

Metformin poisoning treated with high dose insulin dextrose therapy: a case series

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Purpose. We describe the compassionate use of high dose insulin dextrose (HID) for life threatening metformin associated lactic acidosis (MALA) in four patients admitted to intensive care.

Methods. Patients presenting with refractory lactic acidosis believed to be secondary to metformin poisoning were included.

High dose insulin dextrose at 0.5units/kg/hour was infused in 50% dextrose. Frequent blood gas analysis allowed titration of therapy. All patients also received continuous veno-venous haemofiltration.

Results. All four patients recovered to normal or near normal lactate and pH between 10 and 24 hours of therapy. Two patients had significant separation in time between initiation of HID and haemofiltration to suggest an independent effect of HID on improving pH and lactate.

All patients had at least one episode of hypoglycaemia below 4.0 mmol/L with the lowest glucose in any patient during therapy being 3.0 mmol/L. All episodes were corrected with a dextrose infusion without sequelae.

Conclusions. Our study demonstrates that HID therapy appears to be safe in patients with suspected metformin poisoning. It also appears to work to drive down lactate, improve pH and patients' clinical condition. Further evidence is required to assess the effectiveness of HID therapy in the context of MALA.

Keywords: metformin, lactate, insulin, acidosis

BACKGROUND

Metformin

Metformin is the first choice oral hypoglycaemic agent in patients with type 2 diabetes mellitus in the absence of contraindications (1). It is second only to insulin at reducing glycosylated haemo-

globin levels, is well tolerated and has a neutral effect on body weight (2).

The precise mechanism by which metformin improves glycaemic control is incompletely understood. What is known is that it interferes with the mechanism of intracellular energy level detection. Metformin increases the ratio of AMP : ATP leading to activation of adenosine monophosphate kinase (AMPK) (3). This triggers a shift towards catabolic metabolism, the net effect of which is to reduce glucose release from the liver

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into the blood stream via inhibition of hepatic gluconeogenesis (4), (5), (3).

Metformin Associated Lactic Acidosis

The most dangerous side effect of metformin is known as metformin associated lactic acidosis (MALA). An estimate in 2011 from the Netherlands put the incidence at 47 per 100,000 patient years, much higher than the 3–9 per 100,000 often quoted. This same study reported a mortality rate of 31% and noted that both the higher than expected incidence and mortality was likely to be related to the high rate of prescribing in patients with cautions to metformin use such as heart failure and renal impairment (6).

MALA is typically treated in an intensive care unit and management is mostly supportive with fluid resuscitation, correction of hypoglycaemia and other electrolyte abnormalities, renal replacement therapy, vasopressor or inotropic support for severe hypotension and sodium bicarbonate infusion for acidosis unresponsive to fluid therapy (7).

OBJECTIVES

To analyse the observational data we have collected on four patients treated for suspected MALA with high dose insulin dextrose (HID) as a novel compassionate therapy in patients with life threatening metabolic derangements.

Our objectives were to investigate whether HID is a safe therapy in this patient cohort and whether HID helps reverse lactic acidosis in MALA.

METHODS

This is a retrospective observational study of 4 patients treated during 2017 and 2018 in one district general hospital in London, UK.

HID therapy is an infusion of 1 unit of Actrapid (Novo Nordisk, Ltd) per 1ml of 50% dextrose. Treatment is delivered according to the following protocol:

This protocol is derived from Engebretsen et al (8) but adapted for a more cautious insulin dosage due to safety concerns amongst staff members in our unit inexperienced with such therapies. The Engebretsen protocol for β -blocker and calcium channel antagonist overdose is 0.5–2.0 units/kg/h increased by 1 unit/kg/h to a maximum of 10 units/kg/h.

The rate of delivery of insulin is controlled by changing the infusion rate so that a fixed ratio of insulin: dextrose is delivered. Hourly capillary blood glucose measurements were taken and an additional infusion of 10% dextrose initiated by the nurse looking after the patient if hypoglycaemia was detected. If this failed to correct the hypoglycaemia the infusion was stopped and the doctor contacted.

Continuous Veno-Venous Haemofiltration (CVVHF) was performed by Aquarius System with a highly permeable haemofilter (Baxter Aquamax HF12 polyethersulfone- cut off 30 kDa). Systemic anticoagulation with heparin was added when appropriate to the haemofilter. Blood flow ranged from 250 to 360 ml/min (35–60 ml/kg/h) in pre-dilution mode (30%).

Arterial blood samples were collected for blood gas analysis from arterial catheters. This was performed at a frequency according to severity of abnormalities detected and ranged from hourly to 6 hourly during the high dose insulin dextrose therapy (in addition to hourly capillary blood gases).

All other elements of therapy were performed according to treating consultant physician's judgement.

RESULTS

Seven patients were considered for HID for treatment of metformin poisoning during 2017 and 2018. Two patients recovered sufficiently prior to initiation of HID, so the therapy was never started. Five patients received the therapy and their results

Lactate	Insulin dose
≥10 mmol/L	Infusion of 0.5 units of insulin/kg*/h
6–10 mmol/L	Infusion of 0.25 units of insulin/kg*/h
3–5 mmol/L	Infusion of 0.10 units of insulin/kg*/h
1–2 mmol/L	Infusion of 0.05 units of insulin/kg*/h
≤1 mmol/L	Stop Infusion. Normal sliding scale for glycaemic control 8–12 mmol/L

* ideal body weight.

are discussed below. One patient has been excluded from the analysis as they were admitted post cardiac arrest and therefore had another cause of lactic acidosis other than metformin.

The remaining 4 patients were included in the analysis, with clinical details as described in Table 1. In all 4 cases, there was a clear trend towards correction of acidosis and lactataemia with HID therapy, as depicted in graphs 1 and 2. All patients were discharged from ITU and alive at 30 days from admission. We specifically studied case # 1 (graph 3) and case #2 (graph 4), as they were the only cases where HID and haemofiltration were started at significantly different times.

Hypoglycaemic episodes during HID infusion occurred in all four patients with the lowest recorded glucose being 3.0 mmol/L. All were corrected using 10% glucose without complications

(see Table 2 below). Hypokalaemia occurred in one patient on two occasions which was corrected and did not result in complications.

DISCUSSION

The association of metformin with MALA

A systematic review in 2009 found 22 cases of metformin overdose resulting in lactic acidosis and demonstrated a clear correlation between serum metformin, nadir of pH, lactate and mortality (9). In cases of MALA associated with therapeutic doses of metformin a less clear correlation has been found between metformin dose and severity of lactataemia to the extent that doubt has been cast over the causative nature of metformin in MALA. In Duong et al peak metformin did not correlate with creatinine, pH or lactate but only

Table 1. Core data for the patients in the study

Case	Age	Sex	Metformin dose	CKD	Peak creatinine	Nadir pH	30 day survival	Discharge From ITU	Nadir K ⁺	Nadir glucose	Na HCO ₃	CVVHF*
# 1	78	M	1g	No	538	7.15	Yes	No	3.8	3.0	+	+
# 2	68	M	1g	No	338	7.18	Yes	Yes	2.7	3.0	-	+
# 3	73	F	2g	3b	156	7.15	Yes	Yes	>4.0	3.5	-	+
# 4	43	F	20g**	No	240	6.95	Yes	Yes	>4.0	3.3	+	+

* Continuous veno-venous haemofiltration. ** This was an acute overdose of 20 g.

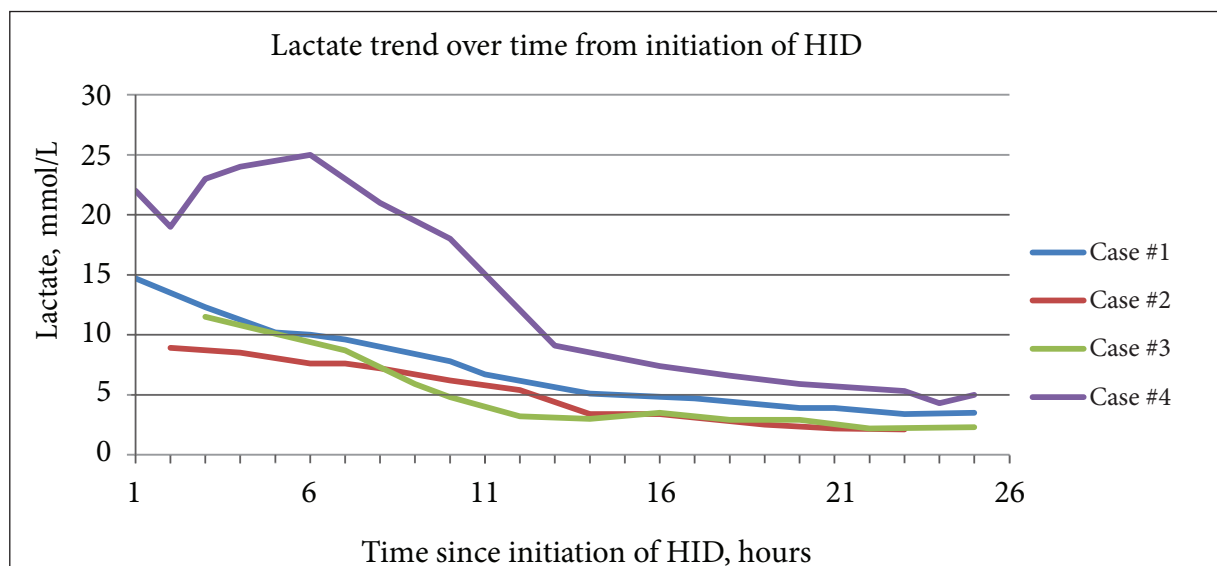


Fig. 1. Trends in arterial lactate in four patients treated with HID from one hour before treatment was initiated until normalization or 25 hours

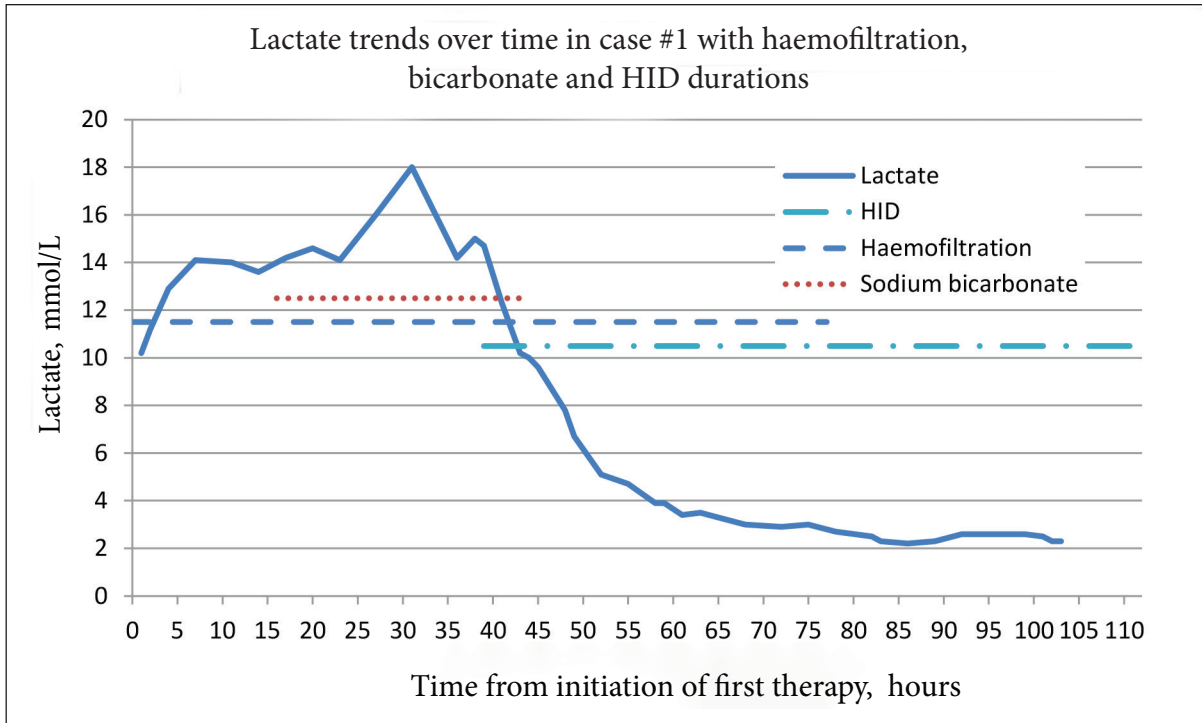


Fig. 2. Case 1 serum lactate trends over time since initiation of first therapy with horizontal bars to show the duration of three different therapies: sodium bicarbonate, HID and haemofiltration

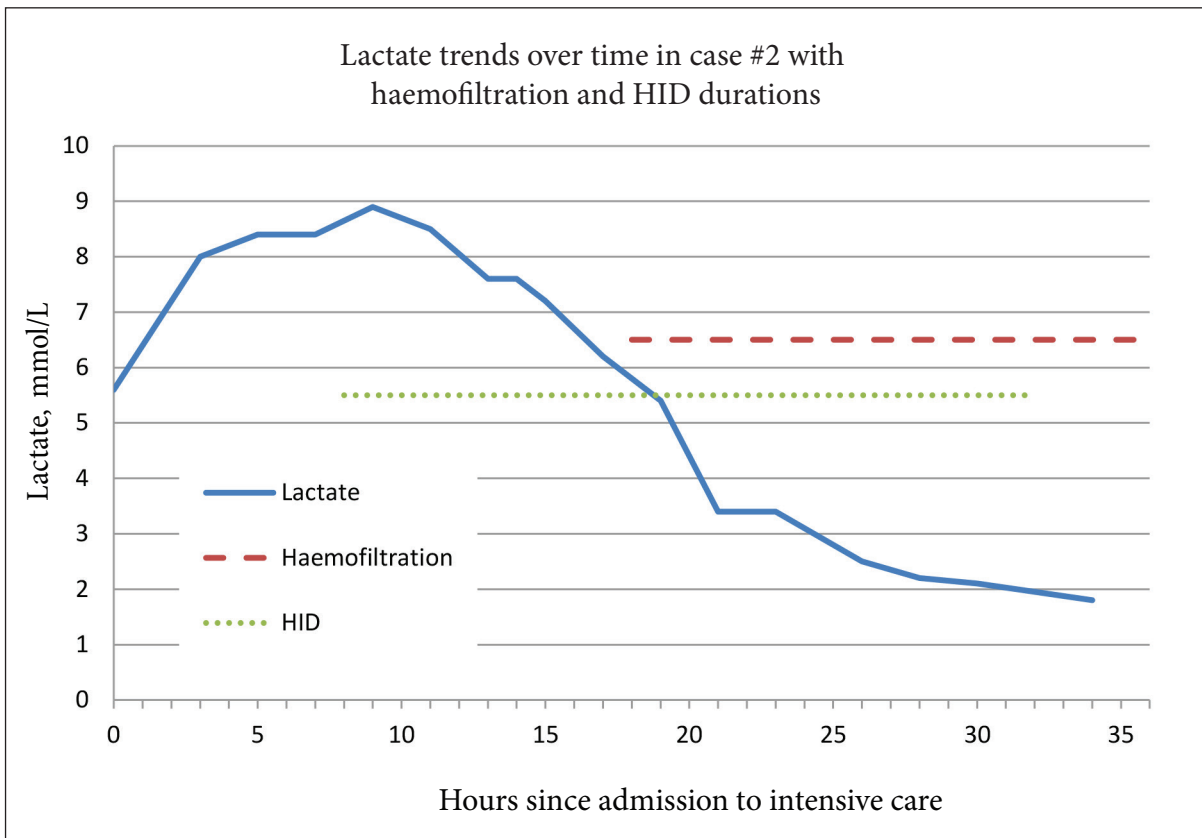


Fig. 3. Serum lactate trend over time in case #2 with horizontal bars to show duration of HID and haemofiltration therapy

one patient with MALA had metformin levels within the therapeutic range. All other cases of MALA had suprathreshold levels of metformin on admission. However, the trend of decreasing levels of metformin over time correlated with improving creatinine, pH and lactate (10).

Pathophysiology of MALA

Lactate is produced continuously in various tissues of the body not just during anaerobic respiration (11). The main pathway by which excess lactate is processed is via the gluconeogenesis pathway in the liver (11). As metformin blocks this pathway lactate builds up within the hepatocytes and eventually spills out into the blood. Under normal physiological conditions this excess lactate never reaches high enough levels to induce acidaemia as both the lactate and the excess hydrogen ions are excreted via the kidneys. The majority of cases of metformin associated lactic acidosis treated in our unit occur due to the following pathophysiological process: dehydration due to vomiting, diarrhoea or reduced oral intake or combination of these; acute kidney injury (often acute on chronic); increase in lactate production due to hypoperfusion of tissues; decrease in renal excretion of hydrogen ions and lactate due to acute kidney injury and inability of the liver to process excess lactate due to metformin. There is positive feedback as lactic acidosis causes further nausea and vomiting (10).

To compound this problem metformin is entirely renally excreted. As kidney function declines metformin's half-life increases. This can be observed in the re-bounce lactic acidaemia that occurs if extra-corporeal renal supplementation therapy is halted too early in cases of MALA. In fact the ability of metformin to induce clinically significant lactic acidosis is correlated to impaired kidney function as opposed to dose of metformin taken or metformin serum levels (12).

High dose insulin/dextrose therapy

HID therapy is also known as hyperinsulinaemia/euglycaemia therapy. As the name suggests, it involves giving an infusion of supra-normal doses of insulin with a simultaneous infusion of dextrose to prevent hypoglycaemia (13). It has become part of the standard management of both β -blocker and calcium channel antagonist overdose for cas-

es resulting in hypotensive shock (14), (7). HID has been demonstrated experimentally to induce a number of positive metabolic and inotropic effects. In a shocked state catecholamine release causes the myocardium to switch from a predominantly fatty acid based energy supply to respiring glucose and lactate. However, lactate production exceeds lactate utilisation with a net release of lactate and free protons. High dose insulin infusions decrease fatty acid uptake even further, have no net effect on glucose uptake and significantly increase lactate uptake and utilisation as an energy source by the myocardium. High dose insulin also increases cardiac output and efficiency without increasing myocardial oxygen demand, unlike catecholamines which increase oxygen demand dramatically (15). Insulin is also a vasodilator which appears to improve tissue perfusion and may also help explain its positive effects on lactate clearance (16).

It is important to note that, to our knowledge, this therapy has not been tested for the management of MALA. Therefore, the potential risks and benefits were unknown to us; the indication to start therapy was as a last resource in patients considered to be in extremis who might otherwise die.

There are several limitations to the study. Firstly we were unable to measure serum metformin. This means we have no proof of metformin intoxication or even use beyond patient history and medication record. Duong et al found that in 15 cases of metformin associated lactic acidosis only one patient had an admission metformin level within the therapeutic threshold whilst all others had levels at least three times the upper therapeutic limit (5 mg/L) (10) suggesting that metformin levels should be an important part of the diagnostic workup.

Secondly, due to the complexity of this group of patients, it is difficult to prove HID made the difference in outcome. Certainly, in two out of four cases there was a reasonable separation in time between the initiation of HID and haemofiltration.

Thirdly, it is a very small study which makes it impossible to draw any conclusions about mortality, nor there is any control group due to the compassionate use of the therapy itself. Further efforts should be made to identify patients likely to respond to HID therapy in the context of

metformin use and, potentially, design a trial to assess its effects on patient outcome.

CONCLUSIONS

Our study demonstrates that HID therapy appears to be safe in patients with metformin poisoning. It also appears to work to drive down lactate, improve pH and patient's clinical condition. There is a rational explanation behind why metformin should act to reverse a lactic acidosis, particularly one caused by metformin. Further evidence is required to assess the effectiveness of HID therapy in the context of MALA.

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References

- Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015 Jan; 38(1): 140–9.
- Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009 Jan; 32(1): 193–203.
- Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001 Oct; 108(8): 1167–74.
- Foretz M, Hébrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, Sakamoto K, Andreelli F, Viollet B. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. *J Clin Invest*. 2010 Jul; 120(7): 2355–69.
- Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, Prigaro BJ, Wood JL, Bhanot S, MacDonald MJ, Jurczak MJ, Camporez JP, Lee HY, Cline GW, Samuel VT, Kibbey RG, Shulman GI. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature*. 2014 Jun 26; 510(7506): 542–6.
- van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *J Clin Pharm Ther*. 2011 Jun; 36(3): 376–82.
- F. Barrueto Jr, "uptodate.com," 2017 February 2017. (Online). Available: https://www.uptodate.com/contents/calcium-channel-blocker-poisoning?search=calcium%20channel%20blocker%20poisoning%20emergency&source=search_result&selectedTitle=1~17&usage_type=default&display_rank=1. [Cited 2018 Nov 29].
- Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol (Phila)*. 2011 Apr; 49(4): 277–83.
- Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. *Ann Emerg Med*. 2009 Dec; 54(6): 818–23.
- Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, Williams KM, Day RO. The Role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case Series and Formulation of a Model of Pathogenesis. *Drug Saf*. 2013 Sep; 36(9): 733–46.
- Brooks GA. The Science and Translation of Lactate Shuttle Theory. *Cell Metab*. 2018 Apr 3; 27(4): 757–785.
- Lalau JD, Mourlhon C, Bergeret A, Lacroix C. Consequences of metformin intoxication. *Diabetes Care*. 1998 Nov; 21(11): 2036–7.
- Woodward C, Pourmand A, Mazer-Amirshahi M. High dose insulin therapy, an evidence based approach to beta blocker/calcium channel blocker toxicity. *Daru*. 2014 Apr 8; 22(1): 36.
- St-Onge M, Dubé PA, Gosselin S, Guimont C, Godwin J, Archambault PM, Chauny JM, Frenette AJ, Darveau M, Le Sage N, Poitras J, Provencher J, Juurlink DN, Blais R. Treatment for calcium

- channel blocker poisoning: a systematic review. *Clin Toxicol (Phila)*. 2014 Nov; 52(9): 926–44.
15. Kline JA, Raymond RM, Leonova ED, Williams TC, Watts JA. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. *Cardiovasc Res*. 1997 May; 34(2): 289–98.
 16. Mégarbane B, Karyo S, Baud FJ. The role of insulin and glucose (hyperinsulinaemia/euglycaemia) therapy in acute calcium channel antagonist and beta-blocker poisoning. *Toxicol Rev*. 2004; 23(4): 215–22.
 17. Adak T, Samadi A, Ünal AZ, Sabuncuoğlu S. A reappraisal on metformin. *Regul Toxicol Pharmacol*. 2018 Feb; 92: 324–32.
 18. El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. *J Biol Chem*. 2000 Jan 7; 275(1): 223–8.
 19. Bailey CJ, Wilcock C, Day C. Effect of metformin on glucose metabolism in the splanchnic bed. *Br J Pharmacol*. 1992 Apr; 105(4): 1009–13.
 20. van Hall G. Lactate kinetics in human tissues at rest and during exercise. *Acta Physiol (Oxf)*. 2010 Aug; 199(4): 499–508.
 21. Hardie DG. Keeping the home fires burning: AMP-activated protein kinase. *J R Soc Interface*. 2018 Jan; 15(138).
 22. Page CB, Ryan NM, Isbister GK. The safety of high-dose insulin euglycaemia therapy in toxin-induced cardiac toxicity. *Clin Toxicol (Phila)*. 2018 Jun; 56(6): 389–96.

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APSINUODIJIMO METFORMINU GYDYMAS DIDELĖS DOZĖS INSULINO DEKSTROZĖS TERAPIJA: ATVEJŲ PRISTATYMAS

Santrauka

Įvadas. Analizuojami keturių pacientų, kuriems buvo metformino sukeltos gyvybei pavojingos laktacidozės, gydymo atvejai. Pacientams intensyvosios terapijos skyriuje taikyta didelės dozės insulino dekstrozės terapija (HID).

Medžiaga ir metodai. Į tyrimą buvo įtraukti pacientai, kuriems pasireiškė gydymui atspari laktacidozė, kuri, kaip manoma, yra antrinė apsinuodijimo metforminu reakcija. Didelė insulino dekstrozės dozė 0,5 vnt./kg/val. buvo infuzuojama kartu su 50 % dekstrozės. Dažnas kraujo dujų tyrimas leido titruoti terapiją. Visiems pacientams taikyta veno-veninė hemofiltracija.

Rezultatai. Visiems keturiems pacientams nuo 10-tos iki 24-tos gydymo valandos laktato ir pH kiekis atsistatė iki normalaus arba beveik normalaus lygio. Dviems pacientams laiko tarpas nuo HID pradžios iki hemofiltracijos buvo ilgesnis. Tai rodo nepriklausomą HID poveikį normalizuojant pH ir laktato koncentraciją.

Visiems pacientams pasireiškė bent vienas hipoglikemijos epizodas, mažesnis nei 4,0 mmol/l, o mažiausias visų pacientų gliukozės kiekis siekė 3,0 mmol/l. Visi epizodai buvo koreguojami be dekstrozės infuzijos.

Išvados. Tyrimo rezultatai rodo, kad HID terapija yra saugi pacientams, kuriems įtariamas apsinuodijimas metforminu. Terapija gali mažinti laktatų koncentraciją, gerinti pH ir paciento klinikinę būklę. Reikia papildomų tyrimų siekiant įvertinti HID terapijos veiksmingumą gydant metformino sukeltą laktacidozę.

Raktažodžiai: metforminas, laktatas, insulinas, acidozė