. Later he suddenly developed severe nausea, vomited and passed a few loose stools. He felt extremely weak and was referred to hospital.

Clinically there was nothing to note except the presence of acidosis, ECG evidence of a previous myocardial infarction, and a raised serum creatinine suggesting chronic renal disease. The diagnosis of lactic acidosis was made and the patient treated with half normal saline and infusion of 4,2% sodium bicarbonate. The acidosis was corrected within 3 hours of administration of 350 mEq sodium bicarbonate. His recovery was uneventful and he was discharged on metformin. His diabetes is now well controlled.

Patient 7

A 58-year-old White male diabetic on phenformin treatment, was known to have mild chronic renal disease and congestive cardiac failure. He presented at hospital with a 2-day history of feeling unwell. On the morning of admission he had become dyspnoeic and confused. His pulse was 80/min, blood pressure 50/0, and respiration was rapid (rate 50/min), deep and sighing. He also

had a 10-cm, hard, non-tender hepatomegaly but no clinical signs of hepatic insufficiency.

The clinical picture was one of severe acidosis and hypotension, and he was given oxygen, intravenous sodium bicarbonate in copious quantities with potassium chloride as necessary. He received Lasix 100 mg followed by 200 mg, which produced no urine flow. He was given 1 g hydrocortisone intravenously, isoprenaline at the rate of 1 μg/min, without any effect, and glucagon 1 mg intravenously *stat* and 3 mg slowly over one hour by continuous infusion, which also had no effect. He also received calcium gluconate, 18 ml slowly intravenously, because of the cardiogenic shock. Two hours after admission his pH was still 6,83 and the rest of the figures unrecordable. The serum sodium at that stage was 138 and potassium 4,6. In spite of all these measures the blood pressure did not rise and the patient died 4 hours after admission.

Patient 8

A 73-year-old White female, a known diabetic for many years, had been treated on a variety of oral antidiabetic agents—latterly chlorpropamide and phenformin. She had been ill for two weeks with chest pain suggestive of myocardial ischaemia. Six days before admission she developed a dry cough which was treated with tetracycline; she had felt very poorly and remained in bed. Her appetite had become extremely poor and she hardly ate, but continued to take her antidiabetic medication. On the night before admission she awoke with severe retrosternal, burning chest pain which was not relieved by trinitrin, and which lasted for over an hour. She vomited once but did not sweat. She became confused, partially dysarthric but still conscious, and was noted to be hyperventilating. She was admitted to hospital, where a diagnosis of myocardial infarction was made and she was given morphine and Valium. She became unconscious, her hyperventilation increased and she became comatose and extremely dehydrated; pulse rate was 100/min with an elevated jugular venous pressure and crepitations at both bases. The biochemical investigations appear in Table II.

She was given large doses of parenteral fluid, including plasma and steroids. The metabolic acidosis was corrected with sodium bicarbonate, the urine output improved and she regained consciousness. Although the ECG showed no evidence of myocardial infarction, the transient rise in enzyme levels was suggestive. Her diabetes was initially controlled on insulin therapy and subsequently easily managed on glibenclamide 5 mg twice a day.

Patient 9

A 60-year-old lean Coloured female, diabetic for 10 years, suffered progressive loss of vision due to diabetic retinopathy and mild hypertension. She had been treated with phenformin 50 mg twice a day and chlorpropamide 375 mg/day for many years, and hypotensive drugs including Rautrax, hydralazine and Aldomet. Having been ill for only one day, she complained of abdominal pain and vomiting, and on admission was found to be stuporous, hypotensive (blood pressure 85/60) and mildly dehydrated. Apart from the investigations mentioned in Table II, she had elevated serum lactate dehydrogenase, creatinine phosphokinase and aspartate amino transaminase. The urine was infected with a Gram-negative organism.

She was treated with half normal saline infusion, 250 mEq sodium bicarbonate and 60 units of insulin in divided doses, and made an uneventful recovery within 12 hours. Before discharge, however, on chlorpropamide 100 mg/day, she developed an episode of frank keto-acidotic coma requiring retreatment with insulin and saline infusions, but made an uneventful recovery and has since been maintained on 300 mg chlorpropamide a day.

Patient 10

A 59-year-old lean male, diabetic for approximately one year, was also suffering from cirrhosis of the liver associated with chronic alcohol abuse, and chronic renal failure; the previous creatinine clearance, a month earlier, had been 16 ml/min. For two months before admission he had been uncontrolled on 6 chlorpropamide tablets (1 500 mg) and 6 phenformin tablets (300 mg) daily. For two weeks before admission he complained of chest pain and melaena and was admitted in a shocked state with severe hypotension, melaena stools and marked pallor. He was severely acidotic with very severe air hunger and his haemoglobin was less than 5 g/100 ml.

The acidosis was corrected readily with intravenous fluid, sodium bicarbonate and peritoneal dialysis. Within 12 hours he became severely alkalotic, with pH 7,5, and the blood sugar had risen to over 980 mg/100 ml. He was given insulin intravenously and the hyperglycaemia was easily controlled. He remained well until he developed a massive melaena and at emergency laparotomy a gastric neoplasm was found. The further outlook must be grim.

Patient 11

A 66-year-old White female, a known diabetic for 26 years, had taken phenformin 50 mg *b.d.* for many years. She also suffered from obstructive airways disease with chronic cor pulmonale and chronic renal disease. In 1971 the creatinine clearance had been 31 ml/min. Having been ill for 3 weeks, with increasing cough and dyspnoea, she was admitted with a diagnosis of bilateral bronchopneumonia. She was found to be normotensive, mildly dehydrated, and hyperventilating out of proportion to the degree of respiratory disease. In view of the phenformin treatment, the diagnosis of lactic acidosis was suspected and confirmed on biochemical testing. She was treated with intravenous fluid and bicarbonate. She was subsequently successfully managed on chlorpropamide 100 mg/day.

DISCUSSION

We are concerned here essentially with the acidotic, non-ketotic varieties (no measurable excess of acetone or acetoacetic acid) of diabetic stupor (Table I), which may occur with either normoglycaemia, mild hyperglycaemia or hypo-

glycaemia. Three varieties of acidosis occur in this situation: lactic acidosis, beta-hydroxybutyric acidosis and a combination of the two (uraemic acidosis may be coincidental). One of these varieties must be present when the anion gap $[(Na^+) - (Cl^- + HCO_3^-)]$ is greater than 20 mEq/litre in the absence of uraemia, drug ingestion such as salicylate, paraldehyde, methanol, or ethylene glycol, and when ketone bodies are insufficient to account for the anion gap.

It has been suggested that in some diabetic non-ketotic acidosis syndromes, beta-hydroxybutyrate might be responsible. From the equations:

$$\text{(i) pyruvate} + \text{NADH} + H^+ \xrightleftharpoons[\text{dehydrogenase}]{\text{lactate}} \text{lactate} + \text{NAD}$$

$$\text{(ii) aceto-acetate} + \text{NADH} + H^+ \xrightleftharpoons[\text{dehydrogenase}]{\text{beta-hydroxybutyrate}} \text{beta-hydroxybutyrate} + \text{NAD}$$

it can be seen that there is an equilibrium between cytoplasmic pyruvate and lactate and mitochondrial aceto-acetate and beta-hydroxybutyrate. The reaction is dependent on the redox state of the cell; that is to say, the presence of excess hydrogen ion favours the accumulation of lactate and beta-hydroxybutyrate. Unfortunately, the sodium nitroprusside test, as used with either Ketostix or Acetest tablets on the plasma and urine, does not detect beta-hydroxybutyrate but only aceto-acetate and acetone.

To diagnose this variety of acidotic non-ketotic syndrome the rapid enzymatic assay for ketone bodies[4] is necessary, and this is unfortunately not in general use. It is, however, uncertain whether a beta-hydroxybutyrate excess syndrome exists in a pure state.[5]

Our 11 patients present the problem of severe acidosis with a marked anion gap and the accumulation of excess lactic acid,[6,7] proven in most and probable in the rest.

Lactate is produced essentially as an end-product of anaerobic glycolysis. Table III shows the normal lactate balance in resting man over a 24-hour period. Nearly all tissues in the body, but particularly skeletal muscle and erythrocytes and also liver, produce lactate. Removal of lactate occurs principally in the liver; its capacity for removal of lactate normally greatly exceeds the production rate. Increased lactate levels in the blood must result from either increased production or decreased utilisation.

TABLE III. NORMAL LACTATE BALANCE (g/24 h)

Production		Uptake	
Red blood cells	34	**Liver**	33
Skeletal muscle	18	**Cardiac muscle**	11
Adipose tissue	9	**Kidneys**	11

The liver can extract ± 240 - 400 g/day; extrahepatic tissue can extract ± 100 g/day.

Liver disease or liver anoxia will result in lactic acid accumulation because of its decreased ability to remove lactate.[8,21] The contributory effect of alcohol is important. The metabolism of alcohol to acetaldehyde and thence to acetate also requires a reduction of NAD to NADH.[9] The resultant increase in the NADH/NAD ratio causes a change in the equilibrium of lactate and pyruvate towards accumulation of lactate.[10] Hence, alcohol ingestion superimposed on any cause for lactate over-production will accentuate the rise in lactic acid concentration.

Lactic acidosis has frequently been described as a complication of phenformin therapy in diabetic patients. In 1959 Lexow[11] reported 3 fatal cases of diabetic coma without ketosis. In the same year Walker and Linton[12] described several instances of metabolic acidosis among a series of diabetics treated with phenformin. Subsequently at least 111 case reports have appeared in the literature, and an additional 80 alleged cases of lactic acidosis have been reported directly to the manufacturers of phenformin. Since treatment with phenformin in therapeutic doses results in a small elevation of the resting blood lactate concentration,[13] and phenformin can experimentally be shown to inhibit oxidative metabolism,[14] a possible link between phenformin treatment and the development of lactic acidosis is clear. Somewhat paradoxically, however, Ungar *et al.*[15] observed that some biguanides, which are effective hypoglycaemic agents *in vivo*, have little or no inhibitory effect on tissue oxidation *in vitro*. Biguanides in certain situations have even been shown to increase oxidative phosphorylation, as in the case of metformin even at high concentrations, according to Meyer.[16] Metformin has hardly ever been reported in relation to lactic acidosis in patients with diabetes mellitus, although it has the same effect on rat hepatic lactate metabolism as phenformin,[8] and in clinical use has been given in much larger doses than phenformin. It has further been observed that patients who have developed hyperlactacidaemia with phenformin do not do so with metformin.

The dose of phenformin required to inhibit lactate utilisation by the liver in animal studies has been considerably greater than that used in treatment of diabetics. However, it is feasible that phenformin might be concentrated to a great extent in the liver, and thus in certain circumstances could reach the concentrations required for inhibition of lactate utilisation. There is experimental evidence which supports this suggestion. Bingle *et al.*[17] found a hepatic concentration of phenformin 20 times that in blood in a case of fatal lactic acidosis that occurred in a phenformin-treated diabetic.

In the seriously ill, shocked or septicaemic patient, Watkins *et al.*[18] showed that lactic acidosis may occur frequently in the absence of phenformin. Nevertheless, a recent review indicates that diabetic patients who are ill for any reason at all, or with any one of the complicating factors listed in Table IV, are more liable to lactic acidosis while on phenformin therapy. Some clinicians[19,20] consider phenformin to be a contributory (background) factor in the development of lactic acidosis, and recommend that it should be withdrawn whenever a risk of lactic acidosis from any other cause arises; also it should not be given to patients with renal or hepatic disease. Phenformin is partially metabolised by the liver and excreted by the kidney; any disease of the liver or the kidney could therefore result in its excessive accumulation. Any

TABLE IV. CONDITIONS WHICH PREDISPOSE TO LACTIC ACIDOSIS

- Chronic renal disease
- Cirrhosis of the liver
- Infection — especially Gram-negative septicaemia and pulmonary infection
- Diabetes mellitus
- Pancreatitis — haemorrhagic
- Shock — hypotension
- Hypoventilation
- Generalised vascular disease with poor tissue perfusion
- Drugs, e.g. phenformin, ethylene glycol, methanol, paraldehyde, fructose infusions, alcohol
- Beri-beri
- Anaesthesia
- Leukaemia and lymphoma

TABLE V. LACTIC ACIDOSIS IN DIABETES

- Clinical characteristics
  - Onset acute (often unsuspected)
  - Depressed level of consciousness, abdominal pain, azotaemia
  - Associated conditions — infection, hepatic disease, renal, alcohol or drug, e.g. phenformin, ingestion
  - Hyperventilation
  - Resistant to $NaHCO_3$, requiring large amounts
  - High mortality
- Metabolic characteristics
  - Acidosis
  - Low serum $NaHCO_3$, low pH
  - Anion gap not accounted for by ketoacids or drugs, e.g. salicylates
  - $[Na^+]$ normal or low
  - $[Cl^-]$ normal or low
  - $[K^+]$ usually high
  - Raised lactate and increased lactate/pyruvate ratio

disease decreasing renal blood flow would also tend to reduce elimination of phenformin.

It is evident from the presenting features (Table V) of our 11 diabetic patients that in each instance there was a complicating problem, e.g. shock, bronchopneumonia, etc., but every patient had been taking phenformin. The survival of 8 of these 11 patients is better than the usually reported 50-65% mortality, but the numbers are small. Awareness of this complication and rapid and energetic treatment (Table VI) are important.

Finally, we emphasise the possibility of prevention of lactic acidosis by the avoidance of phenformin in patients with chronic liver or renal disease, or in those who are liable to myocardial infarction or respiratory infection, or who are suffering from any serious acute medical condition, or who are about to have general anaesthesia. Even moderate amounts of alcohol may be dangerous in phenformin takers.

TABLE VI. SUGGESTED MANAGEMENT

- Prophylactic
  - Avoid phenformin in patients with liver or renal disease, recent myocardial infarction, chronic respiratory disease and alcohol abuse
  - Stop phenformin with acute respiratory infections, hypotension or shock, gastro-enteritis and before general anaesthesia
- Therapeutic
  - Stop biguanide therapy
  - Decrease hypoxia
  - Correct dehydration and hypovolaemia — monitor central venous pressure
  - Correct shock. Avoid vasoconstrictors (e.g. noradrenaline) which cause lactate accumulation
  - Correct acidosis with bicarbonate — never lactate. May require large doses — 200 - 1 000 mEq. Care with serum potassium
  - Forced diuresis — to increase excretion of biguanides
  - ? Methylene blue (1 - 5 mg/kg IV) as H^+ acceptor
  - ? THAM (tris hydroxymethylaminomethane) as a buffer is free of Na^+ and therefore useful in cardiac or renal disease
  - Dialysis may remove drug + lactic acid but fluid usually contains lactate
  - Insulin only if lactate does not fall with other measures.

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