

## A Pediatric Suicide Attempt by Ingestion of Metformin, Glimepiride and Sulpiride: A Case Report and Literature Review

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### Abstract

A case of a pediatric patient poisoning after ingestion of metformin, glimepiride and sulpiride, he was presented to the emergency service with symptoms and signs of hypoglycemia. Using a risk assessment based approach, the management of glimepiride and metformin overdose is discussed. Glimepiride overdose invariably results in profound hypoglycemia that requires resuscitation with IV dextrose and the use of octreotide as an antidote. Metformin overdose rarely causes problems. The acute sulpiride poisoning is poorly reported in the medical literature.

**Keywords:** Pediatric; Suicide attempt; Poisoning; Metformin; Glimepiride; Sulpiride

### Introduction

Children suffering from physical, mental or psychological problems are being increasingly evaluated and treated in pediatric clinical [1]. Pediatric emergency departments frequently admit that a lot of children have attempted to commit suicide. Cases vary depending on both the child's age and some risk factors [2]. The main profile is a female between 12 and 14 years of age that attempted suicide at home using medication especially benzodiazepines. Among those under 10 years, there is a significant predominance of males using non pharmacological methods [3]. Understanding how children react to suicide screening in an emergency department can inform implementation strategies. [4]. Clinicians have frequently worried that medications used to treat pain and suffering might also hasten death [5]. The death of a child can have a devastating effect on the family [6].

### Case Presentation

An 11 year old child was found alone by his mother in his room in coma. A month later, an accident happened to that child who lost partially his sight while playing. After the accident, he was in a state of solitude, anxiety, depression, and fear of potential harm to the other eye.

On 11 December 2015, his mother thought that he had been sleeping. She wanted to wake him up, but it was in vain. She took him to the emergency service of the regional hospital of Kasserine, biochemistry panel revealed normal renal functioning but severe hypoglycemia (0.3 g/L), no lactic acidosis, a rhabdomyolysis (arterial blood gas pH, 7.42; pCO<sub>2</sub> 32.4 mmHg; pO<sub>2</sub> 82 mm Hg; HCO<sub>3</sub> 22.9 mmol/L; creatinine 55 μmol/L, CPK 852 UI/L, thus, He was perfused by glucose solution and transferred to the intensive care unit at the same hospital.

The next day, his mother came back home in order to search his room, she found that he ingested the treatments of his father, which are metformin, glimepiride and sulpiride. He ingested 10 tablets of metformin. (850 mg), 10 tablets of glimepiride (2 mg) and 4 tablets of sulpiride (50 mg); in totality he ingested 8500 mg of metformin, 20 mg of glimepiride and 200 mg of sulpiride. She also found a letter in which he explained the causes of the suicide attempt.

He was perfused by glucose solution during 36 hours. After two days, he quitted the intensive care unit and moved to the pediatric service where he stayed one day before coming back home.

### Discussion

Metformin belongs to a class of biguanide. The biguanide class consists of phenformin, buformin, and metformin [7]. The biguanide metformin is the most commonly prescribed drug for type 2 diabetes (T2D) taken by an estimated 150 million individuals worldwide. [8] Fatal cases, both accidental and intentional, are extremely rare in clinical practice. Metformin is eliminated by the kidneys, and impaired renal function can result in an increased plasma concentration of the drug [9]. Metformin is not metabolized in the liver or kidney but rather excreted intact in the urine. The half-life of the drug measured in plasma is between 4 and 8 h in individuals without renal dysfunction, and the clearance exceeds glomerular filtration rate, consistent with tubular secretion [10]. We identified 120 documents that reported or cited 65 different "therapeutic" plasma metformin concentrations or ranges. The values ranged from 0.129 to 90 mg/L, and the lowest and highest boundaries were 0 and 1800 mg/L. [11]. It is generally considered a safe drug but is rarely associated (0.06 cases per 1000 patient years) with lactic acidosis, inhibits oxygen consumption and impairs mitochondrial function in liver and other tissues especially in dehydrated patients or in the presence of multiple morbidities [12,13].

There are only a few descriptions of metformin intoxications and their effects in pediatric patients, probably due to the fact that this

drug is only rarely used in children with type 2 diabetes mellitus and not licensed for use in children [14].

Blood levels ranging from 0.5 to 2.5 µg/ml are considered within the therapeutic range, whereas concentrations over 5 µg/ml are generally considered toxic [15].

One multicenter case series of pediatric metformin ingestion is based on case reports to American Poison Control Centers. In this study, 55 cases were collected from which 37 children were evaluated in a healthcare facility. The absolute doses ingested in this study ranged from 250 mg to 16.5 g with a mean of 1.71 g. None of these children experienced hypoglycemia [16]. Therefore, Spiller et al. concluded that an ingestion of ≤ 1700 mg of metformin appears not to pose a significant health risk in healthy pediatric patients. There are several limitations to this study: in 10 of the 11 older children there was no laboratory confirmation of metformin exposure. Of all 55 children, 41 ingested a maximum of two tablets of metformin (<1700 mg) and only 37 children were evaluated in a healthcare facility [16]. The metformin dose was unknown in five cases. In only 37 cases was glucose measured and in only 21 cases were pH measurements done. Compared with the doses in this study, the ingested dose of 38.25 g metformin (0.55 g/kg body weight) in our patient was high and correlated with the massively elevated initial serum metformin level of 165 mg/l [16]. Not in any of the other reports on metformin ingestions in childhood. In adult patients, a metformin level of 0.5-2 mg/l is regarded as therapeutic [17]. Metformin concentrations between 4.1 to 84.9 mg/l were measured in 10 of 14 adult patients with lactic acidosis [18]. There are reports on non-survivors with similar high metformin levels: A 42-year-old diabetic male died due to metformin intoxication with a metformin level of 188 mg/l despite veno-venous hemodialysis and a 50-year-old diabetic male died due to severe lactic acidosis with a metformin level of 166 mg/l without hemodialysis treatment [19,20]. Considering these reports, our patient had a high risk for a fatal outcome possibly, the lack of additional risk factors was important for his survival. However, in a recently published review of case reports by Stades et al. no relationship could be established between lactate concentration, metformin levels and mortality during metformin therapy. In an adult case series [21]. Lalau and Race found that a high metformin concentration had a prognostically favourable effect on the survival of patients with lactic acidosis. Our patient did not have any risk factors like renal failure or lactic acidosis [22]. Dell Aglio et al. analyzed 22 cases of acute metformin overdose and observed that the mortality rate in patients with a peak serum metformin concentration of greater than 50 µg/ml was 38%, with a median peak metformin level of 110 µg/ml in no survivors [23]. Another case series of 42 patients reported a mortality rate of 48% among patients with unintentional MTF poisoning. In this study, the most accurate predictor of death was liver dysfunction [24].

Glimepiride is a second-generation sulfonylurea used to treat T2DM [25], it can also be combined with other antihyperglycemic agents [26]. After administration, glimepiride is completely absorbed and the maximum concentration is reached after 0.7-2.8 h (*t*<sub>max</sub>) in healthy volunteers and 2.4-3.75 h in T2DM patients. Terminal half-life was increased from 3.2 to 8.8 h over the range of doses from 1 to 8 mg in healthy volunteers [25], glimepiride is metabolized primarily in the liver, first to its active metabolite via the cytochrome P450 and then to its dehydrogenated inactive metabolite [27]. Glimepiride has high selectivity toward the pancreatic ATP-sensitive potassium channel increases glucose transport, and shows various extra pancreatic effects in muscle and fat cells. For these benefits, glimepiride is prescribed as a

primary monotherapy when metformin monotherapy has failed [28]. Glimepiride should be used with caution in the patients with renal or hepatic disease. Glimepiride was generally associated with lower risk of hypoglycemia compared to other sulfonylureas [26]. Some studies given that glimepiride could be titrated from a starting dose of 2 mg/day to a maximum dose of 6 mg/day [29].

A generic glimepiride/metformin (2/500 mg) fixed-dose combination (FDC) tablet was developed recently [30].

Ingestion of oral hypoglycemic agents places children at greater risk than adults because they are less capable of meeting obligatory glucose demands, and may rapidly become hypoglycemic. Some studies suggest that the absence of hypoglycemia within 8 hours of the estimated time of ingestion signals a benign outcome in children [31].

In 2010, there were 977 such cases reported to US poison control centers. Exploratory sulfonylurea ingestion by children can lead to significant hypoglycemia, even from a single ingestion [32]. Last, there is some evidence that glimepiride may not cause hypoglycemia as severely as other sulfonylureas [33]. Levine and all were founded that 93 patients with accidental sulfonylurea exposures were admitted, with a median age of 1.83 years. Glyburide and glipizide accounted for most sulfonylureas. Hypoglycemia (blood glucose level <50 mg/dL) developed in 25 (58.1%) of 43 patients who ingested glipizide, compared with 10 (25.6%) of 39 patients who ingested glyburide. The overall incidence of hypoglycemia was 44%. Hypoglycemia was more likely to occur with glipizide ingestion than glyburide (odds ratio, 3.89 [95% confidence interval, 1.51-9.98]). No patient with a known time of ingestion developed hypoglycemia after 13 hours [34].

Spiller and colleagues conducted a review of patients called into 10 poison control centers for a 10-year span. In their series, hypoglycemia (defined as serum glucose level <60 mg/dL) developed in 56 (30%) of 185 patients [35].

Quadrani et al. conducted a 5-year review of cases called into a single poison control center. In their case series of 93 ingestions, hypoglycemia (glucose level <60 mg/dL) developed in 25 (27%) of 93 cases [36].

Sulpiride is a benzamide neuroleptic used in the treatment of some psychiatric and gastroenterological disorders. Its antipsychotic, antiautistic, activating and antidepressive properties result from antagonistic action to dopaminergic receptors in the central nervous system [37].

The usual daily dose is 200 to 800 mg orally or by intramuscular injection [38]. The oral bioavailability of sulpiride is poor and it does not appear to have an extensive first-pass metabolism, nor is it extensively protein-bound. Elimination of sulpiride appears to depend primarily on the kidneys. The acute sulpiride poisoning includes mainly neuropsychiatric (agitation, hallucinations, depression) as well as cardiac effects (hypotension, dysrhythmias, and sinus tachycardia) [39].

Therapeutic, steady-state plasma concentrations of sulpiride have been reported and ranged from 0.071 to 1.121 g/mL. Fatal intoxications involving sulpiride have been previously reported [37]. The quantitative methods for the measurement of sulpiride blood concentration are not routinely available and the toxic blood concentration is probably higher than 2 mg/L [37].

Sulpiride toxicokinetic parameters such as *t*<sub>max</sub> = about 3 h, *t*<sub>1/2</sub> = 24.02 h, *k*(*e*) = 0.029 h<sup>-1</sup> were also estimated. They have pointed

out that the absorption rate is similar and the elimination is prorogated in sulpiride acute poisoning compared to therapeutic doses [33].

Treatment of acute sulpiride poisoning includes standard protocols of gastrointestinal decontamination and further symptomatic and supportive measures, among them TdP (magnesium sulphate, isoproterenol, electrotherapy) and NMS treatment (benzodiazepines, bromocriptine, dantrolene, physical cooling) [37].

## Disclosure of Interest

The auditors declare that they have no conflicts of interest concerning this article.

## Statement of Human Rights

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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