

Hazards posed by a banned drug—phenformin is still hanging around

CME

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The Hospital Authority Toxicology Reference Laboratory confirmed six cases of phenformin use, with or without complications, from July 2005 to November 2006. Two of the patients presented with potentially fatal phenformin-induced lactic acidosis. Phenformin was found (or suspected to be) adulterating Chinese proprietary medicine in five of the six cases. We report these six cases to highlight the underrecognised hazards posed by phenformin, a banned drug in Hong Kong.

Introduction

Biguanides were introduced into clinical practice in the 1950s for the treatment of type 2 diabetes mellitus.¹ Phenformin, one of the biguanides, was withdrawn from the US market in 1977 due to its high incidence of associated lactic acidosis.² Thereafter, phenformin was withdrawn from the formularies in many different places, including Hong Kong. Nonetheless, the drug remains available in some countries, for example, China, Brazil, and Italy.³ The use of phenformin and its complications may be underrecognised in Hong Kong. The Hospital Authority Toxicology Reference Laboratory confirmed six cases of phenformin use, with or without complications, from July 2005 to November 2006. We report these six cases to highlight the potential hazards posed by phenformin, a banned drug in Hong Kong.

Case reports

Case 1

A 56-year-old man with a 20-year history of diabetes mellitus presented in August 2005 with anorexia, nausea, and vomiting. The patient had been treated with metformin, acarbose, and insulin in the US until he defaulted follow-up and sought alternative treatment in Mainland China 10 months before presentation. He took four Chinese proprietary medicines (CPMs) bought over-the-counter that claimed to contain herbs only, namely Yi Su Kang Jiau Nang (胰速康膠囊), Xiang Lian Pian (香連片), Ching Shin Bei Dou Gen Pian (清欣北豆根片), and Yan Suan Shiao Bo Jiau Pian (鹽酸小檗碱片), for about 10 months. On admission, the patient was fully alert and afebrile with moderate dehydration. His blood pressure was 142/72 mm Hg, pulse rate was 98 beats per minute, and blood glucose concentration measured by blood glucose meter was 3.9 mmol/L. Initial investigations showed a severe high anion gap metabolic acidosis in a venous blood sample (pH 6.79, with a bicarbonate of 3.9 mmol/L, base excess -30.5 mmol/L) and traces of ketones in his urine. The initial serum lactate concentration was 5.9 mmol/L, which continued to rise to 11.4 mmol/L after admission (see Table for reference intervals). The serum sodium was 135 mmol/L, potassium 6.5 mmol/L, chloride 111 mmol/L, urea 6.7 mmol/L, and creatinine 100 µmol/L. His haemoglobin level was 151 g/L, white cell count $22.0 \times 10^9/L$, and platelet count $350 \times 10^9/L$. Glycosylated haemoglobin (HbA_{1c}) was 8.3%. A chest radiograph was unremarkable and electrocardiography showed sinus tachycardia. Blood and urine cultures were negative.

The patient was started on intravenous fluids, sodium bicarbonate, dextrose, and insulin. Haemodialysis was also started in the intensive care unit to manage the severe lactic acidosis. Within 16 hours of presentation his acid-base status improved to a pH of 7.39, bicarbonate 14.1 mmol/L, and base excess -8.7 mmol/L. The lactate level also fell to 1.7 mmol/L by 22 hours after presentation. The patient was discharged 6 days later on protaphane 18 units per day.

The four CPM products, serum and urine were analysed using high-performance liquid chromatography with diode array detection (HPLC-DAD).⁴ Phenformin and glibenclamide were detected in serum and urine along with one of the CPM products, Yi Su Kang Jiau Nang (胰速康膠囊).

Key words

Acidosis, lactic; Drug and narcotic control; Drugs, Chinese herbal; Phenformin

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Case 2

A 61-year-old woman with diabetes mellitus and hypertension was admitted to hospital in August 2006 with acute confusion. She had been taking phenformin bought over-the-counter in Mainland China for an unknown period. The patient had no fever and her vital signs were stable with a blood pressure of 149/73 mm Hg and pulse rate of 91 beats per minute on admission. Laboratory results revealed a severe high anion gap metabolic acidosis with an arterial pH of 6.78, carbon dioxide partial pressure 1.6 kPa, oxygen partial pressure 17.2 kPa, bicarbonate 1.7 mmol/L, base excess -32.4 mmol/L while the patient was receiving 50% oxygen. The lactate concentration was 6.9 mmol/L and the serum sodium 134 mmol/L, potassium 5.1 mmol/L, urea 11 mmol/L, and creatinine 151 µmol/L. Her blood glucose concentration was 10.5 mmol/L and haemoglobin was 145 g/L, white cell count $53.2 \times 10^9/L$ with 71% neutrophils, and a platelet count of $350 \times 10^9/L$. Blood, urine, and cerebrospinal fluid cultures were negative. The chest radiograph and computed tomographic scan of the brain were normal and the electrocardiogram showed a sinus rhythm.

The patient was treated with intravenous fluids, sodium bicarbonate, and continuous renal replacement therapy in the intensive care unit. She was also started on empirical antibiotics and acyclovir in view of the raised white cell count. Her acid-base status improved during the next day with a pH of 7.39, bicarbonate 17.3 mmol/L, and base excess -6.3 mmol/L. She was discharged 8 days after admission on glipizide 5 mg twice daily.

Analysis of a urine sample using HPLC-DAD and gas chromatography-mass spectrometry (GCMS) yielded phenformin together with other drugs.

Case 3

A 73-year-old woman with a history of diabetes mellitus presented to a private hospital in June 2005 with heart failure. She had been taking a CPM, Ku Le Kang (苦樂康), which claimed to contain herbal ingredients only, for treatment of her diabetes mellitus for the previous 2 months. An echocardiogram reported a normal left ventricular function and ejection fraction. The CPM product was analysed using HPLC-DAD and GCMS. Phenformin and rosiglitazone were detected. Rosiglitazone-associated fluid retention was considered the underlying cause of her heart failure.

Case 4

A 79-year-old diabetic woman, who had been taking a CPM only for an unknown period, presented in October 2006 with confusion. The CPM, Shiao Ke Shu Ping-Jiang Tang Ning Jiau Nang (消可舒平一降糖

芬法敏：禁藥帶來的危害性

從2005年7月至2006年11月期間，醫院管理局毒理學參考化驗室確認了六宗芬法敏（phenformin，又稱苯乙基二胍）的病例。部分病人出現併發症，其中兩名病人更有潛在致命性的乳酸中毒。六宗病例中，有五宗被證實或懷疑芬法敏被摻入中成藥所致。此報告喚起對這種香港已禁售的藥品（芬法敏）的潛藏危害性。

TABLE. Reference intervals of blood pH, blood gas concentrations, and lactate concentration

Blood tests	Reference range
pH	7.35-7.45
Carbon dioxide partial pressure, blood gas	4.7-6.0 kPa
Oxygen partial pressure, blood gas	10-13 kPa
Bicarbonate, blood gas	23-32 mmol/L
Lactate	0.3-1.3 mmol/L

寧膠囊), claimed to be purely herbal. In the accident and emergency department, the patient's blood glucose concentration was 2.2 mmol/L. Following administration of 40 mL 50% dextrose solution she became fully alert. An infusion of 5% dextrose solution was also commenced.

Analysis using HPLC-DAD revealed the presence of glibenclamide, phenformin, and rosiglitazone in the CPM product. Glibenclamide metabolites and phenformin were detected in the patient's urine sample whereas glibenclamide was detected in her blood. Her hypoglycaemia could probably be explained by the glibenclamide finding.

Case 5

A 51-year-old woman with a history of acromegaly due to a pituitary macroadenoma excised transsphenoidally, had diabetes first treated with gliclazide and metformin then, later, insulin due to poor diabetic control. She discontinued the treatment and took a CPM, Huo Yi Jiang Tang Dan (活胰降糖丹), instead, for about 6 months. Her self-monitored blood glucose levels measured by blood glucose metre while taking the CPM ranged from 4.2 to 9.8 mmol/L. Her relatively good glycaemic control suggested adulteration of the CPM with hypoglycaemic agents. The CPM product was analysed using HPLC-DAD and phenformin and glibenclamide were detected.

Case 6

A 78-year-old man with multiple morbidities including diabetes, hypertension, hyperlipidaemia,

ischaemic heart disease, chronic renal impairment, chronic obstructive airway disease, and benign prostatic hyperplasia had been treated with insulin for 8 years to manage his poor diabetic control. He discontinued the treatment and began taking a CPM as alternative therapy for about 1 year. His HbA_{1c} level measured while he was taking the CPM only was 6.2%. Adulteration of the CPM with hypoglycaemic agents was suspected. Phenformin and glibenclamide metabolites were detected in a urine sample by HPLC-DAD and liquid chromatography–tandem mass spectrometry (LCMS/MS) respectively. As the patient had not been prescribed phenformin or glibenclamide, adulteration of the CPM with these medications was very likely. Unfortunately, no CPM sample was available for analysis to confirm this suspicion.

Discussion

Biguanides act as anti-hyperglycaemics by inducing anorexia, decreasing gastro-intestinal absorption of carbohydrates, inhibiting hepatic gluconeogenesis, and increasing cellular uptake of glucose.⁵ Biguanides have been limited as a therapy for type 2 diabetes mellitus by their association with fatal lactic acidosis. The clinical presentation of biguanide-induced lactic acidosis is non-specific, including vomiting, somnolence, nausea, epigastric pain, loss of appetite, hyperpnoea, lethargy, diarrhoea, and thirst.⁶ The causes of lactic acidosis can be categorised as type A due to hypoxia or hypoperfusion, and type B due to systemic diseases, drugs and toxins, or inborn errors of metabolism. Even in patients taking biguanides, other causes of lactic acidosis like acute myocardial infarction, septic shock, and hypovolaemic shock etc should also be excluded. The hallmark of biguanide-induced lactic acidosis is severe lactic acidosis without evidence of hypoperfusion and hypoxia.⁵ Both the patients in cases 1 and 2 who presented with lactic acidosis were haemodynamically stable and probably suffered from type B lactic acidosis. Although all biguanides can cause lactic acidosis, phenformin is associated with the highest risk. The reported incidence of lactic acidosis during metformin therapy was 0-0.084 cases/1000 patient-year, whereas that of phenformin was 0.64 cases/1000 patient-year, an order of magnitude higher.¹ In a literature review of 330 cases of biguanide-induced lactic acidosis, phenformin was involved in 86%, buformin in 9%, and metformin in 5%.⁶ It should be noted that these results may also depend on the extent of background use of each agent. Although it is difficult to establish the market shares of the individual agents involved in those 330 cases because they came from different countries, studies in France and Switzerland have shown that phenformin accounted for more cases of lactic acidosis, despite the wider use of metformin in those countries.⁶ Biguanide-induced lactic acidosis

had a mortality rate of 50.3%.⁶

Insulin deficiency and pyruvate accumulation are central to biguanide-induced lactic acidosis.^{2,7} A low insulin level and fasting state is induced by the anorexia, nausea, and vomiting symptoms of biguanide toxicity, hence promoting fat and protein catabolism. Fat catabolism and oxidation of fatty acids increases the reduced/oxidised nicotinamide adenine dinucleotide (NADH/NAD⁺) ratio. Inhibition of oxidative phosphorylation by phenformin also limits the regeneration of NAD⁺ from NADH. The resultant increased NADH/NAD⁺ ratio inhibits pyruvate dehydrogenase and blocks pyruvate entry into the Krebs cycle. The increased acetyl coenzyme A/coenzyme A ratio, resulting from increased fatty acid oxidation and NADH, also blocks the entry of pyruvate into the Krebs cycle. Protein catabolism yields alanine and other glucogenic amino acids, which are converted to pyruvate. As biguanide inhibits gluconeogenesis by limiting pyruvate carboxylase and formation of adenosine triphosphate, pyruvate cannot be used for gluconeogenesis. Since both the Krebs cycle and gluconeogenesis are blocked, the accumulated pyruvate is metabolised to lactate, with the reaction further driven by the high NADH/NAD⁺ ratio. There are some possible reasons why phenformin carries a higher risk of lactic acidosis than metformin. Metformin has a shorter half-life (1.5 hours) and is excreted predominantly unchanged by the kidney whereas phenformin has a longer half-life (12 hours) and undergoes both hepatic oxidation and renal elimination.⁸ Patients with hepatic dysfunction are at higher risk of phenformin-induced lactic acidosis. Compared with metformin, phenformin has a narrower therapeutic window and a lower dose is required to cause lactic acidosis.⁶ Moreover, the existence of polymorphism in phenformin hydroxylation implies that poor metabolisers are at higher risk.⁹ The role of blood biguanide levels has been studied. The correlation between plasma biguanide concentrations and lactate concentrations has been demonstrated in phenformin but not in metformin.¹⁰ Furthermore, the degree of metformin accumulation does not have any prognostic value in lactic acidosis.^{11,12}

The six cases of phenformin use identified by the Toxicology Reference Laboratory over 17 months, two of whom presented with lactic acidosis, suggest that the use of phenformin, and its complications, may be more common than is generally acknowledged. Cases of phenformin-induced lactic acidosis are still frequently reported in those countries where the drug is still available, like China^{13,14} and Italy.^{3,15} There are also similar reports from countries where phenformin has been banned.^{2,7,16-20} Although phenformin has been removed from the market in most countries, the drug is still available from different sources. For example, phenformin is available as prescribed or

over-the-counter medications in those countries where the drug is still marketed, as adulterants in CPM, and also via the internet. Of these sources, phenformin is particularly dangerous when it is an adulterant in CPM. The disguise of the drug as a harmless CPM may obscure the clinical diagnosis. In our case series, phenformin was either a confirmed or suspected adulterant in CPM in five out of six cases, and obtained as an over-the-counter medication in China by the remaining patient.

Adulteration of CPM with undeclared pharmaceuticals has been frequently reported worldwide. Huang et al²¹ showed that 23.7% of 2609 CPM samples collected in Taiwan were adulterated. Another study found that 7% of 260 CPM products collected in Californian outlets contained undeclared pharmaceuticals.²² Although only 1.2% of 4461 CPM samples collected from the marketplace in Hong Kong were adulterated, this figure may be an underestimate as the more likely sources of adulterated products, such as peddlers or elsewhere outside Hong Kong, were not included.²³ Oral antidiabetic agents, including phenformin, are common adulterants. The US Food and Drug Administration and Health Canada have issued alerts on three CPM products containing undeclared drugs phenformin and glibenclamide.^{24,25} The dangers of taking CPM adulterated with phenformin are manifold. On the one hand, this hinders diabetic control since the dosage of the adulterants is unknown and the usage is unsupervised. On the other hand, phenformin is seldom used as the only adulterant; instead it is commonly used together with oral hypoglycaemic agents. This pattern was illustrated in our case series, in which glibenclamide or rosiglitazone were detected in addition to phenformin in all five cases

involving CPM adulteration. This combination of adulterants poses additional risks to patients. Not only are they at risk of phenformin-induced lactic acidosis, hypoglycaemia is another equally dangerous and probably even more common complication.

Sampling and screening of CPM available in the marketplace for undeclared pharmaceuticals by the regulatory body is essential for deterring such illegal and unethical practices. Education of the general public is also of paramount importance. Those who would like to use Chinese medicine as adjuvant therapy for diabetes mellitus should consult traditional Chinese medicine practitioners instead of taking CPM or drugs from unknown sources. Clinicians need to have a high index of suspicion. Phenformin-induced lactic acidosis should be considered in diabetic patients presenting with high anion gap metabolic acidosis. A detailed drug history is always important. Analyses of CPM, drugs and biological samples for phenformin and other anti-diabetic agents by the laboratory can help to confirm the diagnosis. The most effective way of eradicating this problem may be banning phenformin from all markets where it is still available. Metformin, which is associated with a much smaller risk of lactic acidosis, can always replace phenformin.

The six cases we have reported may represent just the tip of an iceberg. There may be diabetic patients taking phenformin obtained from various sources who have not, as yet, developed any complications who remain undetected. Their first presentation, however, may be in fatal lactic acidosis. Concerted efforts from various parties, including the regulatory body, health care professionals and laboratories, are required to make phenformin-induced lactic acidosis truly obsolete.

References

- Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992;15:755-72.
- Kwong SC, Brubacher J. Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 1998;16:881-6.
- Fimognari FL, Pastorelli R, Incalzi RA. Phenformin-induced lactic acidosis in an older diabetic patient: a recurrent drama (phenformin and lactic acidosis). *Diabetes Care* 2006;29:950-1.
- Lai CK, Lee T, Au KM, Chan AY. Uniform solid-phase extraction procedure for toxicological drug screening in serum and urine by HPLC with photodiode-array detection. *Clin Chem* 1997;43:312-25.
- Gan SC, Barr J, Arieff AI, Pearl RG. Biguanide-associated lactic acidosis. Case report and review of the literature. *Arch Intern Med* 1992;152:2333-6.
- Luft D, Schmülling RM, Eggstein M. Lactic acidosis in biguanide-treated diabetics: a review of 330 cases. *Diabetologia* 1978;14:75-87.
- Kumar A, Nugent K, Kalakunja A, Pirtle F. Severe acidosis in a patient with type 2 diabetes mellitus, hypertension and renal failure. *Chest* 2003;123:1726-9.
- Kreisberg RA, Wood BC. Drug and chemical-induced metabolic acidosis. *Clin Endocrinol Metab* 1983;12:391-411.
- Oates NS, Shah RR, Idle JR, Smith RL. Influence of oxidation polymorphism on phenformin kinetics and dynamics. *Clin Pharmacol Ther* 1983;34:827-34.
- Marchetti P, Benzi L, Cecchetti P, et al. Plasma biguanide levels are correlated with metabolic effects in diabetic patients. *Clin Pharmacol Ther* 1987;41:450-4.
- Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999;20:377-84.
- Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 1995;18:779-84.
- Fang XZ. Clinical analysis of phenformin induced lactic

- acidosis [in Chinese]. *Journal of Internal Intensive Medicine* 1998;4:110-1.
14. Chen ZS, Liu FF. Observation of treatment effectiveness in ten cases of diabetic lactic acidosis [in Chinese]. *Chinese Journal of Misdiagnostics* 2005;5:686-7.
 15. Enia G, Garozzo M, Zoccali C. Lactic acidosis induced by phenformin is still a public health problem in Italy. *BMJ* 1997;315:1466-7.
 16. Ko GT, Chan JC, Chow CC, Yeung VT, Li YK, Cockram CS. Phenformin-induced lactic acidosis: an almost forgotten complication of treatment with biguanides. *Br J Hosp Med* 1995;54:469-70.
 17. Yeoh KG, Lee KO, Cheah JS. Fatal lactic acidosis from imported phenformin—report of two cases. *Singapore Med J* 1996;37:482-4.
 18. Rosand J, Friedberg JW, Yang JM. Fatal phenformin-associated lactic acidosis. *Ann Intern Med* 1997;127:170.
 19. McGuinness ME, Talbert RL. Phenformin-induced lactic acidosis: a forgotten adverse drug reaction. *Ann Pharmacother* 1993;27:1183-7.
 20. Lu HC, Parikh PP, Lorber DL. Phenformin-associated lactic acidosis due to imported phenformin. *Diabetes Care* 1996;19:1449-50.
 21. Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. *J Clin Pharmacol* 1997;37:344-50.
 22. Ko RJ. Adulterants in Asian patent medicines. *N Engl J Med* 1998;339:847.
 23. Leung TH, Chan AWK. Traditional Chinese Medicine in Hong Kong. *Hong Kong Pharmaceutical Journal* 2001;10:6-8.
 24. Sino American Health Products, Inc., issues national recall of herbal products due to the presence of the undeclared drugs glyburide and phenformin. US Food and Drug Administration Website: <http://www.fda.gov/oc/po/firmrecalls/Zhenqi.html>. Accessed 2 Feb 2007.
 25. Health Canada warns consumers not to take the Chinese medicine Shortclean due to potential health risk (17 November 2005). Health Canada website: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_124_e.html. Accessed 2 Feb 2007.