Case Report

A Fatal Case of Metformin and Gliclazide Poisoning and its Management

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(Received: 2 May 2017; Accepted: 14 August 2017)

ABSTRACT

Both metformin and gliclazide have been used extensively in the management of type II diabetes mellitus. Metformin and gliclazide overdose can lead to severe hypoglycaemia refractory to intravenous (IV) dextrose rescue therapy. A 21-year-old man complained of vomiting and felt dizzy after four hours of taking 70 tablets of Metformin 500 mg and 40 tablets of Gliclazide 80 mg. He had major depressive disorder and wanted to commit suicide. He was given IV Dextrose 50% 50 cc immediately. Octreotide had been used successfully to reverse the refractory hypoglycaemia caused by gliclazide overdose. Unfortunately, he developed severe lactic acidosis with acute kidney injury. Dialysis had been done by continuous venovenous haemodiafiltrationa and intravenous sodium bicarbonate 8.4% infusion was given. However, the patient succumbed due to the severe lactic acidosis and kidney failure despite of urgent dialysis. Octreotide infusion helps in preventing refractory hypoglycaemia secondary to sulfonylurea overdose by inhibit calcium-mediated insulin release. Metformin overdose causes severe lactic acidosis due to conversion of glucose to lactate. Sodium bicarbonate therapy in metformin induced lactic acidosis is also controversial. Though sulfonylurea and metformin are the most commonly-prescribed anti-hypoglycaemic agents, thus during prescribing everyone has to be careful about the overdoses and side effects of these drugs.

Keywords: metformin, gliclazide, poisoning, octreotide

INTRODUCTION

Sulfonylurea medications were first used to treat type 2 diabetes in 1954 and they remain in common use today.[1] Metformin and gliclazide overdose can lead to severe hypoglycaemia refractory to intravenous dextrose rescue therapy. The National Health and Morbidity Survey (NHMS) 2011 reported type 2 diabetes prevalence figures of 15.2% and 20.8% for adults above the age of 18 to 30 years, respectively, in Malaysia.[2] The high prevalence of diabetes in our population poses a risk of poisoning either intentionally or unintentionally.[2]

Gliclazide, a sulphonyurea oral hypoglycaemic agent, acts by inhibit potassium efflux through ATP-sensitive potassium channels in pancreatic beta cell membranes.[3] High intracellular potassium level resulted in depolarization and calcium influx, triggering insulin secretion from beta cells.[3] In addition, gliclazide also increases the sensitivity of beta cells to glucose stimulus.[2] In acute poisoning, its onset of action remains unchanged but its duration of action is extended, causing prolonged hypoglycaemia.[4, 5] Its high degree of protein binding at around 94% has deemed dialysis ineffective in treating sulphonyurea overdosed.[6] Traditional approach in sulphonylurea poisoning includes dextrose administration while glucagon and diazoxide will be added in cases with rebound hypoglycaemia.[7, 8] Octreotide, a synthetic octapeptide analogue of somatostatin, also can be used to suppress insulin secretion.[8] In symptomatic intentional overdose of sulfonylurea, both intravenous dextrose and octreotide should be administered to raise the blood glucose level acutely thereby increase glucose delivery to the brain. Octreotide is a somatostatin analogue that inhibits insulin release from the pancreatic beta-islet cells. If intravenous dextrose is being given alone without octreotide, it may cause transient hyperglycaemia that triggers insulin release, leading to recurrent episodes of hypoglycaemia. The increase in insulin release can be reduced by octreotide.[8]

Metformin is a biguanide anti-hyperglycaemic agent that promotes euglycaemia by improving peripheral glucose uptake, decreasing insulin resistance and reducing hepatic glucose production.[9] Lactic acidosis is the major toxicity from acute biguanide poisoning. There is no antidote available.[10] Management of acute poisoning includes gastrointestinal decontamination and symptomatic management with dextrose, sodium bicarbonate and haemodialysis.[11]

CASE PRESENTATION

A 21-year-old man with background of major depressive disorder committed alleged suicide by swallowing 70 tablets of Metformin 500 mg and 40 tablets of Gliclazide 80 mg (both immediate release formulation). He became unwell, started vomiting and felt dizzy four hours after taking the tablets which prompted him to seek medical assistance. On arrival, his Glasgow come scale (GCS) was full but the capillary sugar reading was noted to be 1.5 mmol/L (low). He was given IV Dextrose 50% 50 cc immediately and his sugar improved to 6.3 mmol/L. Despite that, he experienced recurrent hypoglycaemia which is refractory to the subsequent IV dextrose rescue therapy. Consultation was done with endocrinologist and the National Poison Centre (Pusat Racun Negara). Their recommendations were to start him on intravenous dextrose and octreotide. He was started on IV Octreotide infusion 50 mcg/hour infusion as part of the gliclazide poisoning treatment. During octreotide intravenous infusion together with maintenance intravenous dextrose 10%, his hourly sugar levels were in the range of 6 – 10 mmol/L. Throughout the course of admission in the intensive care unit (ICU), he developed severe lactic acidosis with acute kidney injury to the extend needing continuous venovenous haemodiafiltration (CVVHDF) and regular intravenous sodium bicarbonate 8.4% infusion. He was dialyzed via CVVHDF after a discussion with our nephrologist as he was haemodynamically unstable and required triple inotropic support. Unfortunately, his condition deteriorated and he passed away at 32 hours of admission. His family members refused to do the post-mortem examination. The cause of death given was severe lactic acidosis secondary to metformin and gliclazide poisoning. There was no other co-ingestion apart of gliclazide and metformin in this case. His serum and urine toxicology for amphetamines, salicylates, opiods, benziodiazepine and alcohol were all negative. The laboratory services were unable to perform a serum level of metformin and gliclazide.

Table 1 Investigations (during admission)

	Readings	**Normal values**
Haemoglobin	15 g/dL	14 – 18 g/dL
White blood cells	19.5 × 10^9/L	4.0 – 12.0 × 10^9/L
Platelet	129 × 10^9/L	150 – 400 × 10^9/L
Creatinine	179 µmol/L	50 – 110 umol/L
Urea	2.5 mmol/L	4 – 8 mmol/L
Sodium	148 mmol/L	135 – 140 mmol/L
Potassium	2.9 mmol/L	3.5 – 5 mmol/L
Corrected calcium	2.10 mmol/L	2.2 – 2.6 mmol/L
Phosphate	3.58 mmol/L	1.0 – 1.5 mmol/L

Table 2 Serial blood gases result

	Normal range	Arrival	6 hours later ventilated	12 hours later ventilated	18 hours later ventilated	24 hours later ventilated
pH	7.35 – 7.45	6.8	6.828	6.8	6.9	6.9
pO2 in mmHg	80 – 100	45.1	120.2	118	79	73
pCO2 in mmHg	35 – 45	34.5	41.1	45.9	38.4	49
HCO-3 in mmol/L	23 – 29	6.3	6.4	6.5	8.1	6
Base excess	−2 to 2	−27	−27.5	−27.3	−23	−25
Lactate in mmol/L	<1	5	12	15	19	18

DISCUSSION

Intravenous dextrose is used to treat hypoglycaemia and is crucial to raise the blood glucose rapidly during resuscitation in order to increase glucose delivery to the brain.[7] The brain uses glucose at a rate of 20 times that of other body tissues and cannot use free fatty acids directly since they are not transported across the blood-brain barrier. However, ketone bodies (beta-hydroxybutyric acid and acetoacetic acid) are transported across the blood-brain barrier and their metabolism can help supplant the need of glucose. Glucagon is another option to treat hypoglycaemia. Its efficacy depends on body glycogen stores. It increases serum glucose level by stimulating gluconeogenesis using hepatic glycogen. However, it induces insulin release from pancreatic beta cells. Hyperinsulinaemia may worsen the refractory hypoglycaemia.[7] Glucagon (5 mg) intramuscularly (IM) may be used as a temporizing measure while IV access is obtained but it is not a substitute for dextrose. The efficacy of glucagon is dependent upon hepatic glycogen stores which may be depleted in the setting of prolonged hypoglycaemia. The short duration of action of glucagon further limits its effectiveness.[7]

Diazoxide is an antihypertensive agent that produces arteriolar vasodilation and reduced peripheral resistance.[7] Besides that, it inhibits pancreatic insulin release. It has been used to treat sulphonylurea poisoning for over two decades but there are concerns regarding its hypotensive, tachycardia, sodium and fluid retention.[7] So, production of injection diazoxide had been stopped. Its therapy has fallen out of favour with the increased use of octreotide, which was reported to be superior compared to intravenous diazoxide.[5, 12]

Octreotide has been proposed to act by inhibit calcium-mediated insulin release through reducing calcium influx across voltage-gated channels in pancreatic beta cells.[12] Octreotide is administered intramuscularly or subcutaneously in doses of 50 – 150 mcg every 6 hours for 24 hours.[11] It can be continued for another 24 hours if there is recurrence of hypoglycaemia.[12] Octreotide can also be given as continuous infusion.[12] However, it has been reported that continuous infusion is not better than intermittent intramuscular and subcutaneous dosing.[12]

A double-blinded placebo-controlled study involving 40 patients was performed by Fasano et al. in 2007.[6] In that study, researchers concluded that serum glucose levels were consistently higher for the first 8 hours in patients treated with octreotide compared to patients treated with intravenous dextrose only.[6] This clinical picture was not seen in the present case because this patient had also developed severe lactic acidosis from overdose of metformin.

McLaughlin et al. retrospectively reviewed 9 patients with sulphonylurea overdosed (dose range 40 – 125 mg).[14] The investigators concluded that octreotide is effective in preventing recurring hypoglycaemia secondary to sulphonylurea. Risk of rebound

hypoglycaemia was 27 times lesser in octreotide group compared to placebo. In addition, the amount of 50% dextrose used was significantly lower after octreotide administration.[14]

The mechanism leading to metformin induced lactic acidosis is complicated. Metformin promoted the conversion of glucose to lactate in the splanchnic bed of the small intestine.[16] Metformin also inhibits the mitochondrial respiratory chain complex 1 leading to decreased hepatic gluconeogenesis from lactate, pyruvate and alanine. This results in additional lactate and substrate for lactate production.[17]

Sodium bicarbonate therapy in metformin induced lactic acidosis is controversial.[10] Theoretical disadvantages of prolonged sodium bicarbonate including excess sodium load, rebound metabolic alkalosis, decreased myocardial contractility and reflex vasodilation.[11] Therefore, it is recommended to limit its use to patients with severe metabolic acidosis, for example, arterial pH below 7.10. If severe metabolic acidosis is present, sodium bicarbonate may be administered but there are disadvantages with this practice. It can lead to a leftward shift of the haemoglobin dissociation curve, excess sodium load, rebound metabolic alkalosis, disturbances in serum potassium and calcium, decreased myocardial contractility increase carbon dioxide production and reflex vasodilatation after bolus injection.[11]

Extracorporal removal via haemodialysis is the preferred approach if haemodynamically stable. In patients with haemodynamic unstability, continuous venovenous haemofiltration (CVVH) can be performed.[19]

CONCLUSION

Octreotide infusion may help in preventing refractory hypoglycaemia secondary to sulfonylurea overdose. This patient unfortunately succumbed due to severe lactic acidosis from his metformin overdose despite intensive care services. This is a life-threatening condition. Though sulfonylurea and metformin are the most commonly prescribed anti-hypoglycaemic agents, thus during prescribing everyone has to be careful about the overdoses and side effects of these drugs.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

CONSENTS

Written informed consent was obtained from the patient to publish the case. A copy of written consent is available for review by the Chief Editor.

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