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Prolonged Coma after Single, Unintentional Overdose of Insulin: Concurring Factors Leading to a Persistent Neurological Condition

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Abstract We refer the case of a 62-year old female diabetic patient, under insulin therapy since twelve year. She was found unconscious from her husband and the emergency team assisting the patient on site found a newly opened insulin vial of 10 ml half empty. Supposedly she had injected almost five ml of insulin glargine, with a total of 500 UI of insulin, and the plasma glucose value of 29 mg/dl supported the overdose diagnosis. The patient was emergently admitted in an intensive care unit with profound hypoglycemia and hypokalemia, and in deep coma. Dextrose bolus and continuous infusions normalized her glycemic levels only after three days of uninterrupted perfusions, with the patient remaining in coma for another two days after glycemia normalization. Discharged with a paraparetic gait as neurological sequelae, she improved considerably within the next month from the event. The reason of overdose was not clearly formulated, but a tricyclic antidepressant was added on in the therapy after psychiatric consultancy was obtained.

Keywords: *insulin overdose, hypoglycemia, hypokalemia*

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1. Introduction

Insulin overdose is a challenging problem to modern pharmacology and diabetology in general, since causes leading to its presentation differ, as well as the non trivial consequences related to it. Mostly the insulin overdose is encountered in two settings, namely in the unintentional form, and in suicidal cases [1,2]. Wrong dosage might be related to the unintentional overdose of insulin, and is more expectable in patients with poor visual acuity, or dementia patients [3].

Instead, deliberate and intentional insulin overdose is becoming more and more of concern due to the ease of administration and the wide availability as a suicidal means [4,5]. In the latter cases, patients might be already abusing other drugs, mainly psychotropic medications, or alcohol [6]. Although subcutaneous route is logically the most common way of overdosing, oral ingestion of high amounts of insulin has been as well accused of causing severe hypoglycemia [7].

Actually insulin overdose is referred occasionally and in isolated case reports. However, before the era of modern psychopharmacology, insulin coma was a notorious treatment, albeit acceptable for that period of time [8].

2. Case Report

A 62-year-old female with Type 2 diabetes mellitus was found from her husband unconscious in the bedroom at noon. She had injected the morning insulin from a freshly opened vial, and for unknown reasons to him, the vial was found half empty with signs of being used again, almost four hours after the morning injection.

The patient was using insulin glargine (Lantus®) type in vials of 10 mL, and although the exact amount of insulin injected was not possible to determine, her husband witnessed of being almost sure the half-emptied vial was opened precisely that morning. So we assumed she had injected subcutaneously approximately 5 mL of solution, with several signs of abdominal skin puncturing, which means the equivalent of 500 UI of insulin.

The lady was never been a psychiatric subject, and occasionally consumed benzodiazepines in the evening to improve sleep. A blister of tablets of Alprazolam was found in shelf, with two tablets consumed in total (a tablet containing 0,25 milligrams of active drug); her husband approved she took a single tablet the evening before, but wake up in full alertness, with no signs of somnolence. He was unable to explain the reason for the noon injection (s) of insulin, and admitted they did not had consumed the

lunch, after a very slight meal in that morning, composed only from coffee and fruits.

The patient, slightly obese (BMI kg/m^2 [body mass index] resulted 32) was put under insulin therapy twelve years before, due to persistent hyperglycemic values when treated with diet and oral hypoglycemic drugs. Her family doctor prescribed 32 units of insulin glargine daily separated in three subcutaneous injections (10 – 10 – 12) after meals. She was as well moderately hypertensive, treated with Enalapril for a daily dose of 20 milligrams, separated in two administrations.

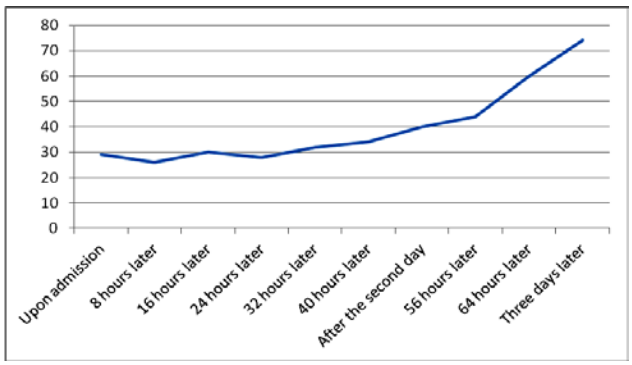
At the emergency room the patient's blood pressure was 140/100 mmHg, with a bradycardic pulse rate of 50/min. The patient was comatose scoring six points at the GCS (Glasgow Coma Scale) with no verbal sounds, eyes closed and withdrawal movements when painfully stimulated.

Upon admission her blood sugar was 29 mg/dl and her potassium plasmatic level 2.8 mEq/L; no other electrolytic changes were suggested in subsequent blood analysis.

She was put under dextrose therapy, through a bolus of 50 ml of 40% dextrose, followed from continuous intravenous infusion of 5% of dextrose. Two infusions of potassium chloride of 30 mmol each were administered as well, with a distance of eight hours from each-other, with potassium level back to normal within the first hospitalization day (potassium values reaching to 3.6 mEq/L).

In spite of this continuous therapy, her glycemic levels remained constantly low (Graphic 1) with a very slow return back to normality only 72 hours after the admission. She never regained completely consciousness with her GCS score remaining to 7-9 points till the fifth day.

Upon discharge from the intensive care unit, she was orientated but obviously exhausted, with a paraparetic gait, that found no explanation in the brain imaging (head CT-scan) that was within normality. Rehabilitative measures were adopted and eventually she regained full motor ability within the second month after the insulin overdose event. During the entire period she had no febrile episodes, and was hemodynamically stable (heart rhythm, blood pressure and blood gas analyses).



Graphic 1. Glycemic values (Ordinate axis; mg/dL) during the continuous dextrose infusion therapy, from admission (29 mg/dL) till the third day of treatment (74 mg/dL). Worth mentioning is that the patient never regained consciousness during this period

Actually the patient is back under insulin therapy, and her gait presents no abnormalities. Interviewed thrice from a psychiatrist, she never admitted clearly that the overdose injection was made for suicidal purposes. Nevertheless, a tricyclic antidepressant was added on the evening therapy, replacing the benzodiazepine abused before as a self-medication.

3. Discussion

Insulin glargine, a long- acting human insulin analog produced by recombinant DNA technology in Escherichia coli, is indicated to improve glycemic control in adults with type 2 diabetes mellitus. Considered as advantageous in terms of causing less frequently hypoglycemic events, nevertheless overdose reports are published [2,9]. Sources have referred as well overdoses of other insulin long-acting preparations, suggesting an overall mortality of 2.7% related to these occurrences [10].

Resistance of brain toward hypoglycemia is a matter of controversies. Authors suggest that patients with hypoglycemic tolerance might have a genetic predisposition to do so, or might show a delayed onset of neurological symptoms [11]. Once considered a form of ischemic damage, modern neuropathology has clearly separated the ischemic damage of brain from the hypoglycemic one [12]. What is impressive in our case, and in other case reports of hypoglycemia related to insulin overdose, is that seizures are very rarely, if ever, mentioned in the clinical stories.

For hypoglycemia to be important enough to become clinically patent, cut off levels have been formulated, with slightly different thresholds approved from different sources, but with values under 60 mg/dL clearly deserving the hypoglycemia definition [13,14].

If we analyze the three-day long history of hypoglycemia of our patient, we should consider several factors that might have contributed to the prolonged coma, which persisted even after the glycemic levels returned to normal.

First, we had to deal with a diabetic patient under insulin therapy for twelve years, and diabetes clearly increases brain damage induced from hypoglycemia [15].

Second, we had a biochemical profile of refractory hypoglycemia for three consecutive days, which might explain the neurological deficit lasting for a month or so after the overdose.

Third, the ancillary role of sedatives consumed the night before (although in a sustained dose), might synchronize with the complexity of the events.

Fourth, the patient was almost fasting for more than twelve hours, with the only meal consumed the evening before the event. The role of fasting is a constant concern in other settings [16].

At the end, electrolyte disorders (hypokalemia for the first day of hospitalization) might have its own importance. Cases of complex electrolyte disorders following insulin overdose have been reported [17].

4. Conclusions

Insulin overdose is a clinical rarity, but its neurological consequences might be important, and fatalities have been reported [18,19]. Cases of long-term and unusual neurological complications following a single overdose of insulin have been published [20]. Obviously, brain is not

the only organ involved, with complications like acute pulmonary edema encountered as well [21].

Continuous educational and psychological support for diabetic patients under insulin therapy is necessary, to avoid unintentional or much more frequently, acts of deliberate injection of insulin overdoses.

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