LACTIC ACIDOSIS FROM PHENFORMIN OVERDOSE — A CASE REPORT

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SYNOPSIS

The case, the first locally, is reported of a young non-diabetic woman who attempted suicide by ingesting about 2250 mg of phenformin, a drug withdrawn from local use since 1977. She typically developed gastrointestinal symptoms followed by hypoglycaemia (blood glucose 12 mg/dl) and lactic acidosis (serum lactate 178 mg/dl) but recovered fully with intravenous sodium bicarbonate replacement. It was subsequently discovered that many local Chinese medicine shops had stocks of the drug. A review of seven other similar cases, the mechanisms leading to phenformin-induced metabolic disturbances, and the treatment of lactic acidosis are briefly presented.

INTRODUCTION

The subject of phenformin-induced lactic acidosis was much discussed in the mid-seventies. Up to 1978, at least 330 cases had been reported in world literature (1). Most of these were of diabetic patients taking the drug in therapeutic dosages. Aggravating situations were identified as impaired hepatic, renal and cardiovascular functions (2). The widespread publicity of this adverse effect of phenformin led to its withdrawal from general use by the Food and Drug Administration of the USA in October 1977, and restriction of its use in many other countries.

Much less has been reported on self-poisoning with phenformin. As far as we know, there were only seven other reports on acute consumption of massive doses of the drug (3 – 9). This report is the first case encountered locally, surfacing exactly eight years after the drug was banned in Singapore on 1 August 1977.

CASE REPORT

S.Y., a 19 year old Thai Chinese housewife, was admitted to Alexandra Hospital on 27 August 1985. The initial history was one of fever, epigastric pain and vomiting of a day's duration. She fainted at home, and on admission she was drowsy but no localising neurological signs were present. Pulse rate was 76 per minute, respiratory rate 20 per minute, blood pressure 130/80 mm Hg, and temperature 36°C. No abnormalities were detected in the heart, lungs and abdomen. Two hours after admission, her husband revealed that she had ingested half a small bottle of liniment. The serum salicylate was only 3.0 mg/dl. Blood glucose on admission was 12 mg/dl, whence 40 ml of 50% dextrose was given intravenously, followed by a slow infusion of 5% dextrose and hourly glucose drinks. The blood glucose level two hours later was 132 mg/dl. The cause of the hypoglycaemia was not obvious then as no further information could be extracted from the patient who vehemently denied ingestion of other drugs. About eight hours later, the patient complained of hunger and thirst and was seen to retch. She was hyperventilating and had a tachycardia of 120 per minute. Blood glucose had dropped to 42 mg/dl. Blood gases showed metabolic acidosis (pH 6.88, pCO_2 13.5 mm Hg, Base excess −31.0 mmol/L, HCO_3 2.4 mmol/L, pO_2 124 mm Hg, 0_2 saturation 97.7%). Serum potassium was 8.2 mmol/L, sodium 125 mmol/L and chloride 91 mmol/L. At that point she admitted to having ingested at least 90 anti-diabetic tablets belonging to her mother-in-law, with whom she had had a disagreement, about seventeen hours previously. Following the ingestion she developed nausea, giddiness and vomiting. The tablets, it was later established, had been purchased from a local Chinese medicine shop about seven years previously. The label on the emptied bottle carried the Chinese characters " 降糖灵片 ", which translate as "sugar lowering tablets". The marked dosage was 25 mg, and this gave us the first clue that the patient had ingested phenformin (at least 2250 mg). The anion gap was 39 mmol/L and a simultaneous serum lactate of 178 mg/dl (normal range 3.5 to 15.8 mg/dl) confirmed that she had lactic acidosis. Over the ensuing eleven hours, she was given repeated intravenous infusions of 8.4% sodium bicarbonate totalling 850 mmol before blood pH was normalised (Figure 1). Blood glucose levels fluctuated, but except for a further drop to 29 mg/dl twenty one hours after admission, was never at dangerously low levels (Figure 2). The patient's condition gradually improved as the acidosis was corrected. Serum lactate fell to 94.9 mg/dl, thence to 15 mg/dl (Figure 1). She was eventually discharged well after seven days in hospital.

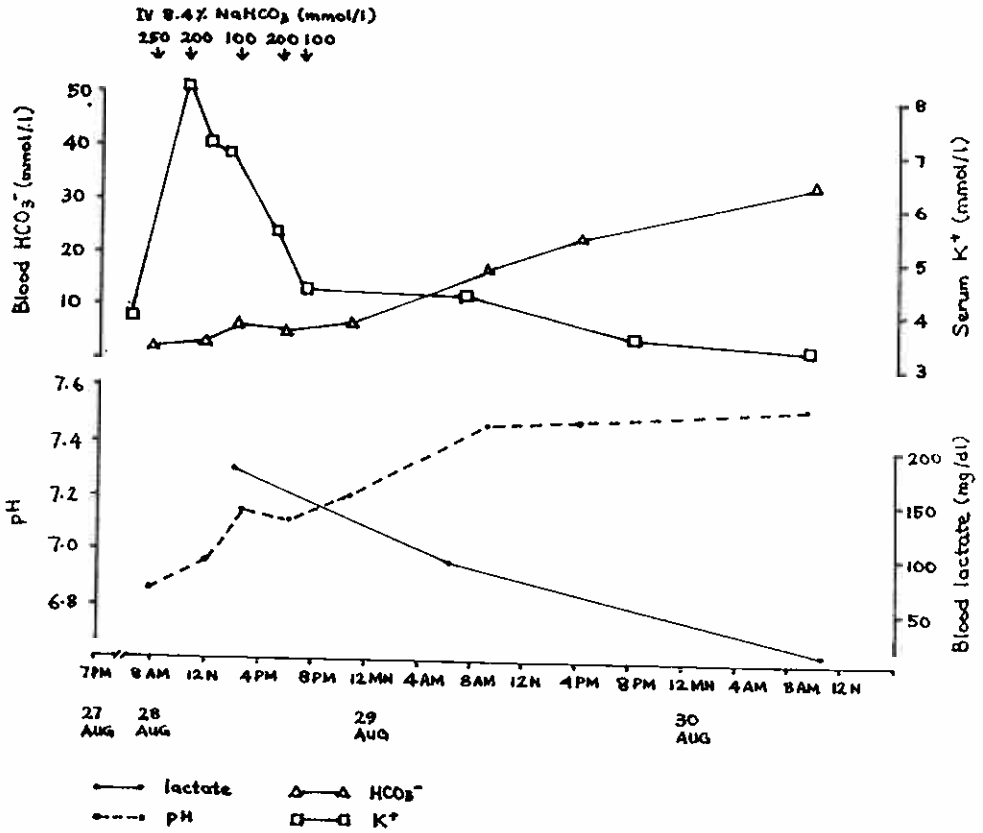

FIGURE 1: Patient's serial blood pH, lactate, HCO_3^- and K^+. The amount and time of administration of intravenous sodium bicarbonate are indicated.

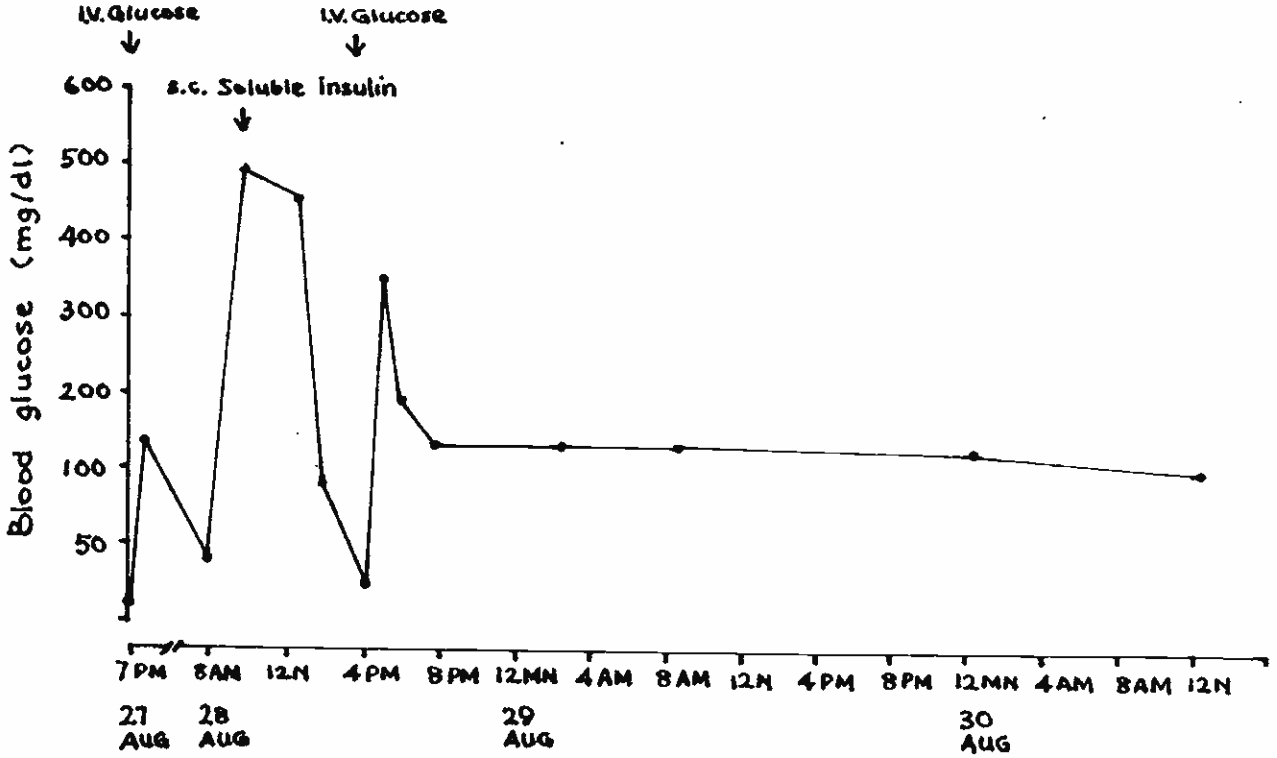

FIGURE 2: Patient's serial blood glucose level.

DISCUSSION

Although plasma phenformin was not measured in our patient, the incrimination of phenformin was never in doubt. The bottle which contained the drug ingested, with only Chinese labelling, is almost identical to another one which bears similar Chinese characters with the additional labelling "Tab phenethyldiguanidi hydrochloridi", an obvious reference to phenethylbiguanide hydrochloride, the standard spelling (Figure 3). This latter bottle belonged to the mother-in-law of a nurse in Alexandra Hospital. It was fortuitous that we were able to lay our hands on it after some casual inquiries. Smaller Chinese prints on both bottles show that the tablets were made in Beijing, People's Republic of China.

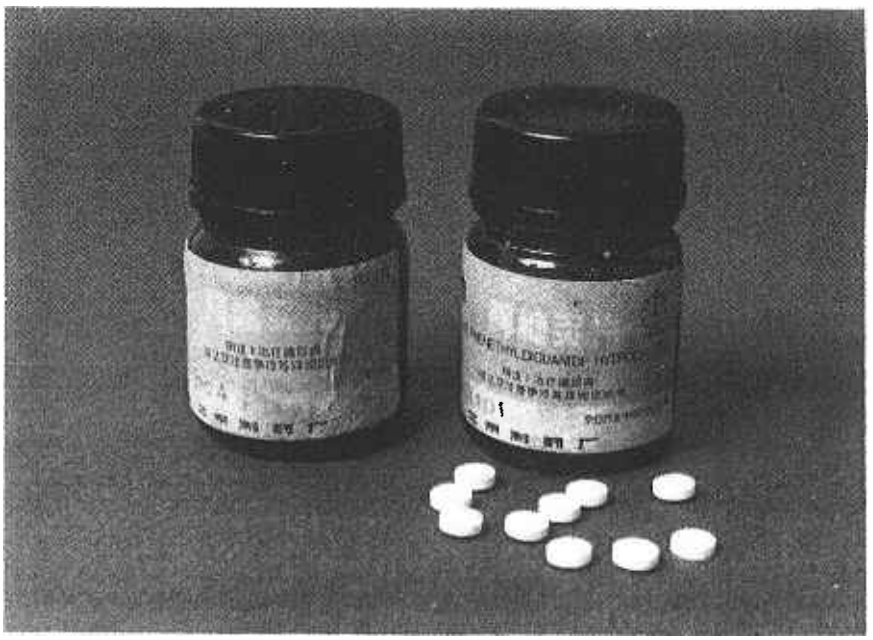

FIGURE 3: The bottle on the left belonged to the patient, and that on the right was the reference bottle.

It is an open fact that self-medication with Chinese medicine is very much a way of life amongst the Chinese here. With the recent interest in travel to China in the wake of a more open-door policy in that country, Chinese products are now more accessible. Although a visit to Chinese medicine stores is not in the published itineraries, it is almost routine for tour operators to offer to take tourists to such places, especially where ethnic Chinese form the majority of the tour group. Indeed, the reference bottle of phenformin referred to above was bought in China during a tour. The purchaser is not a diabetic but bought it with the intention of giving it away as gifts to diabetic friends! With a diabetic population of 1.55% among the local Chinese (10), it should not be surprising that the use of phenformin may be rampant, if covertly.

Following our report of the case to the Drug Inspectorate of the Ministry of Health, a random search was made on Chinese medicine shops. Twenty eight were found to have stocks of between 100 and 5700 similar tablets per shop; these had been obtained from unknown seamen, salesmen and tourists.

As far as we know, there were only seven previous reports of attempted suicides with massive doses of phenformin (3 — 9). Of these, the highest dose ingested was 3000 mg and the lowest 850 mg. An analysis of these cases shows that nausea, vomiting and abdominal cramps are typical early symptoms, occurring within a few hours of ingesting the drug. Two of these seven cases however did not develop these symptoms, but progressed straight to acidotic breathing and mental obtundation. These latter sequelae occurred between 5½ to 24 hours after ingestion. In these respects our patient was no different in presentation from previously reported cases (Table 1). Hypoglycaemia of less than 60 mg/dl occurred in six out of seven cases, and hyperlactataemia in three out of the four in whom serum lactate levels were measured. Hypoglycaemia occurred between 10 and 24 hours and hyperlactataemia between 12 and 39 hours after ingestion. It is interesting that in the first reported case by Dobson (3), both hypoglycaemia and hyperlactataemia were absent, presumably because vomiting, which occurred within one hour of ingestion, minimised absorption of the drug.

Phenformin causes hypoglycaemia by reducing intestinal absorption of glucose (11, 12), inhibiting gluconeogenesis (13 – 15) and increasing peripheral glucose utilisation (16). These effects are believed to result from an alteration of the electrostatic surface potential of mitochondrial membranes (17).

Lactic acidosis is caused by the ability of phenformin to increase lactic acid production peripherally and to impair its removal by the liver and kidneys. Which of these two mechanisms predominates is uncertain, but the work of Dietze et al (18) suggested that a reduction in splanchnic clearance of lactate plays a substantial role.

While there is no doubt that the mainstay of treatment of lactic acidosis is intravenous sodium bicarbonate, there is some controversy regarding optimum dose and speed of restoring the blood pH. The danger of excessive sodium bicarbonate is paradoxical intracellular acidosis causing negative inotropic effect and further impairing hepatic lactate metabolism (19), and cerebral acidosis (20). Ryder (21) reviewed the subject and concluded that bicarbonate therapy should be judicious, along the lines recommended for diabetic ketoacidosis (22). An initial correction of the blood pH by 4 to 6 mmol/L with subsequent modest correction to 14 to 16 mmol/L should suffice (23). However, Cohen (24) is in favour of normalising blood pH within 2 to 6 hours. He pointed out the difference between lactic acidosis and ketoacidosis. In the latter, gluconeogenesis from lactate is actually increased owing to insulin deficiency and hence countering the depressive effect of acidosis on gluconeogenesis is not a special requirement in ketoacidosis. In a review of 330 cases of lactic acidosis in biguanide-treated diabetics (1) there was no difference between the doses of sodium bicarbonate given to survivors and non-survivors (mean ± SEM 549 ± 38 vs 505 ± 54 mmol). Our patient can be considered to have received in total "excessive" bicarbonate. This, however, was given intermittently and necessitated by concomittant hyperkalaemia, and no deleterious effects arose from giving 850 mmol over 11 hours. It is our opinion that the use of bicarbonate in lactic acidosis should be tailored to individual needs.

Other modes of treatment of lactic acidosis include dichloroacetate which, by activating pyruvate dehydrogenase, enhances oxidative metabolism of lactate. This has proved beneficial in animals (25) and man (26). Haemodialysis should be considered in resistant cases and the role of Tris (hydroxymethyl) aminomethane (THAM) which raises intracellular and extracellular pH (27) awaits further evaluation. In

TABLE 1
SEVEN PREVIOUSLY REPORTED CASES OF ATTEMPTED SUICIDE WITH PHENFORMIN

Author	Dose Taken (mg)	GI Symptoms*	Acidotic Breathing	Drowsy Or Coma	Blood Glucose (mg/dl)	Serum Lactate (mg/dl)	$NaHCO_3$ Used (mmol)	Outcome
Dobson 1965	850	+ (1)	–	–	126 (7)	8.1 (7)	—	Lived
Davidson 1966	1500	+ (4)	?	?	12 (11)	–	330	Lived
Bingle 1970	1500	+ ("soon")	+ (24)	+ (24)	25 (24)	–	1250	Died
Strauss 1971	2500	+ (2)	+ (12)	+ (12)	26 (12)	100 (12)	1000	Lived
Cohen 1973	1500-2000	–	+ (14½)	+ (14½)	58 (14½)	142 (15)	1150	Died
Edwards 1976	3000	–	+ (5½)	+ (5½)	22 (20)	276 (39)	?	Lived
Coronho 1976	2500	+ (3)	+ (10)	–	33 (10)	–	1050	Lived
Present Case	2250	+ ("soon")	+ (17)	+ (7)	12 (7)	178 (21)	850	Lived

*GI Symptoms: Nausea; vomiting, abdominal cramps
+ Figures in brackets indicate hours after ingestion

diabetic patients with biguanide-induced lactic acidosis, concomittant ketoacidosis may inhibit pyruvate dehydrogenase and thus limit lactate oxidation. Where the diabetic state warrants it, insulin is recommended (23).

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REFERENCES

1. Luft D, Schmulling RM, Eggstein M: Lactic Acidosis in Biguanide-Treated Diabetics. A Review of 330 Cases. Diabetologia.1978; 14: 75-87.
2. Natrass M, Alberti KGMM: Biguanides. Diabetologia 1978; 14: 71-4.
3. Dobson HL: Attempted Suicide with Phenformin. Diabetes 1965; 14: 811-2.
4. Davidson MB, Bozarta WR, Challoner DR, Goodner CJ: Phenformin, Hypoglycaemia and Lactic Acidosis — Report of Attempted Suicide. N Engl J Med 1966; 275: 886-8.
5. Bingle JP, Storey GW, Winter JM: Fatal Self-poisoning with Phenformin. Br Med J 1970; 3: 752.
6. Strauss FG, Sullivan MA: Phenformin Intoxication resulting in Lactic Acidosis. John Hopkins Med J 1971; 128: 278-81.
7. Cohen RD, Ward JD, Brain AJS, Murray CR, Savege TM, Iles RA: The Relationship between Phenformin Therapy and Lactic Acidosis. Diabetologia 1973; 9: 43-6.
8. Edwards JCW: Phenformin and Lactic Acidosis. Br Med J 1976; 1: 584.
9. Coronho V, Da Silva OA, Lopez M: Acute Self-poisoning with Phenformin. Acta Diabet Lat 1976; 13: 130.
10. Cheah JS, Lim KF, Yeo PPB, Tan BY, Tan YT, Ng YK: Diabetes in Singapoare: Results of a country-wide population survey. Proceedings of 6th Asia and Oceania Congress of Endocrinology 1978; 1: 227-38.
11. Caspary WF, Creutzfeld W: Analysis of inhibitory effect of biguanides on glucose absorption: inhibition of active sugar transport. Diabetologia 1971; 7: 379-85.
12. Czyzyk A, Tawecki J, Sadowski J, Ponikowska I, Szezepanik Z: Effect of biguanides on intestinal absorption of glucose. Diabetes 1968; 17: 492-8.
13. Meyer F, Ipaktchi M, Clauser H: Specific inhibition of gluconeogenesis by biguanides. Nature 1967; 213: 203-4.
14. Cook DE, Blair JB, Lardy HA: Mode of action of hypoglycaemic agents. v. Studies with phenethylbiguanide in isolated perfused rat liver. J Biol Chem 1973; 248: 5272-7.
15. Haeckel R, Haeckel H: Inhibition of gluconeogenesis from lactate by phenethylbiguanide in the perfused guinea pig liver. Diabetologia 1972; 8: 117-24.
16. Butterfield WJH, Whichelow MJ: The hypoglycaemic action of phenformin: Effect of phenformin on glucose metabolism in peripheral tissues. Diabetes 1962; 11: 281-6.
17. Schafer G: Some new aspects on the interaction of hypoglycaemia producing biguanides with biological membranes. Biochem Pharmacol 1976; 25: 2015-24.
18. Dietze G, Wicklmayr M, Mehnert H, Czempiel H, Henftling G: Effect of phenformin on hepatic balances of gluconeogenesis substrates in man. Diabetologia 1978; 14: 243-8.
19. Lloyd MH, Iles RA, Simpson BR, Strumin JM, Layton JM, Cohen RD: The effect of simulated metabolic acidosis on intracellular pH and lactate metabolism in the isolated perfused rat liver. Clin Sci Mol Med 1973; 45: 543-9.
20. Posner JB, Swanson AG, Plum F: Acid-base balance in cerebrospinal fluid. Arch Neurol 1965; 12: 479-96.
21. Ryder REJ: Lactic Acidosis: High-dose or low-dose bicarbonate therapy? Diabetes Care 1984; 7: 99-102.
22. Alberti KGMM, Hockaday TDR: Diabetic coma: A reappraisal after five years. Clin Endocrinol Metab 1977; 6: 421-55.
23. Kassirer JP: Current concepts: Serious acid-base disorders. N Engl J Med 1974; 291: 773-6.
24. Cohen RD: The prevention and treatment of Type B lactic acidosis. Br J Hosp Med 1980; 23: 577-81.
25. Arieff AI, Lerch WJ, Lazarowitz VC: Treatment of experimental lactic acidosis with dichloroacetate. Clin Res 1978; 26: 410A.
26. Starpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI: Treatment of lactic acidosis with dichloroacetate. N Engl J Med 1983; 309: 390-6.
27. Robin ED, Wilson RJ, Bromberg PA: Intracellular acid-base relations and intracellular buffers. Ann N Y Acad Sci 1961; 92: 539-47.