

RAPID DESENSITIZATION WITH INTRAVENOUS INSULIN IN A PATIENT WITH DIABETIC KETOACIDOSIS AND INSULIN ALLERGY

Shirley Shuster, MD¹; Rozita Borici-Mazi, MD, FRCPC²;
Sara Awad, MB, FRCPC³; Robyn L. Houlden, MD, FRCPC³

ABSTRACT

Objective: We report a case of insulin desensitization in a patient with known allergy to multiple insulin preparations who presented with diabetic ketoacidosis (DKA).

Methods: Clinical and laboratory data, and desensitization protocols are presented.

Results: A 65-year-old woman with type 2 diabetes and a documented insulin allergy presented with severe DKA. She was managed initially with intravenous (IV) fluids, sodium bicarbonate, and hemodialysis. An intradermal skin test was positive for 0.01 units/mL of human regular insulin. A rapid desensitization protocol for IV human regular insulin was initiated after pretreatment with methylprednisolone, ranitidine, montelukast, and cetirizine. An initial dilution of 1 unit of insulin in 100,000 mL of 0.9% sodium chloride was started at 5 mL/hour IV. The dilution was increased at 60-minute intervals to 1 unit/10,000 mL, 1 unit/1,000 mL, 1 unit/100 mL, 1 unit/10 mL, then 1 unit/1 mL. The dose was then increased from 1 to 7 units/hour (0.1 units/kg body weight/hour). The anion gap closed after 24 hours, and overlapping desensitization was started for subcutaneous (SC) human regular insulin starting with 0.00001 units with a gradual increase to 7 units before meals and 6 units at bedtime over 5 days.

There were no anaphylactic reactions to IV or SC insulin. She was discharged with human regular insulin SC 4 times daily, oral montelukast, cetirizine, diphenhydramine as needed, and an epinephrine pen. No allergic reactions were reported at follow-up visits.

Conclusion: Rapid insulin desensitization is possible to allow treatment of DKA with human regular insulin IV in patients with known insulin allergy. (AACE Clinical Case Rep. 2020;6:e147-e150)

Abbreviations:

CSII = continuous subcutaneous insulin infusion;
DKA = diabetic ketoacidosis; IV = intravenously; SC = subcutaneous

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes mellitus and is characterized by hyperglycemia, ketonemia, and metabolic acidosis (1). It results from an absolute or relative insulin deficiency and an increase in counter-regulatory hormones in the presence of a precipitating factor, causing increased lipolysis and ketogenesis. Management of DKA involves fluid resuscitation, electrolyte replacement, and intravenous (IV) insulin therapy, which is important to suppress ketogenesis (1). Hypersensitivity reactions to human insulins and insulin analogues are uncommon with estimates ranging from 0.1 to 3 percent of patients (2,3). They are most commonly due to additives in the insulin preparation such as protamine or zinc, and less commonly to the insulin molecule itself mainly through the development of insulin-specific IgE antibodies (4). The clinical presentation can range from local injection site reactions to severe anaphylaxis (5). Allergies due to the development of insulin-specific antibodies necessitate insulin desensitization, and several

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From the ¹Department of Medicine, the ²Division of Allergy and Immunology, and the ³Division of Endocrinology and Metabolism, Queen's University, Kingston, Ontario, Canada.

Address correspondence to Dr. Robyn Houlden, Division of Endocrinology, Kingston General Hospital, 76 Stuart Street, Kingston, ON, K7L 2V7, Canada. E-mail: houldenr@queensu.ca.

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case reports have demonstrated successful desensitization protocols using a series of gradually increasing subcutaneous (SC) doses of a rapid-acting insulin analogue (6-8), or continuous subcutaneous insulin infusion (CSII) delivered through an insulin pump (9-11). There have only been a few case reports demonstrating successful desensitization with IV insulin alone (12), or in combination with SC insulin delivered by CSII (13,14). There have been only 2 case reports outlining an insulin desensitization protocol using IV insulin in patients presenting with DKA and insulin allergy (15,16).

CASE REPORT

A 65-year-old woman presented with DKA with a blood glucose of 34 mmol/L (normal, 3.5 to 11.1 mmol/L), peripheral venous blood gas pH of 6.91 (normal, 7.32 to 7.43), a serum bicarbonate of 4 mmol/L (normal, 22 to 29 mmol/L), an anion gap of 28 (normal, 8 to 12), a serum hydroxybutyrate of 12.05 mmol/L (normal, 0 to 0.37 mmol/L), and a serum creatinine of 76 μ mol/L (normal, 0 to 85 μ mol/L). She had a 6-year history of type 2 diabetes with absent antidiabetic acid decarboxylase (anti-GAD-65) antibodies and normal C-peptide and insulin levels at diagnosis. She had been intolerant to metformin (diarrhea), glucagon-like peptide 1 (GLP-1) receptor agonists (nausea), and dipeptidyl peptidase IV (DPP-4) inhibitors (fatigue). Sodium-glucose cotransporter-2 (SGLT2) inhibitors and sulfonylureas had not been effective in managing hyperglycemia. Introduction of insulin therapy had been associated with documented hypersensitivity to multiple insulin preparations including levemir, glargine, degludec, neutral protamine Hagedorn (Humulin NPH), aspart, and lispro. Her symptoms consisted of a sudden onset of erythema, swelling, and pruritus at the injection site, as well as associated chest pain, wheezing, abdominal pain, and nausea within 1 hour after SC administration, and had commenced within a few days of starting each insulin preparation. Intradermal skin testing was positive at a dilution of 1:10 (0.1 unit/mL) for all insulin preparations listed above. Skin testing was also associated with facial erythema and nasal congestion. The patient had been offered but declined insulin desensitization in an inpatient setting.

Prior to the presentation of DKA, she had not taken any antihyperglycemic medication for 2 months, and had experienced polyuria, polydipsia, nausea, and weight loss for several days. The patient was admitted to the intensive care unit and treated with IV fluids and sodium bicarbonate, as well as hemodialysis given the severity of the metabolic acidosis and concern of anaphylaxis with administration of IV insulin. She was seen urgently by the allergy service, and intradermal skin testing was positive for human regular insulin (Humulin R). She was started on a desensitization protocol for IV human regular insulin after initiation of pretreatment and concomitant therapy including methylprednisolone 80 mg IV twice daily, cetirizine 10 mg orally twice daily, montelukast 10 mg orally once daily, ranitidine 150 mg orally twice daily, and diphenhydramine 50 mg orally as needed. She was given an initial dilution of 1 unit of human regular insulin in 100,000 mL of 0.9% sodium chloride IV at a rate of 5 mL/hour. The dilution was increased at 60-minute intervals to 1 unit in 10,000 mL, then 1 unit in 1,000 mL, then 1 unit in 100 mL, then 1 unit in 10 mL, then 1 unit in 1 mL, so that by 5 hours she was receiving 5 units/hour. No allergic reactions were noted during the rapid desensitization. The infusion was then increased by 1 unit per hour to a final rate of 7 units/hour (0.1 units of insulin IV per kg of body weight per hour). Dextrose at a concentration of 10% in water was started once blood glucose was less than 12 mmol/L.

The dose of methylprednisolone was tapered after the first 24 hours to 40 mg IV twice daily for 24 hours, then 20 mg IV twice daily for 24 hours, then 20 mg IV for 2 days, then discontinued. The anion gap normalized after 24 hours, and the overlapping insulin desensitization was started for SC human regular insulin as outlined in Table 1. IV insulin was discontinued after 4 days of SC insulin. After discontinuation of IV insulin, the patient experienced new onset of abdominal pain and nausea immediately after the scheduled dose of SC insulin, but treatment was continued and symptoms abated with time.

The patient was discharged home with SC human regular insulin, montelukast 10 mg once daily, cetirizine 10 mg once daily, diphenhydramine as needed, as well as an epinephrine auto injector 0.3 mg if needed for anaphylaxis. She was advised against missing doses of insulin and to contact the clinic immediately if she developed

Table 1
Desensitization Protocol for Subcutaneous (SC) Human Regular Insulin

Time	Dose of SC human regular insulin (units)					
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
8:00 AM	0.00001	0.01	2.0	5.0	6.0	7.0
12:00 PM	0.00001	0.1	4.0	5.0	6.0	7.0
4:00 PM	0.001	1.0	4.0	5.0	6.0	7.0
10:00 PM				5.0	6.0	6.0

any reactions. She was seen in follow-up 1- and 2-weeks post-discharge and reported good glycemic control and no allergic reactions.

DISCUSSION

Many protocols for insulin desensitization have been described in the literature, most commonly using small, increasing doses of SC insulin (6-8) or CSII (9-11), and less commonly IV insulin (12). These protocols have also included pretreatment regimens including antihistamines and corticosteroids. Only 2 published cases have reported successful insulin desensitization in patients presenting with DKA (15,16). Nguyen et al (15) described a case of a 58-year-old man with type 2 diabetes with a history of local reactions to SC insulin of pruritic wheals who presented in severe DKA refractory to IV fluids, bicarbonate, and hemodialysis (15). After 24 hours, he was treated with an IV regular insulin infusion at an initial rate of 0.1 units/kg/hour with no allergic reactions. After 2 weeks, he was transitioned to SC insulin with no symptoms at the injection sites. The authors postulated that identical insulin molecules could be associated with a different risk for hypersensitivity reactions depending on the route of injection. Bundy et al (16) reported a desensitization protocol for IV insulin used in a 50-year-old woman with insulin-dependent diabetes and DKA, with a history of anaphylactic reactions to multiple preparations of regular, intermediate-, and long-acting insulin administered SC (16). Skin prick testing was negative to regular insulin at 1 unit/mL. Serial dilutions of regular insulin were prepared at 1:10,000, 1:1,000, 1:10 and 1:1 of the standard 1 unit/mL concentration. The infusion was initiated at 0.00005 units/hour and doubled every 30 minutes to a final dose of 0.5 units/hour.

Our case is unique from the one of Bundy et al (16) in that our patient had positive skin testing to 0.01unit/mL of human regular insulin and in view of this was started on a higher dilution of 1 unit of human regular insulin in 100,000 mL. Secondly, our patient tolerated a more rapid increase in insulin dose (hourly 10-fold increase) and the final dose of IV insulin was higher (equivalent to 0.1 units/kg of body weight/hour) which is the dose typically used to treat DKA. Human regular insulin was selected as it is the most commonly used insulin for intravenous insulin therapy for DKA. Simultaneous desensitization procedures were performed with IV and SC human regular insulin to mitigate the risk for allergic reactions related to the route of injection. A comparative immunogenicity study of 3 brands of insulin in patients with type 1 diabetes showed an increase in the incidence of anti-insulin titer development in patients self-administering via the SC route as compared to IV administration (17). However, unlike the case of Nguyen et al (15), the simultaneous desensitization with SC insulin was started much earlier in the course of treat-

ment (24 hours versus 2 weeks). Our case report confirms that desensitization with IV insulin can be well-tolerated and may serve as a bridge to successful desensitization with SC insulin.

The mechanism of insulin desensitization is not fully understood but induction of anergy or depletion of specific T cells, induction of T regulatory cells, and modulation of antibody production by cytokines have been postulated (18). Recent case reports have demonstrated the role of omalizumab, an anti-IgE monoclonal antibody, for the management of insulin allergy after multiple attempts of desensitization; however, this was not tried in our patient due to the successful management with insulin desensitization (19,20).

CONCLUSION

As anaphylaxis and DKA are both life-threatening conditions, it is important to expand the literature of successful insulin desensitization protocols for patients in DKA. Our case outlines an effective protocol of rapid desensitization for IV insulin that allows treatment of DKA with human regular insulin IV.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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