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(REVIEW ARTICLE)

Diabetic ketoacidosis and olanzapine: Case report and literature review

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Abstract

The use of antipsychotics (AP) is associated with the development of metabolic disorders, such as diabetic ketoacidosis (DKA) and acute dysregulation of glucose metabolism. Hyperglycemic complications from drug use, although rare, are potentially life-threatening, so appropriate follow-up and risk assessment during treatment are necessary. This study reports the case of a patient with bipolar affective disorder using olanzapine who developed severe DKA and reviews the current literature on this association. The research was done in PubMed, Cochrane Database, Scopus, Web of Science, Embase, and Google Scholar databases using the keywords: diabetes mellitus, diabetic ketoacidosis, psychotic disorders, antipsychotics, olanzapine, adverse drug event. Upon analysis of the included epidemiological studies, it was observed that most patients who developed DKA were undergoing treatment with olanzapine and clozapine alone or in combination with other antipsychotics. It was seen that the DKA picture usually occurs between six to twelve months of AP use, similar to the case presented. Before insulin resistance, male gender, and middle age favor the disorder in AP users.

Keywords: Diabetes mellitus; Diabetic ketoacidosis; Psychotic disorders; Antipsychotics; Olanzapine; Adverse drug event

1. Introduction

Type 2 diabetes mellitus (DM) is characterized by pancreatic failure in insulin production and secretion, peripheral hormone resistance, and hyperglycemia. Obesity and physical inactivity are associated with an increased prevalence of DM in recent years. It is a public health problem and therefore needs prevention and/or early diagnosis [1,2]. Other factors trigger pancreatic failure and hyperglycemia, including the use of drugs that reduce insulin secretion by pancreatic β cells, increase hepatic glycogenesis, and cause peripheral resistance to insulin action. Medications related to these mechanisms are glucocorticoids, oral contraceptives, antihypertensives (beta-blockers; thiazide diuretics), nicotinic acid, statins, protease inhibitors, cyclosporins [3]. Antipsychotics may cause DKA in patients with a previous diagnosis of DM or trigger the onset of this comorbidity in previously healthy patients [4]. The treatment of patients with schizophrenia and bipolar disorder using clozapine and olanzapine promotes weight gain, obesity, hypertriglyceridemia, and diabetes mellitus. The side effects of these drugs are apparent. However, the exact mechanism by which they cause metabolic syndrome has not yet been well defined [2]. The use of olanzapine alone is useful in the short-term treatment of major depression and bipolar affective disorder. It is considered to be the first-line drug to treat

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the acute phase of the disease. However, the risk of hyperglycemic complications and other side effects such as sedation, increased appetite, dry mouth, weakness, hypercholesterolemia, hypertriglyceridemia, impaired liver function, hyperprolactinemia, and neutropenia, require appropriate follow-up of these patients, especially in the first months of treatment [5]. Despite the apparent relationship between antipsychotic use and the development of metabolic dysfunction, the prevalence or risk of the onset (incidence) of diabetes mellitus in patients treated with these drugs requires an updated approach [3]. In this sense, the present study reports a rare case of diabetic ketoacidosis in a previously normoglycemic patient who had been using olanzapine continuously for six months to treat bipolar disorder and deepened the knowledge on this subject through a thorough literature review [6].

2. Material and methods

We searched the PubMed, Cochrane Database, Scopus, Web of Science, Embase, and Google Scholar databases (gray literature) using the keywords: diabetes mellitus, diabetic ketoacidosis, psychotic disorders, antipsychotics, olanzapine, adverse drug event. The selection of articles was made by two authors independently. A third author was consulted in case of divergence in the inclusion or not of a particular study. Reports from the last three years related to diabetic ketoacidosis and olanzapine use were selected based on the chosen keywords, human studies, full-text articles, and published in English, Portuguese, or Spanish. Fourteen studies unrelated to the main objective of the review or outside the inclusion criteria were excluded after peer review. We included 23 articles from a total of 37 scientifically validated and relevant published studies from September 2016 to September 2019, cohort, systematic review, integrative review, series and case reports, randomized controlled trials and meta-analysis. The Research Ethics Committee of Potiguar University – Natal/Brazil, approved the research after signature by the patient informed consent, according to Resolution 466/2012 of the National Commission of Ethics and Research in Humans – CONEP – Ministry of Health/Brazil. Protocol number 147/2019.

3. Case report

A 39-year-old male patient comes to the emergency department with a drop in general health, fever, skin-mucous pallor, cold sweating, disorientation, and respiratory distress for four days. It does not know related triggering factors. Has obesity and bipolar affective disorder in daily use of olanzapine for six months. Physical examination revealed a severe general condition: hypocolored, dehydrated, hypotensive, tachypneic, with crackling crackles on pulmonary auscultation and bilateral lower limb edema. Laboratory tests revealed metabolic acidosis, leukocytosis, hypokalemia, and hyperglycemia (HGT = HI). Initially, hydration with hypotonic solution, furosemide, NPH, and regular insulin was instituted, in addition to the use of broad-spectrum antibiotic therapy. Still, the patient developed cardiopulmonary arrest in asystole, reversed after 25 minutes of resuscitation. Admitted to an Intensive Care Unit, evolved with Glasgow Coma Scale (ECG = 3), on invasive mechanical ventilation, using vasoactive drugs and capillary blood glucose ranging from 45mg / dL - HI. After 20 days of hospitalization, the patient improved consciousness level, progressing to lower limb paralysis and emotional lability. Magnetic resonance showed the presence of a bilateral lesion in the base nuclei, of hypoxic-ischemic origin with an uncertain prognosis, and acetylsalicylic acid and clopidogrel were introduced. Due to persistent hypokalemia, insulin pump introduction and withdrawal cycles were instituted based on the patient's fasting blood glucose levels, coinciding with the onset of generalized tonic-clonic seizures and agitation. Medications such as diazepam, phenytoin, and phenobarbital were used with sequential control of the condition, followed by clonazepam and amitriptyline. Due to the maintenance of hyperglycemic levels, olanzapine was discontinued, with the gradual improvement of the patient's capillary blood glucose values. After 20 days, NPH insulin was suspended. The patient was discharged without oral hypoglycemic agents or insulin therapy. The patient was suggested to change lifestyle and follow-up with an endocrinologist.

4. Results and discussion

Second-generation or atypical antipsychotics (AP) are considered the standard treatment for psychotic disorders because they are more effective and less risk of extrapyramidal effects. However, they are associated with the development of signs and symptoms related to pancreatic failure and peripheral insulin resistance, which may lead to the emergence of severe hyperglycemic emergencies, such as Hyperglycemic Hyperosmolar State (HHS) or Diabetic Ketoacidosis (DKA) [7]. The chance of progressing to these complications is rare, with 1-2 events/1,000 people/year of exposure occurring. However, patients who develop AP-induced DKA have high mortality in up to 13% of cases [1-3,8]. The overall incidence rate of diabetes mellitus associated with AP use is 4.4% / year and is higher than the estimated rate in the general United States population. However, it is not yet clear whether the increased incidence of diabetes mellitus is due to the use of antipsychotic medications, the presence of underlying disease, schizophrenia, or other factors such as physical inactivity, autoimmune disease, obesity, high cardiovascular risk and poor access to services of

health [1,8]. The risk associated with atypical APs is higher for clozapine (2.03%), followed by quetiapine (0.80%), olanzapine (0.63%), and risperidone (0.05%) [5-7,9]. Besides, medications such as first-line AP, mood stabilizers (sodium valproate or lithium), clonazepam, antidepressants, antihypertensives, benzodiazepines, statins, sympathomimetics, parasympathomimetics, anticholinergics, corticosteroids, and antidiuretics are associated. To the development of DKA, but to a lesser extent when compared to second-line APs [10]. Thus, DKA, characterized by hyperglycemia, ketoacidosis, and ketonuria, is commonly associated with the use of olanzapine and clozapine alone or related to other PA. In most of the observed cases, DKA occurred in patients using combination therapy [3]. Clinical manifestations of diabetes and metabolic syndrome appear as early as six months after initiation of treatment. However, reports have shown the presence of these symptoms from 4 days after starting the use of AP until four years later [2, 4,11]. Although the association between the use of AP and the development of metabolic disorders is proven, the pathophysiological mechanisms triggering the process are not known, and the report of these events is relatively new. The first reported case of olanzapine induced DKA occurred in 1993, leading to an absolute contraindication to its use in patients with diabetes in some countries of the world [5,12]. The initial phase of drug administration is usually associated with acute dysregulation of glycemic metabolism, being the leading cause of DKA. Although more common, this effect is not limited to the initiation of treatment, but death reports even 60 months after initiation of therapy[4-7,13]. The initial clinical presentation, in this case, differs from what is usual in the pathophysiology of type 1 and 2 DM. There is overlap or predominance of one of them. Thus, patients may present with DKA as the first clinical manifestation of newly diagnosed diabetes and substantial weight loss before DKA, resembling what occurs in type 1 DM. In contrast, most patients have considerable weight gain and insulin resistance, clinical suggestive of type 2 DM. Some patients may also have leukocytosis, related to concomitant pancreatitis or urinary tract infection [3-6,14]. Risk factors for the development of diabetes in atypical antipsychotic users are previous DM, black race, male gender, obesity, and family history in first-degree relatives with diabetes. Such findings were found in the case report of this study, although the patient was younger at the age of 40-60 years, where the phenomenon is more common. [1] Also, previously, sedentary patients are more susceptible to this adverse effect [8-10,15]. Concerning psychiatric disorders, schizophrenia is a significant risk factor, ten times more frequent than in the general population [3,16]. The effects of antipsychotics are considered risk factors for DM in the recent Canadian Diabetes Association guidelines. Glycemic disorders are present in schizophrenic patients who have never used medication to treat this comorbidity. However, antipsychotics corroborate the worsening of blood glucose dysregulation, increasing the risk of developing diabetes mellitus [7,12,16]. Most of the patients who presented with a clinic suggestive of DKA after the use of AP had schizophrenia. These patients appear to be more likely to develop DM even before becoming users of atypical antipsychotics, as this disease alone increases the risk of glucose intolerance [1,15-17]. Approximately 10% of people with schizophrenia and 9.4% of bipolar disorder patients now have Type 2 Diabetes. These data, when grouped and compared with age- and sex-matched controls, represent, on average, twice the rate. Risk of the general population [2,18]. As we have seen, DKA has already been considered a decisive factor in differentiating between type 1 and 2 DM. DKA is the initial clinical manifestation of nature 1 DM in young patients with autoimmune factors against pancreatic cells. However, we cannot generalize this information, since in the cases of AP-induced DKA, 90% of patients were classified as type 2 DM [9-11]. One of the reasons is that the use of AP is associated with appetite stimulation and weight gain, leading to the increased abdominal circumference. Besides, physical inactivity causes obesity and the occurrence of diabetes [5-8] Other mechanisms include increased leptin and TNF-alpha in adipose tissue, causing peripheral insulin resistance, and disruption of AKT1 protein, which plays an essential role in regulating metabolism and normal cell cycle reactions [8-10,19]. The toxic effect of AP affects pancreatic beta cells, causing the primary substrate of energy reactions to be triglycerides and amino acids, increasing serum levels of glycerol and free fatty acids. The drugs that most frequently develop the development of DKA have multiple receptors and use different mechanisms of action, causing a state of hypoinsulinemia that is clinically presented as DKA [1,5,12]. Often the effect preserves the functioning of pancreatic alpha cells, excess glucagon, and stimulation of hepatic gluconeogenesis [3]. Fatal DKA is another form of the initial presentation of DM in individuals using AP [9, 14] The reasons behind the rise in glycemic rates are multifactorial. Antipsychotics are suspected of playing a role in the etiology of the disease. [8] Also, a sedentary lifestyle and the presence of depressive symptoms related to bipolar affective disorder contribute to weight gain and consequent diabetes [3, 16, 20]. Experts from the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and American Association for the Study of Obesity concluded that antipsychotics increase the risk of obesity, diabetes, dyslipidemia, and metabolic abnormalities associated with weight gain. These Specialty Associations recommend, by consensus, that all patients on antipsychotic treatment should be screened and continuously monitored for the presence or absence of diabetes [9-11]. However, studies have shown that significant weight gain occurred in only half of the cases of AP-induced DKA, revealing that insulin resistance and hyperglycemia can occur during PA treatment without changes in weight profile. Thus, it is suggested that these drugs have a direct action on tissues, regardless of eating behavior [3, 5-8] In one of the cases found in the present review, the patient's clinical condition was suggestive of type 1 DM due to the occurrence of schizophrenia-associated DKA under olanzapine treatment for three months [10,15]. During admission, glycated hemoglobin levels of 15% were evidenced. However, after a detailed study, the presence of hyperglycemic effects related to insulin resistance, weight gain, and

other non-immunological phenomena were found, which are associated with the onset of type 2 DM [1,14]. This relationship weakens the hypothesis of pancreatic beta-cell destruction. Olanzapine or cause reversible damage to such cells. Thus, olanzapine treatment could have been an accelerating factor in the development of type 1 DM, in association with other elements [10,12]. Clinical studies have shown worsening insulin resistance with olanzapine, regardless of any change in body weight or mass, suggesting that antipsychotics have a direct effect on insulin sensitivity [8]. A meta-analysis by Burghardt et al. evidenced that the use of atypical antipsychotics significantly reduced insulin sensitivity, as well as resulted in weight gain, which may, therefore, suggest a direct effect of the drug [4]. In the CATIE study, olanzapine increased glycated hemoglobin levels to a greater extent than all other antipsychotics. Similar results were found in other research, showing that treatment with olanzapine and clozapine significantly increased the risk of developing diabetes compared to treatment with aripiprazole, quetiapine, risperidone, and ziprasidone [7]. In a systematic review of adverse events associated with diabetic ketoacidosis in patients exposed to antipsychotics conducted by the Danish Medicines Agency, ziprasidone was associated with a higher number of severe hyperglycemic events. This study also showed a higher prevalence of cases of DKA among olanzapine users (9.36%) [13]. For Dinarmaqueses, the meantime, to progression to DKA was five months, with 33.3% of patients presenting with the disease within two months. As previously reported, most cases have been associated with olanzapine. Interestingly, antipsychotic doses did not exceed the recommended ranges, and no intentional overdose was observed. This suggests the importance of monitoring and monitoring patients not only in high dose cases but also in the correct use of dosage [14-16]. In this context, it is observed that antipsychotics reduce insulin secretion, either by a toxic effect on pancreatic β cells or pharmacological action that disrupts normal insulin secretion, favoring the onset of DKA. [8,17,20] Another clinical study showed that patients treated with olanzapine had biphasic changes in insulin secretion. Initially, insulin secretion decreased in the second week and increased in the eighth in proportion to body weight gain. In this case, olanzapine reduced insulin secretion at an early stage of treatment [10,21]. Leslie and Rosenheck showed that 7.3% of patients on antipsychotic medication were diagnosed with diabetes mellitus during the follow-up period, representing an annual incidence rate of 4.4%. Among the patients analyzed, 0.2% were hospitalized for diabetic ketoacidosis [1,16]. The incidence of DKA is ten times higher in patients using second-generation antipsychotics (SGA) since most have psychological disorders compared to the general population. Three potential mechanisms for explaining this data are then proposed: neglect of early symptoms of type 1 DM in patients exposed to SGA; immune system activation associated with acute psychotic exacerbation; immunomodulatory effects of ESG that may cause loss of tolerance and destruction of beta-immune cells [1,5,13]. The mortality rate in patients with DKA exposed to antipsychotics is 26.5% compared to the reported less than 5% mortality rate in the general population. This underscores the potentially life-threatening risk of patients exposed to antipsychotics. However, due to the presence of silent autopsy, DKA can often be overlooked as a potential cause of sudden death due to underreporting and lack of data regarding the causal factor [6, 17-19] Despite the description of these cases in the literature, routine screening for metabolic complications of antipsychotics is low. Therefore, it is recommended that patients who use these drugs undergo objective and periodic weight and metabolic risk factors assessment. Canada's clinical diabetes guidelines address this recommendation [2].

5. Therapeutic management

The initial approach aims to treat hyperglycemia. DKA should be promptly treated with volume replacement, insulin therapy, and resolution of hemodynamic instability [4-6]. After early treatment of DKA, 36% of patients had complete resolution of symptoms and did not require treatment after discharge; 14% controlled diabetes mellitus with lifestyle changes alone, and 50% remained insulin-dependent, oral hypoglycemic, or both [9-11]. After therapeutic management of the acute phase of the disease, it is essential to have guidance on healthy and regular eating habits, physical exercise, and social life of the affected patients, as these associated diseases contribute to obesity in people with a severe mental disorder [1-3]. Antipsychotic use is the major obesogenic factor, leading to an increase of more than 7% in weight gain among 15-72% of people who use second-generation antipsychotics [8]. Follow-up with a focus on individuals with a family or personal history of diabetes mellitus, dyslipidemia, obesity, and metabolic syndrome is recommended. Routine assessment of body weight (Body Mass Index), waist circumference, blood pressure, fasting glucose, and lipid profile before initiation and during treatment are required. Besides, patients should be advised of the signs and symptoms of hyperglycemia and the risk of DKA [9]. Constant follow-up through glycated hemoglobin and fasting glucose every three months, capillary blood glucose monitoring within the first 3-6 months, is essential, especially if patients have other risk factors for diabetes [10-12]. The psychiatrist should perform this investigation before instituting antipsychotic therapy or when treatment requires increased dosage [2,6] Regular physical activity, smoking cessation, and dietary control are critical. The electrocardiogram should be performed before the beginning, as well as during the maintenance period of the AP. These parameters should be periodically evaluated during the treatment period [1, 5, 9] Antipsychotics are the basis of treatment for severe mental illness. Thus, these medications are necessary to control acute psychosis, and in the long run, prevent relapses. Treatment is associated with a lower risk of hospitalization, suicide, and mortality [17-19]. However, the risk of diabetes needs to be considered, and strategies must be developed to prevent, track, and diagnose this comorbidity. Confirmed the diagnosis is necessary to treat most properly. After the development of

diabetes by using AP, the benefits and risks of maintaining the same medication should be considered, and it is more prudent to switch to another equivalent drug [6]. For hospitalized patients on antipsychotics, it is crucial to perform glycemia and glycated hemoglobin on admission. The optimal frequency of monitoring during entry is unknown, varying among specialist health services. The guidelines suggest patients with pre-existing diabetes or who develop the disease during treatment; the psychiatrist should consider an antipsychotic less likely to cause hyperglycemia [4-7]. Antipsychotic that promotes lower weight gain reduces the likelihood of hyperglycemia, although any decision to change the antipsychotic should balance the risk of relapse of significant psychotic symptoms [8]. Attention will be heightened when there is a previous history of diabetes. In Japan, studies contraindicate olanzapine and quetiapine under these conditions due to the fatal hyperglycemia [11,18] The use of metformin or orlistat is an alternative in preventing or delaying the onset of diabetes mellitus in patients treated with atypical antipsychotics [7,13] The effects of metformin on diabetes risk in people taking antipsychotics have not been studied. Still, a meta-analysis of 12 studies involving 743 people treated with antipsychotics has shown that metformin leads to an average reduction of 3.3 kg in body weight in up to 3 years. Insulin resistance also improved, but there was no change in fasting glucose. Orlistat, on the other hand, did not show good adherence by the study participants due to the side effects of gastrointestinal origin. [6, 8, 16] The DKA occurred after drug combination in more than 50% of cases, suggesting that polypharmacy presents a higher risk than monotherapy. The pharmacodynamic and pharmacokinetic components of these drugs are suspected to increase the serum levels of these drugs and produce harmful effects. Thus, all doctors need to be aware of the side effects of these medications, used alone or in combination. [3,14,21] In patients whose AP was discontinued soon after DKA, there was no need for insulin or oral hypoglycemic agents at the time of hospital discharge [22]. However, in cases of delayed AP detection as the causative agent of DKA, insulin was prescribed at discharge. In general, most patients required treatment with oral hypoglycemic agents or continuous insulin therapy [23].

6. Conclusion

It is necessary that all involved, doctors, patients, family members and health professionals, have knowledge about the risks involved in the use of antipsychotics and the appropriate clinical follow-up, especially in the first months of use, as acute metabolic complications, as well as Peripheral insulin resistance, has been an increasingly common reality in patients treated with these medications. Prompt identification of the causative agent, associated with glycemic control, lipid profile, and body weight is essential to avoid fatal complications. Although the reviewed studies show a higher association between the developments of DKA in schizophrenic patients using antipsychotics, we brought a case that relates the emergence of DKA in a patient with bipolar affective disorder, which is still rare today.

Compliance with ethical standards

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Disclosure of conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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