Metformin Intoxications Requiring Admission to the Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Yatışı Gerektiren Metformin Zehirlenmeleri

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ABSTRACT

Objective: To identify the demographics of patients admitted with metformin intoxication and characterize their clinical courses and treatment options in pediatric intensive care unit.

Material and Methods: The records of patients admitted to the pediatric intensive care unit due to metformin intoxication between 2013 and 2019 were retrospectively evaluated.

Results: There were 22 acute metformin intoxication cases. Mean age of the patients was 13.04±5.46 years (1-18 years), 18 were female. Ingested metformin dose ranged from 1.7 gr to 85 gr (mean 19±22.6 gr, median 10 gr), with coingestants taken in 12 patients. Nausea and/or vomiting were present in 16 (72.7%) of the patients. Hyperlactatemia (lactate > 2mmol/L) was present in 13 (59%) of the patients. Mean peak lactate level was 5.1±5.7 mmol/L (0.9-21 mmol/L). Acidosis was present in 12 (54.5%) of the patients. Mean lowest pH level was 7.28±0.16 (6.9-7.45). There was a positive correlation between lactate level and ingested dose ($r = 0.816$; $p < 0.001$) while pH was inversely related to dose ($r = -0.873$; $p < 0.001$). Six (27%) patients required renal replacement therapy because of profound lactic acidosis despite the intravenous fluid support. Hemodialysis was applied to 5 patients and high dose continuous venovenous hemodiafiltration was applied to 2 patients. 16 years old female patient who ingested 85 g metformin died despite prolonged hemodialysis.

Conclusion: Lactic acidosis associated with metformin intoxication is a potentially fatal condition. Both renal replacement therapies hemodialysis and continuous venovenous hemodiafiltration are effective in the treatment of metformin associated lactic acidosis. Most of the patients with severe metformin associated lactic acidosis require repetitive and prolonged hemodialysis sessions.

Key Words: Continuous venovenous hemodiafiltration, Hemodialysis, Intoxication, Metformin, Lactic acidosis

ÖZ

Amaç: Metformin zehirlenmesi ile çocuk yoğun bakım ünitesine yatan hastaların demografik ve klinik özelliklerini ve tedavi seçeneklerini karakterize etmek.

Gereç ve Yöntemler: 2013-2019 yılları arasında metformin zehirlenmesi nedeniyle çocuk yoğun bakım ünitesine başvuran hastaların kayıtları retrospektif olarak incelendi.

Bulgular: Yirmi iki akut metformin doz aşımı çalışmaya dâhil edildi. Hastaların yaş ortalaması 13.04±5.46 yıl (1-18 yaş)'dı ve hastaların 18'i kızdı. Alınan metformin dozu, 1.7 gr ila 85 gr (ortalama 19±22.6 gr, medyan 10 gr) arasında değişmekteydi ve 12 hastada birlikte alınan başka ilaçlar mevcuttu. Hastaların 16'sında (%72.7) bulantı ve / veya kusma vardı. Hastaların 13'ünde (%59) hiperlaktatemi (laktat> 2 mmol / L) vardı. Ortalama pik laktat seviyesi 5.1±5.7 mmol / L (0.9-21 mmol / L)'di. Hastaların 12'sinde (% 54.5) asidoz mevcuttu. Ortalama en düşük pH seviyesi 7.28 ±0.16 (6.9-7.45)'di. Laktat seviyesi ile alınan doz arasında pozitif bir korelasyon var iken ($r=0.816$; $p<0.001$), pH ile alınan doz arasında negatif korelasyon mevcuttu. ($r=-0.873$; $p <0.001$). Altı (% 27) hastada intravenöz sıvı desteğine

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rağmen derin laktik asidoz nedeniyle renal replasman tedavisi gerekti. 5 hastaya hemodiyaliz, 2 hastaya yüksek dozda sürekli venövenöz hemodiafiltrasyon uygulandı. 85 g metformin alan 16 yaşında kız hasta uzun süreli hemodiyalize rağmen kaybedildi.

Sonuç: Metformin zehirlenmesi ile ilişkili laktik asidoz potansiyel olarak ölümcül bir durumdur. Renal replasman tedavilerinden hem hemodiyaliz hem de sürekli venöz hemodiafiltrasyon, metformin ilişkili laktik asidozun tedavisinde etkilidir. Metformin ilişkili ciddi laktik asidozu olan hastaların çoğu tekrarlayan ve uzun süreli hemodiyaliz seansları gerektirebilir.

Anahtar Sözcükler: Sürekli venövenöz hemodiafiltrasyon, Hemodiyaliz, Zehirlenme Metformin, Laktik asidoz

INTRODUCTION

Metformin is a biguanide anti-hyperglycemic agent used in type 2 diabetes to augment insulin sensitivity without lowering glucose concentration below normal (1). It decreases peripheral insulin resistance, hepatic gluconeogenesis and increases glucose uptake of muscle and adipose tissues. Apart from antidiabetic activity, lowering lipid levels, weight control, cardiovascular protection and a possible anti-cancer effect are among the benefits of this drug (2,3). These advantages lead to a wide and favorable use of this medication, which in turn makes it a potential cause of intoxication in childhood.

Phenformin, an antecedent of metformin in the biguanide group was withdrawn in 1977 because of an association with fatal lactic acidosis (1). Metformin has minor side effects during therapy, such as nausea, vomiting, diarrhea and anorexia. Although less frequently than phenformin, lactic acidosis may be seen with metformin, especially in the presence of concomitant diseases that predispose to increased lactate production. Metformin inhibits complex 1 of the mitochondrial respiratory chain, with dose dependent mitochondrial respiratory failure metformin causes increased production and decreased hepatic clearance of lactate (4). The development of metformin-associated lactic acidosis (MALA) is considered a pathological extension of its cellular effects. Metformin intoxication is relatively uncommon despite an estimated 120 million metformin prescriptions worldwide annually (4,5). Incidence of lactic acidosis is 4.3 cases per 100.000 patient-years for diabetic patients on metformin therapy (6). Metformin associated lactic acidosis (MALA) is associated with a mortality rate of >50% in chronic use (1) . Acute metformin intoxication causes lactic acidosis in dose dependent manner and mortality was reported because of profound lactic acidosis (7,8). Mortality rate ranges between 30%-50% despite the modern intensive care treatment and severe acidosis is associated with higher mortality rates (9,10).

In this study it was aimed to identify the demographics of patients admitted with acute metformin intoxication and characterize their clinical courses and treatment options in pediatric intensive care unit.

METARIAL and METODS

In this retrospective observational study, the records of patients admitted to the pediatric intensive care unit due to metformin intoxication between January 2013 and December 2019 were evaluated. Approval was obtained from the Ethics Committee of Hacettepe University for this study (GO 18/982-33). The data collection included age, gender, dose ingested, coingestants, symptoms, laboratory parameters (blood gases and organ functions), treatment options and outcome. Hyperlactatemia was defined as blood lactate >2 mmol/L and acidosis as pH < 7.35; hypoglycemia as blood glucose level < 50 mg/dl (11).

Statistical analyses

Data were analyzed using the SPSS version 21.0 software program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). As descriptive statistics, the mean, standard deviation values, minimum and maximum values were given. Pearson Chi-Square test and Fisher's exact test were, where appropriate, used to investigate the association between categorical variables. The Student t test was used to compare continuous numerical variables between groups. Correlations between the variables were investigated with Spearman correlation coefficient (r). General Linear Model Analysis was performed by adjusting the metformin dose to test whether the arrival to the hospital in the first hour after ingestion had an effect on the lactate value. p value <0.05 were considered statistically significant.

RESULTS

Twenty-two patients who were admitted to PICU because of metformin intoxication were included in the study. Mean age of the patients was 13.04±5.46 years (1-18 years). 19 (86%) of the patients were female. Totally 18 (81.8%) of the intoxications were intentional and 4 (18.2%) were unintentional. Coingestants were involved in 12 patients (54.5%). Ingested metformin dose ranged from 1.7 gr to 85 gr (mean 19±22.6 gr, median 10 gr). Nausea and/or vomiting were present in 16 (72.7%) of the patients. 11 (50%) of the patients admitted to the emergency room in the first hours of drug ingestion and gastric decontamination and active charcoal were applied to these patients. Only one patient (ingested 70 g metformin) had hypoglycemia during follow up. Hyperlactatemia was present in 13 (59%) of the patients. In the whole study group mean peak lactate level was 5.1±5.7 mmol/L (0.9-21 mmol/L). Among the patients who had at least one lactate level above normal, mean peak lactate level was 7.8±6.2 mmol/L (2.1-21 mmol/L). Acidosis was present in 12 (54.5%) of the patients. In the whole

Table I: Characteristics of patients with metformin intoxication.

Characteristics	All patients (n=22)
Demographics	
Age, mean±SD (range), years	13.04±5.46 (1-18)
Sex, female (%)	18 (81.8%)
Dose, mean±SD (range), g	19±22.6 (1.7-85)
Coingestants	12 (54.5%)
Clinical features	
Nausea and/or vomiting*,	16 (72.7%)
Altered consciousness*,	6 (27.2%)
Cardiovascular instability*,	5 (22.7%)
Acute kidney injury*,	7 (31.8%)
Laboratory parameters	
Hyperlactatemia*,	13 (59%)
Acidosis*,	12 (54.5%)
Lactate, mean±SD (range), mmol/L	5.1±5.7 (0.9-21)
pH, mean±SD (range)	7.28±0.16 (6.9-7.45)
Treatment	
Decontamination*,	11 (50%)
Intravenous fluid*,	22 (100%)
Inotropes*,	5 (22.7%)
Mechanical ventilation*,	3 (13.6%)
Hemodialysis*,	5 (22.7%
Continuous venovenous hemodiafiltration	2 (9%)
Mortality*,	1 (4.5%)

***:*n(%)*

study group mean lowest pH level was 7.28±0.16 (6.9-7.45). Among the patients who have acidosis mean lowest pH level was 7.18±0.15 (6.9-7.34). Characteristics of patients included in the current study are shown in Table I.

There was a positive correlation between lactate level and ingested dose ($r = 0.816$; $P < 0.001$) while pH was inversely related to dose ($r = –0.873$; $P < 0.001$).

Six (27%) patients required renal replacement therapy because of profound lactic acidosis despite the intravenous fluid support. Hemodialysis (HD) was applied to 5 patients and high dose continuous venovenous hemodiafiltration (CVVHDF) was applied to 2 patients. In one patient treatment started with CVVHDF and after hemodynamic stabilization treatment continued with HD. Mean number of HD sessions was 3.6 (1-6 sessions). Two patients treatment started to treat with high dose CVVHDF (26 hours and 50 hours) because of hemodynamic instability due to coingested drugs (nifedipine and metoprolol). Patient who ingested nifedipine and metformin required 3 sessions of HD because of ongoing renal insufficiency after the correction of acidosis with CVVHDF.

Hyperlactatemia was present in 75% (12/16) and 16.7% (1/6) of the patients with and without nausea and/or vomiting respectively. The difference between two groups is statistically significant (p=0.023).

Acidosis was present in 75% (12/16) of the patients with nausea and/or vomiting while acidosis was not present in any of the patients without nausea and/or vomiting. The difference between two groups is statistically significant (p=0.003).

In the patients who arrived to the hospital within first hour after drug ingestion (gastric decontamination and active charcoal applied); mean lactate (2.2±1.2 vs 7.9±7) levels were significantly differed than the patients who didn't arrive to the hospital within first hour (p=0.015). There was statistically significant difference between who arrived to the hospital within first hour after drug ingestion and not in terms of ingested metformin dose (8.7±4.6 vs 29.4±28.6) (p=0.029). General Linear Model Analysis was performed by adjusting the metformin dose; in order to test whether the arrival to the hospital (gastric decontamination and active charcoal) within the first hour after ingestion influenced on the lactate value. It was found that arrival to the hospital within the first hour did not significantly affect lactate levels. The model was statistically significant ($p<0.001$). The model explained 90.2% (R Squared =0.902). It was found that ingested metformin dose had a statistically significant effect on lactate level ($F = 139.88$; $r = 0.880$; $p <0.001$). The effect of whether the patient arrived to the hospital within the first hour after drug ingestion or not on the lactate value was not statistically significant ($F = 1.206$; $r = 0.060$; $p = 0.286$).

Acute kidney injury, cardiovascular instability and alteration of consciousness were present in 7 patients (31.8%), 5 patients (22.7%) and 6 patients (27.2%) respectively. Three patients were intubated because of hemodynamic instability and increased work of breathing.

One of the patients died, she was 16-year-old and was transferred to the pediatric emergency department after 4 hours of ingestion of 100 metformin 850 mg tablets and 84 nateglinide

120 mg tablets in a suicide attempt. Upon arrival to our hospital she was drowsy, had hypothermia (<360C), low blood pressure (70/30 mmHg), and abdominal discomfort. Blood glucose concentration measured at arrival was 64 mg/dl. Laboratory findings revealed profound lactic acidosis (pH: 6.9 lactate: 21 mmol/L). Intravenous bicarbonate was initiated, and an emergency dialysis was planned for the patient for severe lactic acidosis. A femoral catheter was inserted, and bicarbonate HD treatment was administered for 4 hours using a high-flux dialysis filter and bicarbonate dialysate. Consecutive three sessions of HD were performed during the first day of intoxication because of profound lactic acidosis. Despite HD the serum lactate levels remained high and profound acidosis persisted until the second day of admission. She required high doses of inotrope and was resuscitated for cardiac arrest at the 30th hour of admission. On the 3rd day of hospitalization metabolic acidosis was corrected, HD was continued intermittently for renal failure. On follow up, patient remained in coma and multiorgan failure persisted until demise of the patient on the day 10.

DISCUSSION

In the current study it was demonstrated that acute metformin intoxication cause hyperlactatemia and acidosis in a dose dependent manner in pediatric patients. Ingested dose, rather than absence of gastric decontamination and activated charcoal treatment seem to be related to lactic acidosis in case of metformin intoxication. It was found that presence of nausea and/or vomiting may be the indicator of hyperlactatemia and acidosis. In the current study six patients required renal replacement therapy and aside from the patient who died, it was shown that both HD and high dose CVVHDF are effective in the treatment of MALA.

Spiller et al. (12) reported a pediatric multicenter series of 55 cases with metformin intoxication. Patients between 15 months to 17 years of age, ingested metformin ranged from 250 mg to 16.5 g (mean 1.7 g, median 500 mg). 41 children had <1.7 g metformin ingestion. Only mild clinical side effects such as nausea, diarrhea and dizziness were seen without the evidence of hypoglycemia or acidosis. The authors argued that metformin intake below 1.7 g in a previously healthy child appears to be tolerated (12). Mean ingested metformin dose (mean 19.2 g, min-max 1.7- 85 g) in the current study is higher than the previous studies because only the patients who required PICU admission were included in the study. As far as we know the highest amount ingested by a pediatric patient is a 17-year-old boy who ingested 80 g metformin and was treated with hemodialysis (13).

Metformin belongs to biguanide group of antihyperglycemics. It has high solubility in water and negligible plasma protein binding, with a volume of distribution of 63 L to 276 L (14).

The half-life of metformin exhibits two peaks on concentration-time curves. First curve coincides with 2 hours after ingestion; second peak is at 16 hours as a result of accumulated metformin in tissues (15,16). Because of this pharmacokinetic property of metformin, patients with acute metformin intoxication who develop MALA usually required prolonged and repetitive HD sessions. Consistent with previous case series HD was performed for mean 3.6 sessions (1-6 sessions) to treat the lactic acidosis of the patients in this study. Lack of effect of early gastric lavage and activated charcoal on levels of lactate may be related to significant first-pass effect on metformin.

By increasing intracellular AMP/ATP ratio, metformin activates hepatic gluconeogenesis through pyruvate kinase and increases glucose uptake with GLUT4 through AMP activated kinase (AMPK). Metformin favors intracellular anaerobic metabolism, converts glucose to lactate in splanchnic bed of small intestines, as a result increases production of lactate (14). Gluconeogenesis is inhibited, decreasing the amount of lactate use. High dose metformin is shown to bind to mitochondrial membrane to inhibit electron transport chain (16,17). Hyperlactatemia may be due to increased lactate production or decreased lactate clearance. In metformin associated lactic acidosis (MALA) both mechanisms have a role. Once lactic acidosis begins circulatory failure and impaired tissue perfusion lead to higher levels of lactate (18).

In MALA, patients may experience nonspecific symptoms like drowsiness, abdominal discomfort, nausea and vomiting or a more serious course with hypothermia, hypotension, respiratory failure and cardiac arrhythmia (16). In the light of the findings from the current study it can be speculated that beyond other symptoms, nausea and/or vomiting seems to be associated with hyperlactatemia and acidosis.

Correlation of metformin serum levels and the degree of lactic acidosis is under debate. Duong et al. (19) reviewed 115 MALA patients, and found linear relationship between venous lactate and plasma concentrations of metformin in most patients Lalau et al. (20) reported a series of 47 patients, of whom the ones with normal or lower-than-therapeutic range levels of metformin showed worse prognosis. Median plasma metformin level was found to be 20.6 mg/l for survivors whereas 6.3 mg/l for non-survivors (20). In the current study it was found that there was a positive correlation between ingested metformin dose and lactate and a negative correlation with dose and pH (Figure 1). In case of metformin intoxication the dose that was ingested by the patient is an important aspect to take into consideration when organizing the treatment plan. In our study minimum metformin dose that was ingested by a patient who required HD was 15.3 g. Because of this, patients with the history of ingestion of metformin more than 15 g should be considered as HD candidate and these patients should be closely monitored for developing lactic acidosis, which is the preliminary indicator of the devastating effects of metformin intoxication.

Hyperlactatemia cannot be corrected via bicarbonate infusion and potential complications of bicarbonate may be encountered such as electrolyte imbalance, leftward shift of oxyhemoglobin dissociation curve and rebound metabolic acidosis. Bicarbonate may be provided that ventilation is controlled (16,21). Although metformin is a small molecule and can be easily cleared from

plasma with hemodialysis, because of its high volume of distribution and intracellular accumulation total drug clearance is not possible. In line with this, although the patient who ingested 85g metformin had received prolonged hemodialysis (16 sessions for 10 days), autopsy serum still displayed high levels of metformin (4.2 mg/L). In case of metformin intoxication target of HD is the control of lactate neither than removal of drug. In the current study it was shown that both renal replacement therapies (HD and CVVHDF) are effective for lactate clearance. Because HD is more rapid and effective than CVVHDF in terms of lactate clearance primarily HD should be preferred but CVVHDF would be lifesaving in case of hemodynamic instability caused by metformin itself or coingestants (22,23).

CONCLUSION

Metformin intoxication associated lactic acidosis is a potentially fatal condition. MALA develops in dose dependent manner and our study didn't show this effect to be changed by early gastric decontamination and active charcoal. Both renal replacement therapies (HD and CVVHDF) are effective in the treatment of MALA. Most of the patients with severe MALA require repetitive and prolonged HD sessions.

REFERENCES

1. Prikis M, Mesler EL, Hood VL, Weise WJ. When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis. Kidney Int 2007;72:1157-60.
2. Aljada A, Mousa SA. Metformin and neoplasia: implications and indications. Pharmacol Ther 2012;133;108-15.
3. Berstein LM. Metformin in obesity, cancer and aging: addressing controversies. Aging (Albany NY) 2012;4:320-9.
4. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, et al. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012;122:253-70.
5. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol (Phila) 2013;51:949-1229.
6. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010:CD002967.
7. Suchard JR, Grotsky TA. Grotsky, Fatal metformin overdose presenting with progressive hyperglycemia. West J Emerg Med 2008;9:160-4.
8. Timbrell S, Wilbourn G, Harper J, Liddle A. Lactic acidosis secondary to metformin overdose: a case report. J Med Case Rep 2012;6:230.
9. Peters N, Jay N, Barraud D, Cravoisy A, Nace L, Bollaert PE, et al. Metformin-associated lactic acidosis in an intensive care unit. Crit Care 2008;12:149.
10. 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;54:818-23.
11. McNamara K, Isbister GK. Hyperlactataemia and clinical severity of acute metformin overdose. Intern Med J 2015;45: 402-8
12. Spiller HA, Weber JA, Winter ML, Klein-Schwartz W, Hofman M, Gorman SE, et al. Multicenter case series of pediatric metformin ingestion. Ann Pharmacother 2000; 34:1385-8.
13. Soyoral YU, Begenik H, Emre H, Aytemiz E, Ozturk M, Erkoc R. Dialysis therapy for lactic acidosis caused by metformin intoxication: presentation of two cases. Hum Exp Toxicol 2011;30:1995-7.
14. Ali S, Fonseca V. Overview of metformin: special focus on metformin extended release. Expert Opin Pharmacother 2012;13:1797-805.
15. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996;30:359-71.
16. Seidowsky, A., S. Nseir, N. Houdret, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 2009;37: 2191-6.
17. Carvalho C, Correia S, Santos MS, Seiça R, Oliveira CR, Moreira PI. Metformin promotes isolated rat liver mitochondria impairment. Mol Cell Biochem 2008;308:75-83.
18. Turkcuer I, Erdur B, Sari I, Yuksel A, Tura P, Yuksel S. Severe metformin intoxication treated with prolonged haemodialyses and plasma exchange. Eur J Emerg Med 2009;16:11-3.
19. Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, Williams KM, et al. The Role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case Series and Formulation of a Model of Pathogenesis. Drug Saf 2013;36:733-46.
20. Lalau JD, Race JM. Race, Metformin and lactic acidosis in diabetic humans. Diabetes Obes Metab 2000;2:131-7.
21. Yang PW, Lin KH, Lo SH, Wang LM, Lin HD. Successful treatment of severe lactic acidosis caused by a suicide attempt with a metformin overdose. Kaohsiung J Med Sci 2009;25:93-7.
22. Nguyen HL,Concepcion L. Metformin intoxication requiring dialysis. Hemodial Int 2011;15 Suppl 1:S68-71.
23. Giuliani E, Albertini G, Vaccari C, Barbieri A. pH 6.68--surviving severe metformin intoxication. QJM 2010;103:887-90.