

# An Unusual Case of Metformin Associated Lactic Acidosis

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## Summary

Metformin associated lactic acidosis (MALA) is a rare, but serious complications of Type 2 diabetes mellitus treatment with a mortality rate of around 50%. It most commonly occurs in the setting of hepatic, cardiac or renal insufficiency. We report the case of an elderly female with MALA and concomitant starvation ketosis in the absence of any known risk factor, who went undiagnosed for a period of at least a month and made a complete recovery in the hospital

*Key Words:* Metformin, MALA, Biguanide

## Introduction

Lactic acidosis is a well-known, but rare complication of biguanide therapy. We present a case of lactic acidosis secondary to metformin therapy with associated ketosis from vomiting and poor intake.

## Case Report

A 70 year old Chinese female was admitted to the medical service in February 2001 with a two week history of poor feeding, nausea and vomiting. She was a nursing home resident with a history of Type 2 diabetes mellitus and hyperlipidemia. Her medication included metformin 500 mg tds, and tolbutamide 250 mg tds. She had been previously admitted about a month ago (on the same drug regimen) to the surgical service with similar complaints.

No organic pathology was found and she was

discharged to the nursing home three days later when her symptoms had abated. On physical examination, she was alert, moderately dehydrated and tachypneic. Vital signs were stable except for a respiratory rate of 26/min. Her abdomen was mildly distended and nontender. The rest of the systemic examination was normal. Her initial blood tests were significant for the following:

WBC 15,400/mm<sup>3</sup>, Hb 10.4g/dL, Na<sup>+</sup> 146 mmol/L, K<sup>+</sup> 5.3 mmol/L, Cl<sup>-</sup> 107 mmol/L, HCO<sub>3</sub><sup>-</sup> 4mmol/L, creatinine 178umol/L, glucose 4 mmol/L. Her arterial blood gas showed a pH of 7.01, PCO<sub>2</sub> of 8 mmol/L, PO<sub>2</sub> of 131 mmol/L, HCO<sub>3</sub><sup>-</sup> of 2 mmol/L. Urine analysis revealed ketone +4, albumin +, with no glycosuria.

Lactic acid level was 22mmol/L (normal range 0.5 - 2mmol/L). A diagnosis of metformin associated lactic acidosis (MALA) was made and the patient was transferred to the intensive care unit. She

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was prophylactically intubated for progressive drowsiness and given multiple doses of sodium bicarbonate along with intravenous hydration. A repeat lactate level was 15mmol/L. The patient improved rapidly and was extubated without event the following day. On day 5, her arterial pH was 7.49 and creatinine 93  $\mu\text{mol/L}$ . She was discharged on day 7 on tolbutamide. She was seen in the outpatient clinic a month later and found to be in good health. Her lactate level was 1.3mmol/L. On retrospective review of her previous admission in January, it was noted that her serum  $\text{HCO}_3^-$  was 9mmol/L, creatinine 101 $\mu\text{mol/L}$  and she had a high anion gap of 35. The urine examination showed ketones +4 with no glucose. Blood gas and serum lactate level were not done. The acidosis was not investigated at that time.

### Discussion

Biguanide induced lactic acidosis is a dreaded complication of diabetic therapy with a mortality rate of about 50%. It is 10-20 times more common with phenformin when metformin. Because of this complication, phenformin was withdrawn from clinical use in many countries in the 1970's. Biguanides inhibit gluconeogenesis in the liver and kidney, increase the uptake of glucose in the skeletal muscle and reduce the concomitant hypertriglyceridemia. At the cellular level, they act by fixation to the mitochondrial membrane and inhibit cellular oxidative phosphorylation; thereby increasing the anaerobic metabolism of glucose with resultant lactic acid production.

Most cases of MALA occur in patients with renal, hepatic or cardiac dysfunction. Very rarely, it has been known to occur in the absence of any such risk factors. In a large study conducted in France

on 49 MALA patients, it was observed that neither arterial lactate levels nor plasma metformin levels were of prognostic significance in relation to mortality rate which was 55%<sup>1</sup>. Death in these patients appeared instead, to be associated with hypoxic disease or other underlying illnesses. The treatment of MALA includes volume resuscitation, inotropic support, bicarbonate therapy and bicarbonate hemodialysis.

Large amounts of urine ketones with low blood sugar values represent the picture of starvation ketosis. Starvation ketosis does not produce a significant metabolic acidosis; the presence of which should prompt the clinician to look for other causes of acidosis. This case has some interesting aspects. MALA occurred in the absence of any known risk factors. While it could be argued that the prerenal state secondary to dehydration could have caused metformin accumulation and lactic acidosis, the presence of the acidosis during her previous admission (when her creatinine was normal) makes this possibility unlikely. She had a superimposed starvation ketosis from poor feeding and prolonged vomiting. She survived this potentially fatal condition even though it remained undetected for a period of over a month. In our search of the medical literature, we could not find a similar case reported.

### Conclusion

MALA is an uncommon complication of metformin therapy with potentially high fatality. Although it is unlikely to occur in the absence of renal, cardiac or hepatic risk factors, physicians should still have a high index of suspicion when any patient on metformin presents with acid base abnormalities.

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### References

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