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Peripheral Intravenous Insulin Infusion Infiltration Presenting as “Insulin Resistance”

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Abstract

Objective—We present the case of a 66-year-old woman who developed hypoglycemia following the prolonged infiltration of a high dose continuous peripheral intravenous insulin infusion.

Study Selection—Case report.

Data Synthesis—The patient was post-lung transplantation and was receiving high doses of glucocorticoids. Despite increasing the peripheral intravenous insulin rate, hyperglycemia persisted. We discovered that the intravenous insulin infusion line infiltrated, resulting in a large subcutaneous insulin depot, estimated to be 450 units of regular insulin. She subsequently experienced prolonged hypoglycemia that was managed with concentrated dextrose containing fluids. In our literature search, there were no similar case reports. The literature on insulin overdose, usually from suicide attempts, can help guide the management of iatrogenic hyperinsulinemic hypoglycemia. Important management considerations include anticipated duration of hypoglycemia, supplemental glucose, fluid management, and electrolyte monitoring.

Conclusion—Peripheral intravenous insulin infusion infiltration should be considered when patients do not respond to increasing rates of insulin infusion.

Keywords

insulin; intravenous infusions; drug overdose; hypoglycemia; diabetes mellitus; extravasation

Introduction

Medication errors involving insulin can have serious clinical consequences, which is why insulin is on the Institute for Safe Medical Practices list of high-alert medications in the acute care setting (1). While hyperglycemia as a result of insulin underdosing or omission is more common, overdosing insulin causing hypoglycemia is also a relatively frequent insulin medication error (2). Infiltration of a peripheral intravenous (IV) insulin infusion represents

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a unique clinical scenario of insulin overdose. Initially, patients may appear “insulin resistant” as the insulin infiltrating into the subcutaneous tissue will have a slower onset of action compared to intravenous insulin. If not recognized, the rate of the insulin infusion may be continually increased in response to hyperglycemia and this cycle may lead to inappropriately high amounts of insulin administration. It may take several hours before the IV site is visually abnormal and by then a large depot of subcutaneous insulin will exist, placing the patient at risk for prolonged hypoglycemia.

Based on our literature review, there are no case reports of hypoglycemia from insulin overdose by insulin infusion infiltration. In this case report, we will present a case of peripheral IV insulin (regular) infusion infiltration resulting in hypoglycemia, and provide a brief overview of insulin overdose as well as potential management options.

Case Report

A 66-year-old 90 kg Caucasian woman with a history of interstitial lung disease was admitted for worsening dyspnea on exertion. She subsequently received a bilateral lung transplant. Prior to admission she was prescribed prednisone 20 mg daily for her lung disease. She had no prior personal or family history of diabetes mellitus.

The patient's serum glucose levels and rates of the regular insulin and dextrose infusions are shown in Figure 1. Post-transplantation, she received methylprednisolone 1000 mg IV $\times$ 1, then 125 mg IV every 8 hours $\times$ 4, then the equivalent of 16 mg IV daily. She became hyperglycemic and was started on an insulin infusion (regular insulin) via an antecubital 16 gauge peripheral IV. She remained hyperglycemic despite insulin infusion up titration and 12 hours after initiating the insulin infusion, she had peak blood glucose of 420 mg/dL. The patient was on the IV insulin infusion for approximately 24 hours before the blood glucose decreased below 200 mg/dL. The highest rate of the insulin infusion was 22.2 units/hour at 33 hours. The insulin infusion was stopped once the patient was noted to have infiltration of the peripheral IV catheter. She had received approximately 450 units over 38 hours. Based on the lack of glycemic response to the insulin infusion, the peripheral IV line may have infiltrated from the beginning of the infusion, although this is difficult to interpret in the setting of postoperative high dose glucocorticoids.

Over the following 24 hours, she was intermittently hypoglycemic, with the lowest blood glucose of 61 mg/dL. She required a 20% dextrose infusion at 50 mL/hr with additional dextrose 12.5 gram boluses as needed. Her renal function was normal other than a transient post-operative decrease of estimated glomerular filtration rate 30-50 mL/min/1.73 m². She had normal hepatic function and there was no evidence of sepsis. She was hypokalemic to 3.4 mmol/L (normal 3.8-5.1 mmol/L), and hypophosphatemic to 1.9 mg/dL (normal 2.6-4.9 mg/dL). Serum magnesium was 2.0 mg/dL (normal 1.8-2.4 mg/dL) and hemoglobin A1c was 5.3% (normal 4.3-5.6%). Trends of the serum electrolytes are demonstrated in Figure 1, although interpretation is limited by the fact that electrolyte replacement could not be determined during chart review. An insulin level was drawn 8 hours after the insulin infusion was discontinued. Results returned two days later and the serum insulin level was elevated at 61.9 mU/L (normal 3.3-22.1 mU/L). Her blood glucose eventually normalized with

decreased dextrose requirements. Approximately 34 hours after the IV insulin infusion was stopped, the high dose dextrose infusion began to be titrated down, and it was eventually stopped at 74 hours.

Discussion

Given the common use of peripheral IV insulin infusions in the hospitalized setting, we were surprised that there are no case reports of insulin overdose due to insulin infusion infiltration. A similar state of hyperinsulinemic hypoglycemia is seen with overdose due to subcutaneous insulin administration, usually as the result of an attempted suicide. In both conditions, with large doses of insulin, the prolonged hypoglycemia is out of proportion to its textbook pharmacokinetics. For example, a 39-year-old non-diabetic woman overdosed on 300 units of subcutaneous lispro insulin and required supplemental glucose for more than 11 hours (3), two times longer than would be expected from the usual pharmacodynamics properties (4). Prolonged hypoglycemia could be due to the cumulative effect of insulin or delayed insulin absorption due to local hypo-perfusion from mechanical pressure (5). Theoretically, very high insulin levels may overwhelm receptor-mediated clearance, especially in the liver, which could result in a prolonged half-life.

For these reasons, authors such as Ohyama et al have suggested that the duration of hypoglycemia may be better estimated by the total dose of insulin rather than the insulin type (5). Based on a review of 33 Japanese cases of subcutaneous insulin overdose that range from 50 units of regular and premixed insulin to 3000 units of NPH insulin, they report a correlation of recovery time in hours from hypoglycemia (y) and insulin units (x) as $y = 0.045x$ ($r = 0.88$, $p < 0.001$), and with cases of less than 1500 units of subcutaneous insulin, $y = 0.062x$ ($r = 0.88$, $p < 0.001$). For our patient, the latter equation would predict a recovery time of 28 hours. This slightly underestimates the 34 hours of high rates of dextrose requirements, but is likely within the error of the equation. This equation may be less useful in situations where the exact amount of administered insulin is unknown, such as the exact time an IV insulin infusion infiltrates. Others have suggested using plasma insulin concentrations to help determine basal glucose infusion rate (6). Clinical utility of serum insulin levels may be limited by laboratory processing time. At our institution, serum insulin is processed weekly with same day results, although with laboratory approval, immediate processing is available. In addition, if the patient had previously received exogenous insulin, then endogenous insulin antibodies may interfere with the insulin assay (7).

Other similarities between IV insulin infusion infiltration and subcutaneous insulin overdose include consideration of patient specific factors such as renal and hepatic function, underlying diabetes mellitus, or other states of insulin resistance such as from glucocorticoids. Patients with a history of diabetes may have insulin auto-antibodies or a decreased counterregulatory hormone response which may produce a different response to insulin overdose than in those without this history.

While experiences from subcutaneous insulin overdose are helpful in determining management in IV insulin infusion infiltration, several important differences remain. IV insulin infusion infiltration more likely occurs over several hours in a compartment whereas

subcutaneous insulin overdose is more likely to occur in depots during discrete episodes. These differences may result in distinct pharmacokinetics. Also, IV insulin infusion infiltration occurs in the hospital setting while subcutaneous insulin overdose is more likely to occur in the community with a more variable time of presentation to medical care. As a result of closer monitoring, patients who are hypoglycemic due to IV insulin infusion infiltration will likely have shorter durations of untreated hypoglycemia and better outcomes. For example, in one study, a significant independent predictor of poor neurological outcomes after subcutaneous insulin overdose included delay in treatment of greater than 6 hours (8). This treatment delay would be unlikely to occur in the setting of frequent blood glucose checks required with IV insulin infusion protocols.

Immediate therapy should include dextrose containing solutions and close monitoring of blood glucose and electrolytes. Given frequent monitoring and potential preference for central venous access to deliver highly concentrated dextrose solutions, admission to an intensive care unit should be considered. If patients are NPO, they may require large amounts of dextrose fluid, which will need to be carefully managed in patients who are sensitive to volume overload. Clinicians may be tempted to avoid hypoglycemia by giving more dextrose than what is required for the degree of hyperinsulinemia. In the setting of hyperinsulinemia and excessive carbohydrate intake, de novo lipogenesis could occur resulting in acute hepatic steatosis (9).

Once the hyperinsulinemia resolves, it can be difficult to determine when a non-diabetic no longer requires supplemental dextrose. While patients with diabetes will become hyperglycemic in response to excess dextrose, patients without diabetes will remain euglycemic and the clinician may mistakenly believe that the patient continues to have a dextrose requirement. In high dose insulin therapy for calcium channel blocker and beta-blocker overdose, there is a similar degree of uncertainty for true dextrose requirements. Although dextrose management is not well described in this literature, successful protocols may offer guidance in management. A prospective observational study using a hyperinsulinemia/euglycemia protocol was performed in calcium channel blocker overdose in seven patients in the critical care setting (10). The protocol recommends regular blood glucose monitoring and IV dextrose to maintain serum glucose from 110-150 mg/dL. In their study, one patient had a blood glucose < 65, which was not clinically significant, and otherwise no hypoglycemia. When considering supplemental dextrose down titration in IV insulin infusion infiltration, a relatively restrictive target serum glucose range could guide titration.

Close monitoring of electrolytes is critical as insulin enhances intracellular shifts in potassium, phosphorus and magnesium (11). Similarly, in healthy individuals undergoing hyperinsulinemic-euglycemic clamp study, hypokalemia, hypophosphatemia and hypomagnesemia have been observed (12, 13). These electrolyte disorders may result in neuromuscular, central nervous, and cardiovascular complications that require close monitoring. In addition, common nursing practice is to apply compression and/or heat to an area after IV infiltration. This needs to be avoided for infiltration of an IV insulin infiltration as this may increase the rate of insulin absorption.

While glucose administration is the standard of care, there are case reports of off-label drugs used in subcutaneous insulin overdose (14, 15). In these reports, it is difficult to interpret the effectiveness of glucagon administration for example, given glucose co-administration and gradual insulin clearance. In most circumstances, glucose administration and supportive care are likely sufficient in caring for these patients.

Conclusion

Peripheral IV insulin infusion infiltration is likely an underreported phenomenon with significant clinical consequences including hypoglycemia and prolonged hospitalization. Given the paucity of literature, clinical experience with subcutaneous insulin overdose may be translatable, although subtle differences exist between the two conditions. In clinical practice, insulin infusion protocols should include checking the IV site for infiltration if the patient does not respond to increasing rates of insulin infusion.

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Figure 1.

Serum glucose trends after intravenous insulin infusion infiltration. Reference range: serum potassium 3.8-5.1 mmol/L, serum phosphorus 2.6-4.9 mg/dL, serum magnesium 1.8-2.4 mg/dL.