SUCCESSFUL MANAGEMENT OF HIGH-DOSE METFORMIN INTOXICATION. ROLE OF VASOPRESSIN IN THE MANAGEMENT OF SEVERE LACTIC ACIDOSIS

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Case Report

We report the case of a 49 year old, 100 kg male patient who, in a suicidal attempt, ingested an estimated dose of 40 to 45 grammes of Metformin. Three hours he presented to AE Department. Due to deterioration of consciousness and a marked irritability, he was sedated, intubated and ventilated at the receiving hospital.

On induction of anesthesia (for intubation), the patient hemodynamics became very unstable prompting the initiation of both Epinephrine and Nor-Epinephrine Intra-venous (IV) infusions. Glucose 10% IV infusion and Insulin IV infusion were also started. The pre-transfer management also included Hydrocortisone IV justified by the marked hemodynamic instability and mediocre response to inotropic support. Arterial Blood Gas (ABG) analysis showed severe acidosis and Lactate level of 34 mmol/l, in addition to a Hyperkalemia of 7 mmol/l. He was then transferred to our Intensive Care Unit (ICU) to start Continuous Veno-Venous Hemofiltration (CVVH).

On arrival to the ICU, patient was sedated, ventilated. His pupils were dilated and non-reactive. His hemodynamic was refractory, demanding significant inotropic support (at approximately 1mcg/kg/min of Nor-Epinephrine and Epinephrine). The systolic BP was at best 80 to 100 mmHg. His CVP was 19 mmHg. Arterial blood gas revealed a PaO2 of 50 kPa, and a PaCO2 of more than 10 Kpa despite hyperventilation. The arterial blood pH remained as low as 6.8. Lactate level was beyond the maximum titration limit of our ABG machine. ****Blood Sugar was at 11 g/l.

The administration of 500 mls of Molar Sodium Bicarbonate failed to improve the metabolic acidosis and despite the initiation of CVVH, using Prisma System, the pH remained around 6.80 on repetitive analysis.

As Catecholamines requirements were increasing with limited benefit on hemodynamic parameters, the decision to introduce Vasopressin IV infusion was taken. We used Pitressin*, diluted in Dextrose 5% solution for a final concentration of 1 IU/ml. The initial dose was 6 IU/hour.

Rapid improvement of ABP parallel with rapid decrease of Epinephrine requirement allowed to be stopped by the next morning, less than 12 hours from the introduction of Vasopressin. We also noted a slow but consistent rise of the pH.

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Table 1
pH and Base-Excess recorded first 48 hours of admission

Time (hours)	Base Deficit	pH
A&E	"OUT OF RANGE"	6.8
ICU admission	-28.3	6.79
4	-28.7	6.79
8	-26.7	6.86
16	-17.4	7.12
24	-16.8	7.13
28	-16.1	7.16
32	-15	7.17
40	-12.6	7.22
48	-9.8	7.28

The patient continued to rapidly improve from hemodynamic point of view and the Nor-Epinephrine was gradually weaned and stopped over few days. The Vasopressin infusion was gradually decreased and stopped as the stabilization of the hemodynamic state was confirmed.

A Tracheostomy was performed followed by a successful weaning of Ventilator three days later.

The patient was discharged to the HDU and then to a medical ward before leaving the hospital.

Discussion

Metformin is a Biguanide oral anti-diabetic agent. The pharmacological action of this molecule depends on decreasing Glucose transit through intestinal mucosal cells and decreasing gluconeogenesis as well as increasing peripheral glucose utilization.

There are only few cases of Metformin overdose in the literature. To our knowledge, the highest dose reported as overdose was 25 g, at the time of our case. Dell'Anglio et al reported, more recently, a suspected much higher dose at 75 to 100 g[1]. Our patient's overdose remains however very significant at, 40 to 45 g of Metformin.

Except in multiple drugs intoxication, combined with Metformin and considering the mode of action of Metformin, hypoglycemia is not a major issue[1] in either normal therapeutic range or overdose. Lactic acidosis, however, is a well documented complication of Metformin overdose[1-5], with risk of fatal outcome in over 50% of cases[2]. This risk is considerably increased if treatment is initiated after cardiovascular collapse occurs[2]. High plasmatic metformin level above 150 mcg/ml, high lactatemia and low pH would predict increased risk of mortality[2,3,4].

Lactic acidosis is not due to tissue hypoxemia and anaerobic metabolism but to reduction of cell redox function. The negative inotropism effect of Metformin could also contribute to the ability of hepatocytes to extract circulating lactate. This kind of Lactic acidosis, in the absence of anaerobic metabolism is known as type B Lactic acidosis. Prognosis of type B Lactic acidosis does not necessarily correlate with the level of lactatemia[15].

Aggressive therapy should be initiated as a soon as possible. The use of CVVH, when bicarbonate administration fails to correct the acidosis remains a corner stone in the management of its complication[8,9,10].

With this severe acidosis, Metformin overdose concomitantly presents with a refractory hemodynamic status[6,7], of which the support can be very difficult. Death can be the unfortunate outcome in these overdoses if the intensive therapy fails to reverse the general trend of acidosis and circulatory failure. There is a vicious circle that starts with the acidosis and continues with the circulatory failure. A lot of emphasis is made for the treatment of acidosis[8,9,10], but less clear advice is given for the modality of hemodynamic support. The use of high amounts of Nor-Epinephrine and Epinephrine is not always efficient in supporting the cardio-vascular system in the context of severe metabolic acidosis.

We believe that our case supports that early use of Vasopressin can be very useful in the treatment of precarious haemodynamic states and circulatory failure in relation with Metformin overdose and probably in those circulatory failures linked to severe acidosis. This role could be due to the fact that below a pH of 6.9, the Catecholamines can be of limited effect[6]. In addition, Vasopressin seems to compromise regional perfusion less than does Noradrenaline. This would help in limiting the aggravation of metabolic acidosis as could be seen with Epinephrine and Norepinephrine.

It is also well accepted that, in case of under-utilization of lactate, like in Metformin overdose cases, the treatment of the underlying cause is of a major importance. The CVVH in such case is less efficient than in cases of Mineral metabolic acidosis.

The treatment of organic metabolic acidosis should be geared towards the correction of the cause rather than the symptoms[8]**.** This would mean that Renal dialysis techniques are not **necessarily** the unique answer to Lactic acidosis caused by Metformin overdose. Some authors found, however, that CVVH is successful in the treatment of such acidosis[5]. More recently, it is high flow CVVH that was recommended for Metformin overdose. In these circumstances, the CVVH would be efficient in the treatment of Lactic acidosis either by clearance of the Metformin or by the improvement of hemodynamic state of the patient.

Why Vasopressin?

It is admitted that the sympathetic effects of Catecholamines are less strong in acidotic conditions (()). Although a range of pH between 7.4 and 7 is considered, by some authors, to be compatible with the activity of Catecholamines, these drugs would loose their effect however if the pH decreases below 6.9[6,7].

In Metformin overdose complicated by a severe lactic acidosis, the hemodynamic instability is mainly due to the deep vasodilatation that occurs and not to the effect of acidosis on the myocardium[10].

Conclusion

Intoxication by high dose of Metformin could lead to fatal outcome, mainly by the detrimental effects on the hemodynamic function. In this scenario, Catecholamines are not necessarily efficient. The management of severe lactic acidosis associated with Metformin overdose should include aggressive hemodynamic support and early introduction of Vasopressin. High flow, lactate-depleted CVVH could also be beneficial in reversing the trend towards fatality.

References

1. Dell'aglio DM, Perino LJ, Todino JD, Algren DA, Morgan BW: Metformin overdose with a resultant serum pH of 6.59: Survival without sequalae; *J Em Med*, 2008, in press.
2. Perrone J, Phillips C, Gaieski D: Occult Metformin Toxicity in Three Patients with Profound Lactic Acidosis, *J Emergency Medicine*, 2008.
3. DM Dell'Aglio, LJ Perino, ZN Kazzi, BW Morgan, MD Schwartz and RJ Geller: Mortality in acute metformin overdose is predicted by serum pH, lactate, and metformin concentration, *J Toxicol Clin Toxicol*; 44 (2006), p. 712.
4. Nisse P, Mathieu-Nolf M, Deveaux M, Forceville X, Combes: A fatal case of metformin poisoning. *AJ Toxicol Clin Toxicol*; 2003, 41(7):1035-6.
5. Ben Harvey RSCN, Ceri Hickman RSCN, Gillian Hinson, MRPharmS, Tanya Ralph RSCN, Anton Mayer MRCPCH: Severe lactic acidosis complicating metformin overdose successfully treated with high-volume venovenous hemofiltration and aggressive alkalinization; *Pediatr Crit Care Med*; 2005, 6:598-601.
6. Smith NT, Corbascio AN: Myocardial resistance to metabolic acidosis. *Arch Surg*; 1966, 92:892-896.
7. Huang YG, Wong KC, Yip WH, et al: Cardiovascular responses to graded doses of three catecholamines during lactic and hydrochloric acidosis in dogs. *Br J Anaesthesiol*; 1995, 74:583-590.
8. Levraut J, Ciebiera JP, Jambou P, et al: Effect of continuous veno-venous hemofiltration with dialysis on lactate clearance in critically ill patients. *Crit Care Med*; 1997, 25:58-62.
9. Hilton PJ, Taylor J, Forni LG, et al: Bicarbonate-based haemofiltration in the management of acute renal failure with lactic acidosis. *Q J Med*; 1998, 91:279-283.
10. Teale KFH, Devine A, Stewart H, Harper: The management of metformin overdose, Case Report, NJH, *Anaesthesia*; July 1998, 53(7), pp. 698-701.