

Intentional Insulin Overdose Associated with Minimal Hypoglycemic Symptoms in a Non-Diabetic Patient

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ABSTRACT

Non-accidental suicidal insulin overdose is a rare presentation among non-diabetic patients. It seems to be more common among working medical professionals.

Objectives: *To present the case of a young patient, who despite injecting a large dose of rapid-acting insulin presented with only mild symptoms, and to familiarize the medical professionals involved in managing this condition with the recognition, pathophysiology and appropriate therapeutic interventions.*

Materials and methods: *We report the case of a previously healthy non-diabetic young medical professional who presented with a rapid-acting insulin overdose. On initial assessment the patient was alert and oriented, and glucose measurement was 1.4 mmol/L. The oral glucose gel and intramuscular glucagon failed to raise the glucose. Hypokalaemia, hypomagnesaemia, hypophosphataemia, lactic acidosis and ECG changes completed the presentation.*

Outcomes: *The treatment consisted of dextrose infusion and appropriate electrolytes replacement. An uneventful recovery was made, so 36 hours later the patient was discharged with psychiatric follow-up.*

Conclusions: *Insulin overdose should be considered as a differential diagnosis in hypoglycaemic patients when blood glucose fails to correct as expected. Improper management carries a significant risk of hypoglycaemic encephalopathy, which can cause lifelong cerebral changes.*

CASE REPORT

A young medical professional is brought to the emergency department (ED) by ambulance, following insulin overdose 3.5 hours previously.

There was a history of chronic alcohol abuse, physical self-harm and substan-

ce misuse (paracetamol/codeine); no regular medications or allergies.

After drinking approx. 300 mls of vodka, the person impulsively decides to commit suicide by injecting in the abdomen (4 times over 90 minutes) a total of 10 mls (1000 units) of Actrapid[®] insulin (100 units/ml) from a vial procured for this purpose 3 months before. On the

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onset of the hypoglycaemic symptoms, the person became scared, however, and informed family members. The family called the emergency services who attended the patient approx. 2.75 hours after the overdose. On initial assessment, the GCS was 15/15 and the capillary glucose 1.4 mmol/L. Oral glucose gel (20 g) was administered; after 15 minutes the capillary glucose was still 1.4 mmol/L. After 1 mg of glucagon, the capillary glucose rose to 2.9 mmol/L. An 18 G IV access was established and a bolus of 250 mls of dextrose 10% was given. This increased the capillary glucose to 13.3 mmol/L; the remaining 250 mls was given over 90 minutes.

On arrival, the patient was alert and oriented; GCS 15/15, capillary glucose 9.3, blood pressure 127/79 mmHg, pulse 109 bpm, temperature 35.1°C, respiratory rate 16, SaO₂ 100% on room air. Clinical examination was unremarkable.

A second 18 G IV access was established and blood drawn for a full blood count, urea and electrolytes, liver function tests, plasma glucose, creatinekinase, amylase, CRP, salicylates/paracetamol levels.

Initial ECG: sinus tachycardia with a normal axis and a QTc of 492 msec. The ECG was repeated after 5 minutes and the QTc was 477 msec. Also multiple ventricular extra beats were noticed on the monitor during telemetry.

The laboratory results showed hypokalaemia (K⁺ 2.7 mmol/L), mild hypomagnesaemia (Mg²⁺ 0.71 mmol/L) and hypophosphatemia (PO₄-0.75 mmol/L), raised WBC (17.6 *10⁹/L with neutrophilia), and a plasma glucose of 7.9 mmol/L. The rest of the blood test results were within normal range. An infusion of 1L 0.9% NaCl with 40 mmols KCl was started on the second cannula.

An ABG performed one hour later revealed compensated lactic acidosis (PH 7.39, lactate 3.2 mmol/L, bicarbonate 20.6 mmol/L, base excess - 4.4 mmol/L), a glucose of 4.4 mmol/L and a potassium of 3.1 mmol/L (after glucose and potassium replacement was started).

When dealing with hypoglycaemic unconscious patients, some differentials to exclude are: insulin and oral hypoglycaemic agents overdose, Addison's disease, adrenal crisis, alcoholism, insulinoma, hypopituitarism (panhypopituitarism), pheochromocytoma, glucagon deficiency.

Because the blood glucose was gradually falling since presentation, the infusion of dextrose 10% was replaced with dextrose 20%. The patient required titration of the infusion (150-250 mls/h) over the first 12 hours in order to maintain glycaemia between 4 and 7 mmols.

As there was concern about possible cerebral oedema if high volumes of fluid were given (with the amount of insulin in the system and the requirements of dextrose), the infusion of NaCl and KCl was stopped (approx. 10 mmols KCl already taken) and replaced with one of 30 mmols of KCl in 100 mls of dextrose 5% over 1 hour. In view of the abnormal ECG and hypomagnesaemia, an infusion of 2 g of magnesium sulphate in 100 ml of dextrose 5% over 30 minutes was given. A repeated ECG showed persistent sinus tachycardia and a normalising QTc of 462 msec. The patient was also started on a regime of Pabrinex® and chlordiazepoxide.

A repeated ABG at 5 hours from presentation revealed a normalizing acid/base profile (PH 7.42, lactic acid 1.9 mmol/L, bicarbonate 23 mmol/L, base excess -1.8 mmol/L), glucose 9.6 mmol/L, potassium 3.7 mmol/L.

After 8 hours of therapy, the dextrose infusion was stopped in order to assess glycaemic stability. After 5 minutes the patient showed symptoms of hypoglycaemia (capillary glucose 2.8 mmol/L). The infusion was restarted, an oral high carbohydrates diet was introduced, and the patient was gradually weaned off the dextrose infusion over the first 24 hours. The patient also required an extra 20 mmols of KCl in the first 12 hours in order to maintain potassium levels. The ECG on discharge revealed a heart rate of 92 bpm and a QTc of 402 m/sec.

The patient made an uneventful recovery and was discharged after 36 hours with normal physiological parameters and biochemical values. Psychiatric follow-up was organized upon discharge. □

DISCUSSIONS

Despite the increasing numbers of insulin-dependent diabetics, deliberate insulin overdoses are rarely reported. The 2005 annual report of the American Association of Poison Control Centers reported 3.934 insulin exposures out of a total of 2.424.180 substance exposures (1). Analysing 25 patients (14 female, average age 46 years) who required ICU ad-

mission over a period of 6 years, Mégarbane et al. reported only 13 diabetic patients and 5 non-diabetic medical personnel. Co-administration of other substances, mainly benzodiazepines, was reported for 68% of cases (2). Regarding the medical profession, Hawton et al. showed that insulin-overdose suicide is more common among working than among non-working medical professionals (3).

A German epidemiology study (160 cases) revealed similar numbers: 53% female, average age 44 years; 89% were suicidal/parasuicidal cases; rapid-acting insulin was used by 57%. Regarding outcome, the mortality and cerebral defects rates were both 2.7%, and there was a 94.7% full recovery rate (4).

Actrapid® is a fast-acting and short-acting insulin used in the management of diabetes and hyperglycaemic states. The main toxic effect is generated by hypoglycaemia, which can be confirmed using Whipple's triad: (1) signs/symptoms specific to hypoglycaemia, (2) low plasma glucose associated with the signs/symptoms and (3) signs/symptoms resolution after plasma glucose correction.

According to the producer, for therapeutic purposes, onset is within 30 minutes via subcutaneous administration, with a maximum effect at 1.5-3 hours and a total duration up to 8 hours (5). Ingestion is inoffensive as the drug is digested and not absorbed (6). Improper storage conditions (recommended storage at 2-8 degrees C (7)), may affect the potency of the drug. At room temperature insulin lasts approx. one month. In our case the vial of insulin was stored at room temperature for 3 months before use. This may explain the relatively mild hypoglycaemic effect associated with such a large dose (1000 units).

In the case of an overdose, the hypoglycaemic effect depends on the dose, individual susceptibility to insulin (diabetic vs. non-diabetic), absorption factors (administration route, area of the body, local blood flow) and co-administration of other drugs/toxics. Lypodystrophy at the injection site and the presence of anti-insulin antibodies in long-term diabetics may decrease absorption and prolong the effects.

Usually with an overdose the duration of action is extended and the peak effect delayed (6). The accumulation effect of insulin, the extended insulin half-life (secondary to insulin receptor saturation with exogenous insulin) and the decreased absorption from the injection

site (secondary to hypocirculation caused by mechanical pressure) may explain the prolonged effect seen with overdoses (8,9). Based on this, Ohyama et al. postulated that with huge doses of insulin the effect depends on the dose rather than the type of insulin (9).

The symptoms and effects of insulin overdose can be grouped in two classes: features secondary to sympathomimetic effect (nausea, vomiting, sweating, hyperventilation, tachycardia, labile blood pressure, hyperventilation) and neuroglycopenic effects (abnormal behaviour, altered level of consciousness, lethargy, coma, cerebral oedema, hypertonia, hyperreflexia, extensor plantar response) (6). Most common electrolytes disturbances include hypokalaemia, hypomagnesaemia and hypophosphataemia (6). Also cardiac side-effects associated with hypokalaemia and hypomagnesaemia (prolonged QTc and ventricular extra beats) were seen in our case. Sometimes non-cardiac pulmonary oedema and abnormal liver function results may feature (6). In patients with longstanding diabetes or who use beta blockers, the sympathomimetic effects may not be obvious despite severe hypoglycaemia (6). The most significant complication associated with insulin overdose is hypoglycaemic encephalopathy. Structures such as the cortex, caudate, putamen and hippocampus are particularly vulnerable. Diffusion-weighted MRI is a valuable tool for diagnosing this complication (10).

Measurements of the C-peptide and insulin levels on presentation could be useful to differentiate between exogenous and endogenous insulin administration, particularly in unconscious hypoglycemic patients or patients unable to obtain history from. The C-peptide is a marker for endogenous insulin, as it is a cleavage product of the pro-insulin molecule. The levels will be low in patients presenting with exogenous insulin overdose and high in patients presenting with hypoglycemic medication overdose.

Glucose administration with euglycaemia maintenance is the main stem treatment (hyperinsulinemic-euglycemic clamp). This can be achieved using a 0.5-1 g/kg bolus in unconscious patients followed by various concentrations of intravenous dextrose. If concentrations more than 10% are required, a central route or large antecubital vein is recommended due to a high corrosive action on small veins and also a high risk of tissue necrosis if it extravasates.

Intramuscular glucagon administration is another option; this may not be efficient in patients with low glycogen storages (chronic liver disease, malnutrition, chronic alcohol abuse, etc). Monitoring of glucose should be done each 15 to 30 minutes initially and then hourly once the level of consciousness has improved and the blood glucose is stable.

For our patient glucagon administration revealed a mild increase of the capillary glucose (rise of 1.5 mmol/L) although the patient was a chronic alcohol user that associated alcohol with the insulin OD. This showed that the patient still had adequate glycogen reserves despite of the chronic alcohol usage. This was probably an advantage of the young adult age and only relatively short history of chronic alcohol consumption.

Oral intake in the form of high-carbohydrate food/fluids can be restored as soon the level of consciousness normalises and it is safe. Oral glucose gel can be used in the pre-hospital setting even with unconscious patients (rubbed against oral mucosa) when IV access or glucagon is not available.

Levels of electrolytes, especially potassium, magnesium and phosphate, should be monitored closely and corrected as appropriate in order to prevent serious cardiac side-effects. In our case, the patient had an abnormal ECG, thought to be a consequence of the low potassium and magnesium, and required potassium and magnesium supplementation. No ECG changes associated with hypophosphataemia were noticed (QRS widening, T wave peaking, PR prolongation, torsades de pointes).

With diabetic and non-diabetic insulin overdose, serial measurements of insulin plasma levels can help to adjust the glucose infusion rate. Maintaining euglycaemia is important as prolonged glucose excess can lead to hepatic steatosis, abnormal liver function results and lactic acidosis (11). Kolterman et al. revealed, using in vivo studies, the relationship between plasma insulin levels and plasma glucose disposal (12). Based on this, a glucose titration protocol was elaborated by Lee et al. (Table 1)

(13). In our case the insulin plasma concentration was not measured on admission, but based on average glucose requirements to maintain euglycaemia (aprox. 180 mls of glucose 20% per hour) and body weight (75kg) we may approximate that the patient's insulin plasma levels were more than 700 mU/L. The average glucose use in the first 12 hours was aprox. 8 mg/kg/h, almost 4 times more that the normal adult rate.

Analysing 33 cases (all ethnic Japanese), Ohyama et al. hypothesised that the duration of the hypoglycaemia depends on the dose of insulin rather than the type of insulin used in the overdose. The correlation formula is $y=0.045X$, where y – time (h) and X – insulin dose (units) (9). According to this, in our case the duration of hypoglycaemia should have been approx. 45 hours. However, the glucose infusion was discontinued 28 hours after the overdose. A possible explanation for the difference could be the altered potency of the insulin due to improper storage.

Apart from pharmacological interventions, surgical excision of the injected site was used for high-dose long-acting insulin overdoses and unstable glucose levels (14).

The two most significant predictors of unfavourable outcome after insulin overdose are: medical treatment delayed for over 6 hours and mechanical ventilation delayed for more than 48 hours (2). In the same study, the authors reported a significant correlation between the duration of ICU stay and delay in therapy, a weak correlation between the duration of glucose infusion and the amount of injected insulin, and no significant correlation between plasma insulin levels and the amount of injected insulin. Also, the dose and type of insulin can predict the duration but not the severity of hypoglycaemia (2).

Alcohol co-administration leads to a poorer prognosis by inhibiting gluconeogenesis and increasing sensitivity to insulin (15). Also, alcohol increases the production of lactic acid. In our case it was noticed that the elevated lactic acid level on presentation normalised with therapy.

Because insulin overdose can lead to poor outcomes if not treated promptly, it should be considered as a differential diagnosis in hypoglycaemic patients when blood glucose fails to correct as expected. ■

Insulin plasma levels (mU/L)	Glucose infusion rate
100-300	2 mg/kg/min
600-800	8.75 mg/kg/min
>1000	10 mg/kg/min

TABLE 1. Glucose infusion rate based on the insulin plasma levels (after Lee et al.).

LEARNING POINTS:

- Insulin overdose carries significant morbidity if not treated promptly (eg. hypoglycaemic encephalopathy)
- Delayed medical treatment predicts an unfavourable outcome
- Glucose replacement should be administered promptly, targeting euglycaemia

- Monitor and correct electrolytes appropriately; ECG is useful in this instance
- Prolonged over-correction (hyperglycaemia) is detrimental for the liver function.

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