Diabetologia 14, 75–87 (1978)

Diabetologia

Originals

Lactic Acidosis in Biguanide-Treated Diabetics

A Review of 330 Cases

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Summary. The paper presents an analysis of clinical symptoms, signs and laboratory data of 330 diabetic patients who developed lactic acidosis after having been treated with biguanides (phenformin, buformin, metformin). From the review of the literature an attempt is made to find special features that predisposed patients to develop lactic acidosis such as accompanying illnesses and additional medications, to describe the course of illness and also the factors that influenced the prognosis. Of the patients that developed lactic acidosis 50.3% died. These patients were older, they suffered more frequently from cardiovascular shock, their acidosis was more severe, the whole blood lactate concentration was higher, and the degree of renal insufficiency was more advanced. From our observations we conclude that the treatment of diabetes mellitus with biguanides should be reserved for specially selected patients.

Key words: Diabetes mellitus, phenformin, buformin, metformin, lactic acidosis, adverse drug effects

In 1918 Watanabe [1] first described the hypoglycaemic action of guanidine. In the 1920's diguanides (synthalin A and synthalin B) were introduced for the treatment of diabetes mellitus. A few years later these drugs came into disrepute because of hepatotoxic effects in animals. These observations and the introduction of insulin led to the withdrawal of these agents. It was not until 1953 that substituted biguanides with a hypoglycaemic action were synthesized and in 1956 these were first used in the treatment of diabetics [2–5]. Of the large number of biguanides only three are in common usage:

1. Phenformin (1-(β-phenethyl)-biguanide)
2. Buformin (1-butyl-biguanide)
3. Metformin (1,1-dimethyl-biguanide).

Walker and Linton [6] in 1959 described the clinical picture of severe metabolic acidosis without ketosis in biguanide-treated diabetics. The accumulation of lactic acid soon became recognized as the cause of the acidosis. This severe metabolic disturbance was initially only rarely described and there was uncertainty whether the biguanides were the causative drugs [7]. Recently more and more cases have been reported from the USA, Great Britain, the Scandinavian countries, France and Germany. The laboratory proof of a markedly elevated concentration of biguanides in plasma and of lactate in whole blood has been made possible by the development of sensitive and specific biochemical methods [8–10]. This now allows for a reliable correlation between the use of biguanides and the development of lactic acidosis [11].

After a thorough review of the available literature, an attempt has been made to find characteristic features of patients suffering from lactic acidosis. These features include their histories, accompanying illnesses, additional drugs that were taken, course of their illness, and factors influencing the prognosis.

The biochemical aspects of lactic acidosis and the action of biguanides will not be discussed. Several reports over the past years have dealt with this subject [12–18].

Methods

The literature was reviewed by means of the Index Medicus and by collecting references of other published cases. In the evaluation of the case reports the following criteria had to be fulfilled:

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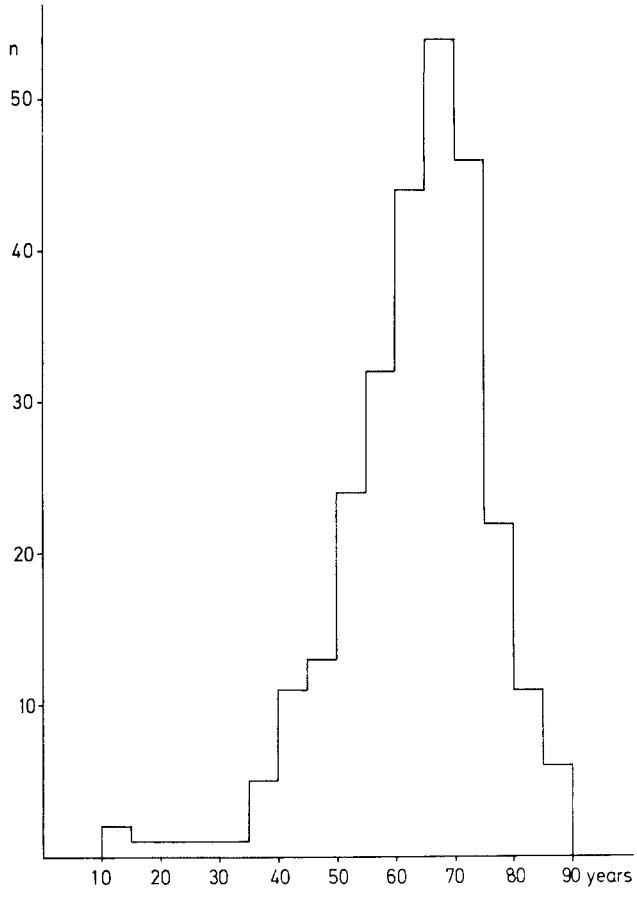

Fig. 1. Age distribution of 274 diabetic patients with lactic acidosis during biguanide treatment

1. The patient had to be a diabetic.
2. The patient was taking biguanides before developing lactic acidosis.
3. The patient had developed typical signs and symptoms suggestive of lactic acidosis.
4. A metabolic, non-ketotic acidosis and/or an elevated whole blood lactate was found.

A critical elevation of whole blood lactate or lowering of pH could not be used as a criterion because the state of lactic acidosis has so far not been biochemically clearly defined [12, 13, 18–21].

References in which groups of patients with only mean values, standard deviations, or minimal and maximal recordings were described were excluded from our evaluation. Repeated case reports of the same patients were discarded while compiling the data; the references are, however, included in the index.

The data were collected in a 92-item-questionnaire, were then transferred to three punch-cards and evaluated in an IBM 1800 computer.

As statistical parameters we used the mean value and the standard error of the mean (SEM). Comparisons of the mean values of the different groups were performed by using the two-tailed F-test. The difference of the mean values was regarded as significant at the 0.05 level.

The data bank is available for further evaluation.

Results

Between 1959 and 1977 at least 429 cases were reported which fit the criteria previously mentioned [6, 21–159].

In 99 cases the clinical, laboratory, and treatment data could not be associated with specific patients, so that these had to be excluded, leaving a total of 330. Nine reported cases of attempted suicide with biguanides were also excluded from the study [25, 35, 40–42, 48, 57, 62, 66, 68, 90].

1. Age and Sex Distribution

The average age was 64 years (n = 274). The youngest patient was 13 years old, the oldest was 90 years old (Fig. 1). In 67 cases the sex was not reported. Of the remainder, 32.7% were males, and 67.3% were females. The male average age was 62 ± 1 year (M ± SEM, n = 82, range: 15–87 years), the female average age was 65 ± 1 year (n = 167, range: 13–90 years).

A significant difference in the age distribution between males and females did not exist.

2. Duration of Diabetes Mellitus before Development of Lactic Acidosis

The duration of diabetes was reported in 174 patients. For 25 patients the diagnosis was established within 1 year before the development of lactic acidosis. Sixty-seven patients had suffered from diabetes for 1–6 years and 82 had diabetes for longer than 6 years.

3. Treatment of Diabetes Mellitus

3.1. Treatment with Biguanides

For only 3 of the 330 patients was the treatment not specified. Phenformin was used in 281 cases (1 patient had been treated with metformin previously and developed lactic acidosis 9 days after he was changed to phenformin). Buformin had been administered to 30 of the patients and metformin to 12 others. Another 4 patients had taken a combination of phenformin (100–150 mg/d) and metformin (1000–1500 mg/d).

3.1.1. Dose of Phenformin: At the time the lactic acidosis developed the average phenformin dose was 123 ± 4 mg/d (n = 213). The dosage was slightly higher in men (128 ± 7 mg/d, n = 63) than women (117 ± 4 mg/d, n = 135), but the difference is not statistically significant.

Only in 8 cases did the phenformin dose range between 200 and 300 mg/d; one patient had received 400 mg/d.

The diabetes had been treated with phenformin for 1 year in 81 cases, for 2 years in 23 cases, for 3 years in 16 cases, for 4 years in 4 cases, for 5 years in 3 cases and for longer than 5 years in 21 cases.

The doses for 48 patients had been increased or the treatment started with biguanides two weeks prior to the development of lactic acidosis. A sex difference in the duration of phenformin therapy was not demonstrable.

3.1.2. Dose of Buformin: For only 24 of 30 patients was a dose reported. In this group as in the previous one, the dose had occasionally increased before the development of the lactic acidosis. The "usual" therapeutic dose was 258 ± 25 mg/d (n = 24), and the "actual" dose at the time of the lactic acidosis was 329 ± 30 mg/d (n = 24).

3.1.3. Dose of Metformin: Dosages were reported in 10 of 12 patients. They ranged between 500 and 2400 mg/d (1595 ± 182 mg/d, n = 10).

3.2. Additional Treatment of the Diabetes Mellitus

A combination of drugs was reported in 119 cases – 32 men, 76 women. The sex of 11 patients was not given. Combinations with sulfonylurea drugs were most frequently used (33 times with tolbutamide, 26 times with glibenclamide, 40 times with other sulfonylurea compounds). Nineteen patients received insulin concomitantly; one patient received insulin and tolbutamide.

4. Accompanying Illnesses

4.1. Frequency

At the time of treatment with biguanides 214 patients were reported to have other illnesses. Most frequently the patients had cardiovascular disease (n = 135), renal disease (n = 98), infectious processes (n = 45), hepatic disease (n = 39), and pulmonary disease (n = 16). See Table 1.

4.2. Treatment of the Accompanying Diseases

4.2.1. Antibiotics: At least 14 patients received antibiotics before lactic acidosis became apparent.

Table 1. Frequency of accompanying illnesses

		Survivors	Deaths
	n = 143	No autopsy n = 65	With autopsy n = 80
Cardiovascular disease	44%	43%	64%
Renal disease	35%	31%	51%
Infectious processes	25%	9%	28%
Pulmonary disease	19%	11%	35%
Hepatic disease	15%	9%	28%
Shock	24%	60%	
Anuria	17%	22%	

Table 2. Complaints before establishing the diagnosis of lactic acidosis (n = 195)

Symptoms	Number of patients
Vomiting	100
Somnolence	98
Nausea	71
Epigastric pain	69
Loss of appetite	52
Hyperpnoea	50
Lethargy	29
Diarrhoea	27
Thirst	8

Drugs used were tetracyclines (n = 5), gentamycin (n = 4), ampicillin (n = 3), cephalothin (n = 2), chloramphenicol (n = 2), and rifampicin, ethambutol, cycloserine, thiamphenicol, penicillin, nalidixic acid, trimethoprim/sulfamethoxazole (once each).

4.2.2. Digitalis: At least 20 patients were digitalised. Digoxin derivatives were used predominantly.

4.2.3. Diuretics: Diuretics were used on 32 patients, most frequently thiazide-derivatives (n = 14), furosemide (n = 14), spironolactone (n = 6), carbonic anhydrase inhibitor and mercurial diuretics (n = 1).

4.2.4. Other Drugs: In addition to the above mentioned drugs the patients were also receiving the following: antihypertensive agents (n = 18), barbiturates (n = 4), steroids (n = 2), and allopurinol (n = 1). This allows one to infer the existence of associated diseases.

4.3. Alcohol

In 17 cases the patients were alcoholics or had taken large amounts of alcohol before lactic acidosis developed.

5. Symptoms at the Onset of Lactic Acidosis

The symptoms in 195 patients before the diagnosis of lactic acidosis was made are listed in Table 2.

6. Clinical Findings at the Time of Diagnosis

6.1. State of Consciousness

A disturbed state of consciousness was reported for 177 of 212 patients. According to the descriptions of the various case reports we have tried to further subdivide the degree of unconsciousness (1: normal, 2: somnolence, 3: coma with reaction to external stimuli, 4: coma without reaction to external stimuli). It appeared that the state of somnolence predominated. In group 4 the blood glucose concentration was lowest (124 mg/100 ml) and the serum urea concentration was highest (146 mg/100 ml). The differences from group 1 (mean concentrations 195 mg/100 ml and 103 mg/100 ml respectively) are statistically significant ($2\ p < 0.05$). Significant differences for whole blood lactate concentration and osmolality could not be ascertained between the different groups.

6.2. State of the Peripheral Circulation

Skin colour and skin turgor were rarely mentioned. The following clinical findings were described: Dehydration was apparent in 62 cases, skin pallor in 62 cases, cyanosis in 27 cases. Often a combination of these signs existed. The most common finding was a combination of "pallor" and "dehydration".

6.3. Evidence of Ketosis in the Expired Air

This clinical observation typically found in diabetic ketoacidosis was only described eight times.

6.4. Type of Respiration

The respiratory rate varied correspondingly with the severity of the metabolic acidosis; a respiratory rate of over 20/min was found in 94 cases. A Kussmaul-type respiration was described in 70 cases. The respiratory rate was normal in 13 patients; one patient had a respiratory rate below 12/min.

6.5. Cardiovascular State

The present data suggest that the majority of the patients at the time of diagnosis manifested no symptoms of cardiovascular shock, and therefore no diminished supply of oxygen to peripheral tissues. Only in 13 patients was cardiovascular shock described as the probable first sign of a severe attack of lactic acidosis. Signs of shock appeared later or during the course of treatment in 117 patients suffering from other symptoms of lactic acidosis. This classification is unreliable because the appearance of symptoms and clinical findings was only rarely listed in chronological fashion.

The average value for the pulse rate was 93 $\pm$ 2/min ($n = 106$). A tachycardia of over 100/min was reported for 33 patients. In 5 cases the heart rate was described as "normal"; in 5 others it was "increased". The average systolic blood pressure (SBP) was 120 $\pm$ 3 mmHg ($n = 183$). In 72 cases the SBP at the time of diagnosis was below 100 mmHg, 12 patients had a "normal" SBP, and 20 patients had a "low" SBP. The average diastolic blood pressure was 72 $\pm$ 2 mmHg ($n = 166$).

6.6. Body Temperature

In 89 cases the average body temperature was 35.6 $\pm$ 0.2 degrees C. The lowest recorded temperature was 26.7 °C. Eight other patients had a "lowered" body temperature, 13 were "normothermic", and 2 patients had an "elevated" body temperature.

6.7. Urine Output at the Time of Diagnosis

Of 76 patients 29 had a normal urine production (over 40 ml/hour), but 47 patients had urine flow of less than 40 ml/hour. Ten patients were described as being anuric, and a further 59 patients developed anuria during the course of treatment.

6.8. Central Venous Pressure (CVP)

A lowered CVP (less than 4 cm H_2O) existed in 20 cases, a normal CVP (4–10 cm H_2O) in 43 cases. A CVP of more than 10 cm H_2O was recorded in 21 cases.

6.9. Myocardial Infarction

In 4 cases myocardial infarction was diagnosed simultaneously with lactic acidosis. During treatment an additional 13 patients suffered a myocardial infarction.

7. Biochemical Findings at the Time of Diagnosis

In the present investigation only laboratory findings are evaluated which have significance for the clinical routine diagnosis (Table 3).

The laboratory examination indicated a decom-

Table 3. Laboratory findings at the time of diagnosis of lactic acidosis and their prognostic significance.
Anion gap: $Na^+ + K^+ - HCO_3^- - Cl^-$
Osmolality: $2 \times (Na^+ + K^+) + \frac{\text{blood sugar (mg/dl)}}{18} + \frac{\text{serum urea (mg/dl)}}{6}$

		All patients			Survivors			Deaths			2p
		Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	
pH		6.95	0.11	278	7.00	0.12	122	6.91	0.17	118	< 0.001
pCO_2	mmHg	21	1	152	22	1	78	19	1	64	n.s.[a]
Bicarbonate	mmol/l	6.7	0.2	233	7.5	0.4	117	5.8	0.3	95	< 0.001
pO_2	mmHg	106	4	63	105	7	20	104	5	31	n.s.
Lactate	mmol/l	16.9	0.5	268	15.6	0.8	116	18.5	0.8	114	< 0.02
Pyruvate	mmol/l	0.4	0.05	74	0.4	0.08	31	0.5	0.08	32	n.s.
L/P-ratio		71	10	73	81	19	30	60	11	32	n.s.
Anion gap	mmol/l	37	1.0	143	36	1.3	67	37	1.9	60	n.s.
Creatinine	mg/100 ml	3.3	0.2	113	3.3	0.3	58	3.4	0.3	40	n.s.
Serum urea	mg/100 ml	118	4.0	191	101	6.5	71	129	5.5	94	< 0.005
Na^+	mmol/l	138	0.6	145	138	0.8	73	138	0.9	55	n.s.
K^+	mmol/l	5.5	0.1	167	5.5	0.1	79	5.5	0.1	63	n.s.
Cl^-	mmol/l	97	0.8	125	98	1.1	61	95	1.2	47	n.s.
Phosphorus	mmol/l	1.9	0.2	17	1.7	0.3	8	2.2	0.2	9	n.s.
Blood sugar	mg/100 ml	173	8.7	249	173	13.3	114	175	13.1	108	n.s.
Osmolality	mosmol/l	318	1.5	118	314	2.1	51	322	2.2	53	< 0.02

[a] n.s.: not significant, 2 p > 0.05

pensated metabolic acidosis with a marked ventilatory response (Fig. 2). The oxygen pressure was elevated due to marked hyperventilation. Of all patients, 81% had pO_2-values above 80 mmHg, indicating that the oxygen supply to peripheral tissues was not diminished due to cardiovascular or pulmonary insufficiency. The lactate concentration in whole blood was elevated to 16.9 mmol/l, with a raised lactate-pyruvate ratio fluctuating over a wide range. Serum urea and creatinine concentrations were elevated at the time of diagnosis. Unfortunately, little information is available about renal function before the onset of lactic acidosis. At least eight phenformin-treated patients had a normal serum creatinine concentration (less than 1.2 mg/100 ml) at the time of diagnosis.

The glucose concentration of the blood was not systematically changed; in most cases it is slightly elevated, but 26% of the patients with known blood sugar concentrations had values below 80 mg/100 ml (Fig. 3).

The osmolality was moderately increased due to the elevation of glucose and urea.

The separation of groups according to pretreatment with different biguanides revealed little. Metformin pretreated patients appear to show minor metabolic disturbances although only the difference in the lactate concentration in whole blood between phenformin- and metformin-pretreated patients is statistically significant (2p < 0.02). Though the dif-

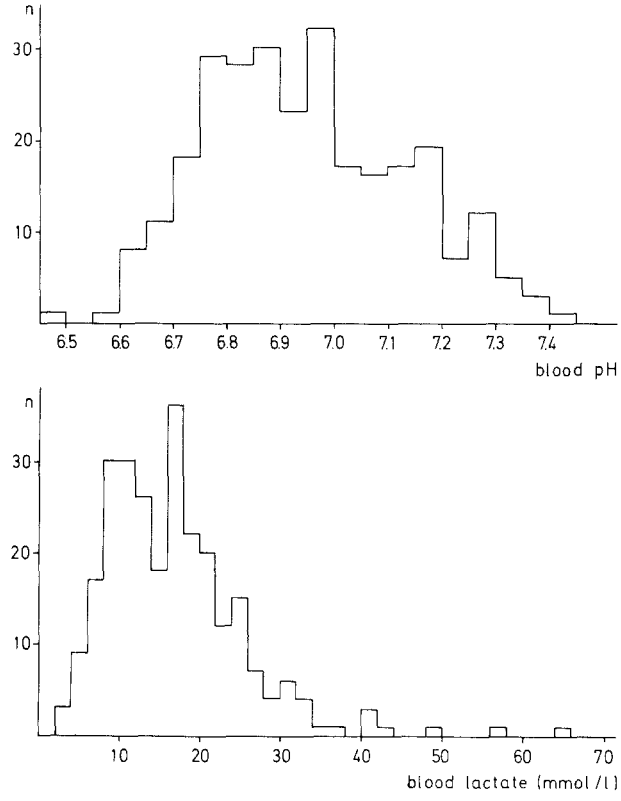

Fig. 2. Distribution of pH values (n = 278) and of the lactate concentration in whole blood (n = 268) at the time of diagnosis of lactic acidosis during treatment of diabetes mellitus with biguanides

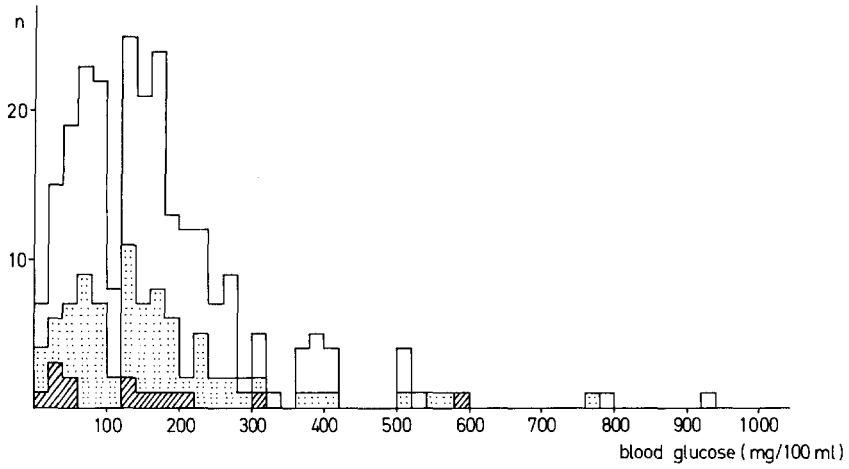

Fig. 3. Distribution of the concentration of glucose in the blood at the time of diagnosis of lactic acidosis. Hatched area: therapy with biguanides and insulin. Dotted area: therapy with biguanides and sulfonylurea compounds. Blank area: therapy with biguanides only

Table 4. Laboratory findings at the time of diagnosis of lactic acidosis due to different biguanide compounds. Mortality rate: number of dead patients and of all patients in brackets

		Phenformin-therapy			Buformin-therapy			Metformin-therapy		
		Mean	SEM	n	Mean	SEM	n	Mean	SEM	n
pH		6.95	0.12	241	6.98	0.35	26	7.10	0.58	6
Bicarbonate	mmol/l	6.6	0.3	205	7.5	1.1	13	7.8	0.7	12
Lactate	mmol/l	17.3[a]	0.6	227	16.1	1.6	25	12.8[a]	1.4	11
Anion gap	mmol/l	37.4	1.1	131	45.1	8.8	3	34.3	5.7	5
Creatinine	mg/100 ml	2.9[b]	0.2	84	4.3[b]	0.6	23	6.3	1.1	5
Serum urea	mg/100 ml	114[b]	4	172	160[b]	20	12	111	29	3
Blood sugar	mg/100 ml	176	9.6	213	150	24	22	172	50	11
Osmolality	mosmol/l	317[b]	1.6	109	331[b]	3.8	4	327	14	2
Mortality		52% (128/246)			50% (13/26)			18% (2/11)		

[a] $2p < 0.02$;
[b] $2p < 0.05$

ferences in the creatinine and serum urea concentrations and the osmolality are striking, only between the phenformin- and the buformin-pretreated patients were the differences significant ($2p < 0.05$) (Table 4).

8. Course of the Illness

The time elapsed between the onset of symptoms to the time of diagnosis and from this stage to complete recovery (normalization of the acid-base-balance) or death was very short.

In 46% of 150 patients the diagnosis of lactic acidosis was made within 24 hours of the onset of symptoms, and 73% were diagnosed within 72 hours. The diagnosis of the remaining 27% was scattered over a period of up to 60 days. However, this long period is questionable because in this group there may have been patients who suffered only minor gastrointestinal disturbances.

The duration of treatment for 132 of 208 patients (= 64%) was less than 24 hours; in 88% of the cases the outcome of the illness was decided in 72 hours.

The duration of the illness was therefore very short – in 64% of patients less than 96 hours. There is no sex difference in the duration of symptoms before diagnosis, the length of treatment or the total duration of the illness.

9. Treatment of the Lactic Acidosis

9.1. General Treatment Measures

For shock the following treatments were used: vasopressor drugs (n = 47), steroids (n = 45) and volume expanders such as dextran, gelatine preparations, plasma, albumin, and whole blood (n = 28).

Ventilation had to be either assisted or controlled in 16 patients. A further 14 patients received furosemide to enhance their diuresis while 14 patients were digitalised.

9.2. Specific Treatment Measures

Information about specific treatment measures is available in 236 of all reported cases. Dose of treatment or outcome of therapy are not mentioned in about one half of these case reports.

Therapy consisted of three main approaches:

1. Alkalinisation. In nearly all patients (n = 216) restoration of pH was attempted with sodium bicarbonate. The amount of sodium bicarbonate used corresponded to the decrease of pH. The mean pH in patients receiving up to 400 mmoles during the first 24 hours was 7.02, the mean pH in patients receiving more than 800 mmoles was 6.86.

Other buffers, such as THAM (n = 17) and sodium lactate (n = 3) have been used only rarely, because the first one offers no advantage and the second one has been abandoned because of pathophysiological considerations.

2. Haemodialysis (n = 39) and peritoneal dialysis (n = 34). These methods have been recommended with different media (bicarbonate, acetate, lactate) in order to control complications due to the necessary alkalinisation (sodium and volume overload), to restore normal acid-base-balance and to eliminate accumulated biguanide and lactate. Recently very good results have been published with haemodialysis [117].

3. Administration of insulin and glucose (n = 94) has been suggested in order to activate the pyruvate dehydrogenase system. Probably the overall effect of insulin is only positive if considerable amounts of ketone bodies participate in the metabolic acidosis.

The demonstration of an average anion gap of 36 mmol/l in the survivors (Table 3), which is accounted for by lactic acidaemia of 15.6 mmol/l, indicates the presence of considerable amounts of acid anions such as ketone bodies.

Methylene blue infusion (n = 16) has not been used in recent years.

10. Outcome of the Treatment

In 42 cases no mention of the outcome was made. Of the remaining patients 49.7% survived (54.4% of the males and 48.7% of the females). In 80 cases (= 27.8%) a post-mortem examination was performed, but the findings in 60 patients only were recorded (see Table 1). A further 22.5% died without a post-mortem examination being carried out.

Discussion

1. Diagnosis of Lactic Acidosis

Till now exact information about the incidence of lactic acidosis in biguanide treated diabetics is not available, because not all cases diagnosed have been published or reported to the national drug administrations, not all suspected cases have been confirmed by evaluation of the lactate concentration in whole blood, and probably a large number were not even suspected. Lactic acidosis in diabetics on biguanide therapy is diagnosed only to some extent because:

a) the clinical picture consists of symptoms and signs both of severe metabolic acidosis (vomiting, abdominal pain, nausea, air hunger, heavy laboured breathing) and of accompanying illnesses. These may be considered as the cause of the whole clinical picture, but only rarely is the function of the organs impaired to such a degree (e. g. cardiac insufficiency, myocardial infarction with cardiogenic shock, acute pulmonary insufficiency, renal insufficiency) to explain the severe metabolic acidosis. Mean systolic blood pressure and heart rate demonstrate that shock does not generally exist. The oxygen pressure excludes a hypoxia of peripheral tissues due to circulatory or ventilatory failure. A chronic impairment of renal function as the cause of the severe metabolic acidosis is not plausible in the light of the moderate elevation of creatinine and serum urea. An acute renal failure takes only two to three days to reach creatinine concentrations of about 3 mg/100 ml. Pronounced metabolic acidosis is unusual after this short time.

b) the laboratory examinations are equivocal and point to other complications of diabetes mellitus. Among 64 of 249 patients the concentration of blood glucose was less than 80 mg/100 ml at the time of diagnosis leading to the preliminary diagnosis of hypoglycaemia, especially in patients treated with a combination of biguanide and insulin or sulfonylurea compound. In 24 cases the blood sugar concentration was more than 350 mg/100 ml and in 55 cases mostly moderate reactions for ketone bodies in plasma could be demonstrated. Ketone bodies in urine were found in 78 patients. The expired air of 8 patients smelled of acetone. Thus diabetic ketoacidosis may be erroneously diagnosed, which may delay or prevent the correct diagnosis of lactic acidosis. On the other hand it is not correct to diagnose lactic acidosis and to exclude diabetic ketoacidosis if there is no reaction or only a moderate reaction for ketone bodies with the nitroprusside reagent, since it reacts with acetone and acetoacetate only but not with 3-hydroxy-butyrate. Only the measurement of lactate in whole blood can finally elucidate the origin of the acidosis. The decision is important because the therapeutic regimens and the prognosis are quite different [160, 161].

2. Treatment of Diabetes Mellitus

Adult diabetics are involved predominantly, which is in accordance with the indications of biguanides for

the treatment of diabetes mellitus. Half of the patients were over 62 years old. Women were more frequently involved than men. Similar proportions are described for the incidence of diabetes mellitus in adults [162] and for the incidence of diabetic ketoacidosis; so that lactic acidosis does not favour either sex [163–165].

The number of published cases does not correspond with the real number of patients with lactic acidosis induced by the different biguanides. Probably phenformin induced lactic acidosis is commoner than the literature indicates. With more than 300 reported cases of phenformin induced lactic acidosis there is now little cause to publish single observations. Studies in France and Switzerland suggest that phenformin is more likely to produce lactic acidosis than metformin. In France 76% of all biguanide treated diabetics receive metformin, the remaining 24% receive phenformin, but only 14% of the published cases of lactic acidosis happened during metformin therapy, the remainder occurring during phenformin therapy [166]. Similar results were obtained in Switzerland [167]: The average shares in the Swiss biguanide market are: buformin 63%, metformin 23%, and phenformin 8%. The share in the reported cases of lactic acidosis (n = 31) are: buformin 84%, metformin 3%, and phenformin 13%. Furthermore metformin induced lactic acidosis seems to occur only with marked renal impairment [25]. The lowest serum creatinine concentration observed in our collected metformin cases was 3.0 mg/100 ml, whereas during phenformin therapy lactic acidosis was observed with normal – or approximately normal – creatinine concentrations (Table 4).

Besides some cases described in connection with metformin treatment are unclear and must be considered questionable [27, 166, 168].

Lactic acidosis occurred with all three drugs while being used in a normal therapeutic dose. During the first two weeks after starting therapy or increasing the dose the diabetic patient appears more prone to develop lactic acidosis. Of the reported cases, 15% occurred at this time. One possible explanation is that the patient is suffering from a concommitant illness which is requiring additional diabetes therapy, and because of this biguanide therapy is commenced or increased.

In approximately one third of the cases, biguanides were used in combination with sulfonylurea drugs or insulin, so that a link between these drugs and the occurrence of lactic acidosis can be discussed. Sulfonylurea compounds alone have so far only rarely been associated with clinically relevant lactic acidosis [169]. An elevation of the concentration of lactate in the whole blood after insulin administration is well known [170, 171], but it does not reach the levels described here.

3. Accompanying Illnesses

The presence of accompanying illnesses was always pointed out, as these have often been thought to be responsible, at least in part, for the lactic acidosis. In almost two third of the described patients such additional diseases are mentioned, but this should not be a surprising finding in 64 years old diabetic patients (at least concerning cardiovascular and renal diseases). It is possible that there were many more patients with other complications that were either not diagnosed or not mentioned: in post mortem examinations on 21 of 32 patients renal disease was found which had not been diagnosed clinically. Similar proportions are found in the other diseases. However, it is not justified to assume that all patients had associated severe illnesses. Even the patients who initially had markedly elevated serum urea and creatinine concentrations cannot be regarded principally as having advanced chronic renal failure since at least 6 had serum concentrations of creatinine less than 1.8 mg/100 ml after recovery from lactic acidosis [172]. In general biguanide induced lactic acidosis occurred only rarely in the presence of normal renal function and in the absence of other diseases. However, it may be caused by only mild renal dysfunction due to acute gastroenteritis or biguanide induced gastrointestinal disturbances.

In some cases the treatment of the accompanying illness was mentioned. The part additional drugs play in the development or aggravation of lactic acidosis is uncertain, though alcohol certainly favours the development of lactic acidosis [173].

4. Treatment of Lactic Acidosis

The treatment is obviously unsatisfactory because the mortality rate remains 50%. To elucidate the relation between outcome and given dose of a particular treatment, it is necessary to have regard to the severity of the disease in the individual patient given that dose. The severity of lactic acidosis is characterized by the factors being of prognostic significance: pH, bicarbonate, lactate, serum urea, osmolality, age, and systolic blood pressure. Till now it is impossible to compare the effectiveness of different therapeutic regimens (e. g. bicarbonate therapy alone vs. bicarbonate therapy and haemodialysis) because the number of patients in the different groups with identical therapy and sufficient clinical data is too few.

It is surprising that the mortality rate in patients with sufficient treatment data is only about 23 to 35% according to different treatment measures, because the mortality rate of the whole group is 50%. It is evident that cases successfully treated are published more frequently with detailed description. This is true for bicarbonate therapy as well as combined insulin-glucose-infusion and haemodialysis. Therefore published mortality rates of about 30% for a particular treatment do not unequivocally mean a real superiority. A summary of treatment data is given in Table 5.

Table 5. Dosage of treatment in the first 24 hours after diagnosis of lactic acidosis

Treatment	Survivors Mean Dose	SEM	n	Deaths Mean Dose	SEM	n	p
$NaHCO_3$ (mmol)	549	38	67	505	54	35	n.s.[a]
Insulin (IU)	72	18	27	58	6	10	n.s.
Glucose (g)	128	17	22	104	20	12	n.s.

[a] n.s.: not significant, $2\ p > 0.05$

Table 6. The mortality of lactic acidosis in the varying age groups. Mean values are given with SEM

Age	Surviving patients	Fatal outcome	Mortality
0–20 years	3	0	0%
2r–40 years	6	2	25%
41–60 years	43	29	40.3%
over 60 years	74	90	54.9%
Mean age	62 ± 1 (126)	66 ± 1 (121)	$2\ p < 0.01$
males	58 ± 2 (42)	67 ± 2 (33)	$2\ p < 0.005$
females	63 ± 2 (75)	66 ± 1 (77)	$2\ p > 0.05$

5. Prognosis

There appears to be no sex difference. The mortality rate rises with age (Table 6). Accompanying illnesses are slightly more frequent in patients who died; this can be due to the additional information gained by the post-mortem examination (Table 1). Patients who showed evidence of shock at the time of diagnosis of lactic acidosis or who developed signs of shock in the further course of illness are found significantly more frequently among the dead patients (Table 1). The mortality of patients with shock was 70%. The systolic blood pressure at the time of diagnosis has prognostic significance too: it is significantly higher in survivors (135 ± 4 mmHg, n = 86) than in dead patients (112 ± 5 mmHg, n = 77).

A difference in the phenformin dose in patients who recovered (125 ± 6 mg/d, n = 98) and those who died (120 ± 5 mg/d, n = 92) cannot be established.

Patients who died of lactic acidosis had a significantly more severe metabolic acidosis at the time of diagnosis than the survivors. Their lactate concentration in whole blood and their serum osmolality was significantly higher. There is also a statistically significant difference in the serum urea concentration, but not the serum creatinine concentration. Patients who died had more markedly elevated serum urea concentrations. Possibly the biguanide intoxication is more pronounced in patients whose renal function is, at least temporarily, more severely impaired. These patients have a poorer prognosis.

6. Conclusions

Biguanides are used for the treatment of adult overweight diabetic patients. A life-threatening metabolic disturbance resulting from its use – lactic acidosis – has been reported with increasing frequency. Because of the high mortality rate of this disturbance it should be examined whether new guide lines regarding its use can be established, in order to prevent this adverse effect.

We suggest that in the following instances biguanides should not be used for the treatment of diabetes mellitus:

a. Patients over 60 years of age

b. In the presence of accompanying illness, such as

– cardiovascular disease (coronary heart disease, angina pectoris, myocardial infarction, cardiac failure),

– renal disease (pyelonephritis, diabetic renal disease, elevated serum urea in post-renal obstruction such as prostatic hypertrophy) or proliferative retinopathy, since this complication of diabetes mellitus is almost always associated with diabetic renal disease,

– hepatic disease (hepatitis, cirrhosis, fatty change)

– infectious processes (gangrene, pneumonia, etc).

c. In states which can by themselves result in an accumulation of lactate such as:

– shock of varying origin
– diabetic ketoacidosis
– operations
– pulmonary insufficiency
– alcoholism
– weight-reducing diets or fasting

Treatment with biguanides should be stopped immediately, if

a. one of the above mentioned conditions exists,
b. gastrointestinal disturbances are noted,
c. the endogenous creatinine clearance drops below normal, since phenformin in therapeutic dose has accumulated in diabetics with normal serum creatinine concentration and reduced endogenous creatinine clearance [174].

Should lactic acidosis still continue to develop in biguanide-treated diabetic patients despite adhering to these strict criteria then the indications for its use in diabetes therapy should be thoroughly reevaluated [175].

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Received: May 5, 1977,
and in revised form: August 16, 1977

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