Serum Phenformin Concentrations in Patients with Phenformin-associated Lactic Acidosis

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SUMMARY

Phenformin concentrations were measured in serum from seven patients with phenformin-associated lactic acidosis, and initial values ranging from 20 to 625 ng./ml. were obtained. Five of the seven patients had serum concentrations within the usual therapeutic range of up to 241 ng./ml. Serum phenformin concentrations were measured serially, and apparent half-lives of 5, 25, and 30 hours were obtained in three patients with serum creatinine concentrations of 1.7, 7.6, and 6.0 mg./dl., respectively. Although the half-life of phenformin was prolonged in azotemic patients, no correlation between serum creatinine concentration and serum phenformin could be demonstrated; furthermore, the severity of lactic acidosis as measured by arterial pH and lactate concentration did not correlate with the serum creatinine concentration. DIABETES ***26*:628-31, July, 1977.**

Lactic acidosis in diabetics is frequently associated with the use of phenformin.[1-6] It has not been known whether these patients develop lactic acidosis because their serum phenformin concentrations are unusually high or because phenformin is toxic to these diabetics at so-called therapeutic concentrations. We therefore undertook a prospective study to measure serum phenformin concentrations in patients with phenformin-associated lactic acidosis.

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METHODS

Lactic acidosis was defined as metabolic acidosis with an arterial lactate concentration greater than 5 mM (normal 0.5-1.6 mM) or an unexplained anion gap greater than 20 mEq./L.

Serum was assayed for phenformin by gas chromatography and chemical ionization mass spectrometry.[7] Lactic acid was measured by an automated method (DuPont Automatic Clinical Analyzer method N-111), using plasma separated from arterial blood drawn into tubes containing potassium oxalate and sodium fluoride. Arterial pH was measured with a standard blood gas apparatus.

House officers and nursing staff at Confederate Memorial Medical Center were asked to notify one of the authors whenever any patient was suspected of having lactic acidosis during the period July 1, 1974, through December 31, 1975. We believe that all cases that occurred were identified by this method; no additional cases were found when charts coded under the heading *electrolyte disorders (acidosis)*[8] were reviewed. When a patient was transferred to our hospital from another institution, the records of the referring institution were examined to determine the time and amount of the last dose of phenformin.

RESULTS

Thirteen cases of lactic acidosis occurred in 12 different patients during the 18-month study. Seven of these patients were diabetic; six of the diabetic patients were taking phenformin (table 1, patients 1-6).

One diabetic patient not taking phenformin had ketoacidosis (moderate-positive ketonemia with serum diluted 1:12) with mild lactic acidosis superimposed (arterial lactate 5.7 mM). One additional patient (patient 7, table 1), with metastatic oat-cell carcinoma of the lung, was not diabetic and not known to be taking phenformin; nevertheless, this patient was hypoglycemic and had a serum phenformin concentration of 46 ng./ml., which was almost 10 times greater than the serum blanks. Patients 1-5 survived; patients 6 and 7 died in the hospital after recovery from lactic acidosis.

Initial serum phenformin concentrations ranged from 20 to 625 ng./ml. (table 1). Serial samples from three diabetic patients were assayed, and apparent half-lives of 5, 25, and 30 hours were obtained (figure 1).

Lactic acidosis has been thought to be more likely to occur in situations in which high serum concentrations of phenformin are expected, such as overdosage or renal failure. We examined the effects of renal function by looking for a correlation between serum creatinine and lactate concentrations or pH; we found no correlation either in our patients or in patients reported in the literature (table 2). The half-life of phenformin in serum of normal subjects is probably 5 to 12 hours.[7,9] Even though a high serum creatinine concentration seemed to be associated with a prolonged half-life of the drug (figure 1), we were unable to demonstrate a positive correlation between serum phenformin and serum creatinine concentrations (figure 2). For example, patient 2, who had the highest serum phenformin concentration (625 ng./ml.), had a creatinine of only 1.7 mg./dl., whereas patient 3, whose serum phenformin level was only 188 ng./ml., had a creatinine of 7.6 mg./dl. This lack of correlation may be due to the different dosage regimens in this small series; for example, patient 2 was taking four

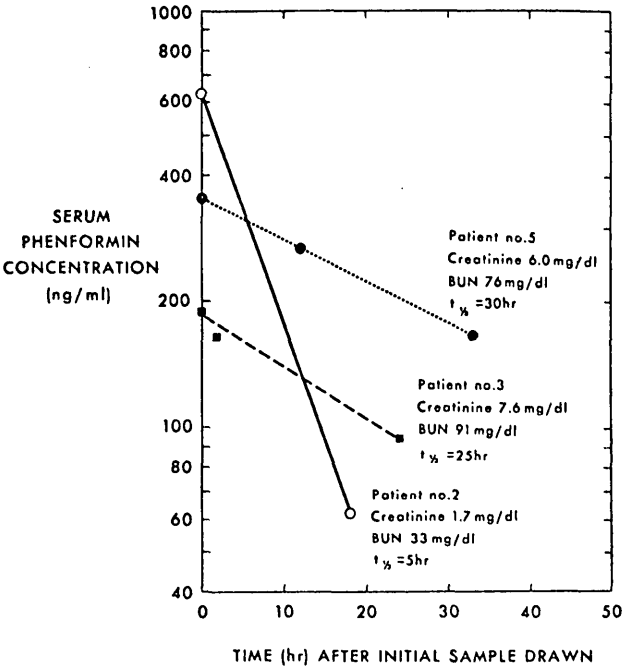

FIG. 1. Serial measurements of serum phenformin concentrations in three patients with phenformin-associated lactic acidosis.

TABLE 1

Summary of clinical data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	71	46	52	82	56	68	55
Sex	F	F	F	M	F	F	F
Phenformin dosage (mg./day)	150 mg. daily begun 1 wk. before	Increased from 50 to 200 mg. daily 3 days before	50 mg. daily	100 mg. daily	unknown	50 mg. daily	unknown
Time (hr.) between last dose of phenformin and time blood first drawn for phenformin assay	30½	—	—	26	—	7½	—
Initial serum phenformin concentration (ng./ml.)	193	625	188	202	352	20	46
Arterial plasma lactate (mM)	23.6	18.6	5.9	8.7	11.4	6.0	14.4
pH	7.05	6.86	7.17	7.25	7.24	7.19	6.90
Serum urea nitrogen (mg./dl.)	110	33	91	20	76	43	30
Serum creatinine (mg./dl.)							
Admission	3.9	1.7	7.6	—	6.0	1.2	2.0
After recovery	1.1	1.4	5.6	—	5.0	0.6	1.1
Serum glucose (mg./dl.)	93	239	120	364	282	600	15
Urine ketones	Small	Small	Small	Small	None	None	None
Total serum protein (gm./dl.)	6.4	—	6.9	6.6	7.0	5.4	5.4
Serum albumin (gm./dl.)	3.88	—	3.23	3.60	3.93	3.65	2.77
Blood pressure	86/58	72/40	80/50	160/86	180/100	unobtainable	124/64

TABLE 2

Summary of statistical data

	This series		Combined literature data*	
	Correlation coefficient	Probability	Correlation coefficient	Probability
Creatinine vs. lactate	r=0.28	$P \approx 0.6$	r=0.21	$P \approx 0.5$
Creatinine vs. pH	r=0.43	$P \approx 0.4$	r=0.38	$P \approx 0.3$
Dose of phenformin vs. lactate	r=0.86	$P = 0.06$	r=0.15	$P \approx 0.3$
Dose of phenformin vs. pH	r=0.86	$P = 0.06$	r=0.029	$P \approx 0.9$

*Based on values reported by Cleaver and Carretta,[4] Simpson et al.,[5] and Oliva.[18]

times as much phenformin as patient 3. A better correlation of phenformin concentration with renal function might become apparent in a larger series in which patients taking equal doses could be compared. In fact, if patient 2 were omitted, a direct correlation would exist in our series.

We next examined the effects of phenformin dosage. There appeared to be a significant correlation ($P = 0.06$) between the initial serum phenformin concentration and the phenformin dose (figure 2). Arterial lactate and pH also seemed to correlate with phenformin dosage in our patients (table 2); however, when we reviewed a large number of cases from the literature, no correlation of lactate or pH with dose was found (table 2).

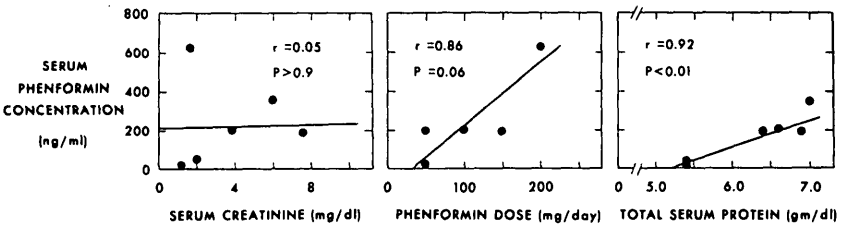

FIGURE 2

The relationship of serum phenformin concentration and serum creatinine, dose of phenformin, and total serum protein in patients with phenformin-associated lactic acidosis.

DISCUSSION

We believe the data reported here to be the first reliable measurements of serum phenformin concentration in patients with phenformin-associated lactic acidosis. Assan et al.[10] recently reported concentrations 10-100 times greater than those we found, but they also reported phenformin concentrations in nonacidotic patients that were approximately 100 times greater than therapeutic concentrations we have found[7,11] or than other investigators using gas chromatography with electron capture,[12] gas chromatography with mass spectrometry,[9] or isotope dilution techniques[13] have reported. We cannot explain the high values found by Assan et al., but it should be pointed out that the sensitivity of their colorimetric method is about 1,000 ng./ml., whereas our method will detect as little as 5 ng./ml. and is highly specific for phenformin.[7]

Our observations suggest that renal function may not be a major determinant of serum phenformin concentration or of the severity of lactic acidosis, although it does seem to influence the half-life of phenformin (figure 1). However, the interpretation of our observations must be tempered by several considerations. First, azotemia is transient in many of these patients.[1] Indeed, four of our patients had a serum creatinine concentration of 1.4 mg./dl. or less after recovery from lactic acidosis (table 1); a similar return of creatinine to normal occurred in seven of the 21 patients reported by Bengtsson et al.[6] The half-life of phenformin might be expected to decrease as hypovolemia is treated and renal perfusion improves; we did not measure serum phenformin concentration often enough in individual patients to examine this possibility. Second, uremia might alter the absorption, excretion, metabolic conversion, tissue concentration, or binding of phenformin to plasma proteins, as in the case of diphenylhydantoin and other drugs.[14,15] Although serum phenformin concentration correlated statistically with serum protein concentration (figure 2), only about 20 per cent or less of phenformin in serum is bound to protein.[9,16] Third, the concentration of phenformin in serum may not accurately reflect the concentration in tissues, and at present no data are available concerning tissue concentrations in humans. Finally, about one third of an administered dose of phenformin is metabolized in humans to N^1-p-hydroxy-β-phenethyl biguanide.[13]

We did not measure the serum concentration of this metabolite in our patients, and its biologic activity in human beings is unknown.

When patients are given phenformin timed disintegration capsules 50 mg. three times a day, serum concentrations of 102-241 ng./ml. are found two to four hours after the last dose.[11] Five of our seven patients with phenformin-associated lactic acidosis had serum concentrations of less than 241 ng./ml. Although blood might have been drawn for phenformin assay in some of these patients after the concentration had peaked, these values are considerably lower than the 2,000 ng./ml. measured in a nondiabetic who attempted suicide by taking an overdose of the drug and who developed lactic acidosis.[11]

At first glance our data give the impression that very high concentrations of phenformin might not be required for lactic acidosis to develop. However, these measurements were made at various time intervals after the patient's last dose of phenformin (table 1), and thus the concentration of phenformin could have been higher at earlier times. The peak concentrations cannot be estimated for several reasons, the foremost of these being that assumptions or even measurement of half-life of the drug during convalescence may be inapplicable during severe metabolic acidosis. It is not unreasonable to expect that the half-life could be prolonged considerably during the 24 hours prior to admission if the patient is dehydrated and glomerular filtration rate transiently reduced. If this were the case, peak concentrations might not have been much higher than those measured. On the other hand, if the half-life were not temporarily prolonged, we can estimate that peak concentrations were higher than those observed.

It would be nice to be able to predict which diabetics are at risk of developing lactic acidosis if treated with phenformin, so that the drug could be given safely to other diabetics. Previous guidelines suggested that patients with impaired renal function or other patients in whom high concentrations of the drug might accumulate are the patients at risk.[17] However, very high serum concentrations of phenformin may not be necessary for lactic acidosis to develop, and patients without azotemia are clearly susceptible, especially when high doses of phenformin are given. At present, then, it seem impossible to predict which diabetics will develop lactic acidosis when treated with phenformin.

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