# Diabetic ketoacidosis after the treatment of anaphylaxis

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## Summary

Anaphylaxis is a rapidly progressive potentially lethal condition, and epinephrine is the most crucial medication in its treatment. In this study, we present a case of diabetic ketoacidosis in a young woman that was precipitated by the administration of epinephrine to treat anaphylaxis. This patient had diabetes mellitus and poor glycemic control and developed ketoacidosis despite having evidence of ongoing endogenous insulin production and having been treated with exogenous long-acting insulin less than 24 h prior to the event. This is a rare, serious, adverse side effect of life-saving medication. This report demonstrates that the risk of diabetic ketoacidosis should be considered when administering epinephrine to patients with diabetes, even in the absence of complete insulin deficiency.

**Learning points:**

- Epinephrine directly suppresses insulin secretion, stimulates lipolysis, and causes ketone body generation.
- High-dose catecholamine administration can cause unexpected diabetic ketoacidosis in patients with risk factors.
- Early administration of insulin may not protect patients from developing ketoacidosis in the setting of high-dose catecholamine administration.

## Background

This case report demonstrates a rare and severe adverse effect of a commonly used medication class. Awareness of the potential for diabetic ketoacidosis in patients being treated with catecholamines may improve outcomes in the treatment of severe anaphylaxis or shock.

## Case presentation

An 18-year-old American Black female was admitted to the hospital for drainage of a pilonidal abscess. At admission, she also had evidence of a urinary tract infection, chlamydia cervicitis, and bacterial vaginosis. Her history was notable for atypical diabetes mellitus with features of both type 1 and type 2 diabetes (diagnosed 4 years earlier) and anaphylaxis to tomatoes. Her hemoglobin A1c was 13.2% (121 mmol/mol IFCC) suggesting chronically poor glycemic control, and during the admission, she was continued on her home dose of insulin glargine 20 units (0.3 units/kg) nightly with a rapid-acting insulin correction factor of 1 unit per 25 mg/dL (1.4 mmol/L) glucose higher than 150 mg/dL (8.3 mmol/L) given every 4–6 h in the setting of poor oral intake. After drainage of her abscess, she was kept on maintenance non-dextrose containing i.v. fluids with 20 mEq/L potassium chloride (KCl) and her blood glucose ranged from 168 to 347 mg/dL (9.3 to19.3 mmol/L).

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D S Brenner and others

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The morning after her procedure, she ate breakfast and received her prescribed dose of rapid-acting insulin. Two hours later, she was administered trimethoprim/sulfamethoxazole intravenously and 30 minutes later developed tongue itching which progressed to audible wheezing, tachypnea, and nasal flaring. She rapidly developed facial edema, inaudible voice, somnolence, and worsening respiratory distress. Aggressive treatment for anaphylaxis was initiated including three doses of i.m. epinephrine 0.3 mg over 15 min. She was also started on continuous i.v. epinephrine at 0.1 mg/h, although this was rapidly discontinued and only delivered a total dose of epinephrine 0.02 mg i.v. She also received diphenhydramine 50 mg, famotidine 20 mg, hydrocortisone 100 mg (all given i.v.), continuous nebulized albuterol and was briefly placed on non-invasive positive pressure ventilation. After these treatments, her respiratory distress, mental status, and facial swelling improved. During this period, she was due for her noon dose of rapid-acting insulin, but she neither ate nor received the insulin due to the anaphylactic episode.

## Investigation

Fifteen minutes after the symptoms of anaphylaxis began to improve, the patient's laboratory tests were notable for sodium 137 mmol/L, potassium 3.1 mmol/L, chloride 102 mmol/L, bicarbonate 18 mmol/L, blood urea nitrogen (BUN) 6 mg/dL (2.1 mmol/L), serum creatinine 0.5 mg/dL (44 μmol/L), glucose 257 mg/dL (14.3 mmol/L), and anion gap 17 mmol/L. At that time, her pH was 7.36 and $P_aCO_2$ was 33 mmHg. Although the patient's anaphylactic symptoms improved, over the subsequent 4 h, the patient reported persistent chest, abdomen, and thigh pain, as well as dyspnea and hypoxemia to an oxygen saturation of 91%.

Four hours after the anaphylactic reaction, repeat studies revealed sodium 134 mmol/L, potassium 3.0 mmol/L, chloride 97 mmol/L, bicarbonate 12 mmol/L, BUN 6 mg/dL (2.1 mmol/L), serum creatinine 0.6 mg/dL (53 μmol/L), glucose 351 mg/dL (19.5 mmol/L), anion gap 25 mmol/L, pH 7.36, $P_aCO_2$ 33 mmHg, urine ketones over 80 mg/dL (13.8 mmol/L), and whole blood lactic acid of 6.9 mmol/L, consistent with diabetic ketoacidosis. Serial chest X-rays demonstrated significant pulmonary edema and a right-sided pleural effusion.

## Treatment

She was started on i.v. normal saline with potassium chloride as well as an insulin infusion at 0.1 units/kg/h

as per our pediatric diabetic ketoacidosis protocol. She was also treated with hydrocortisone 20 mg every 6 h as continued treatment for severe anaphylaxis. Her hypoxemia and pleural effusions were treated with non-invasive positive pressure ventilation and resolved over 8 h. Her anion gap began to narrow after 12 h of treatment and ultimately normalized after 23 h.

## Outcome and follow-up

The patient was transitioned to an oral diet with her home insulin regimen without complications and discharged for outpatient follow-up of her pilonidal abscess and other infections.

## Discussion

The abrupt development of diabetic ketoacidosis after epinephrine treatment in this patient was unusual and likely related to the relatively rapid administration of repeated doses that was required to treat her anaphylaxis. While there is only a single previous case of anaphylaxis-induced diabetic ketoacidosis (1), there are plausible physiologic mechanisms. Epinephrine suppresses insulin secretion and directly stimulates lipolysis, two key factors in diabetic ketoacidosis physiology. Adult humans infused with epinephrine experience rapid and dramatic suppression of insulin secretion, even in the setting of iatrogenic hyperglycemia (Fig. 1) (2). Perhaps even more importantly, epinephrine is a potent stimulator of lipolysis, and the released fatty acids can serve as precursors for hepatic ketone body formation during a low insulin state (Fig. 1). Furthermore, the infusion of catecholamines directly stimulates ketone body generation through an insulin-independent pathway (3, 4). Both our patient and the previously reported patient had received long- or intermediate-acting insulin prior to the anaphylaxis, suggesting that the epinephrine-induced lipolysis and ketone body formation may be the more important mechanism for the development of ketoacidosis in these patients. Additionally, both of these patients had poor glycemic control, suggesting that this may be an important risk factor.

Several other mechanisms could have contributed to the development of ketoacidosis in this patient. Although catecholamine-mediated lipolysis and insulin suppression was likely the primary driver of ketoacidosis, in this patient, it is possible that decreased hepatic and muscular insulin sensitivity mediated by beta-adrenergic activation (5) played a role in exacerbating this episode. Additionally,
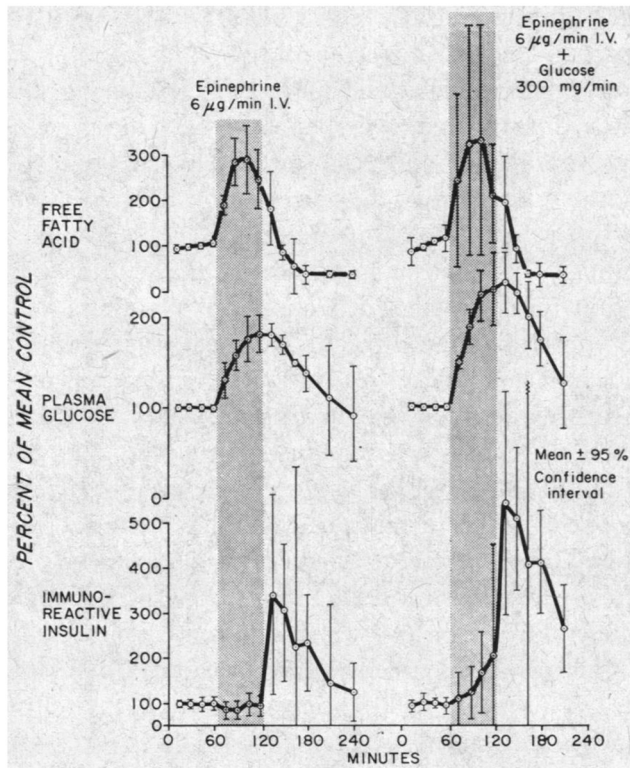
**Figure 1**
Reprinted with permission (2). Infusion of epinephrine leads to suppression of insulin secretion and hyperglycemia. In healthy human volunteers, the infusion of epinephrine alone (left traces) leads to elevated serum free fatty acid and glucose concentrations with concurrent suppression of insulin secretion. Simultaneous infusion of glucose and epinephrine (right traces) still leads to elevated free fatty acid and glucose concentrations with concurrent suppression of insulin secretion. In both sets of traces, once the epinephrine is discontinued, there is an abrupt increase in insulin secretion.

while we have focused on the role of epinephrine in this case, she did also receive i.v. corticosteroids. Corticosteroids could have contributed to ketoacidosis by increasing insulin resistance and suppressing insulin secretion (6), although higher doses of corticosteroids are frequently administered to patients without resultant ketoacidosis. It is also possible that the patient's poor baseline glycemic control could have predisposed her to develop ketoacidosis in the setting of physiological stressors, but she never had any prior episodes of ketoacidosis; not even during a prior 1-month period during which she took no insulin at all. Additionally, she had no signs, symptoms, or laboratory values consistent with ketoacidosis prior to her treatment with epinephrine which suggests that the ketoacidosis was directly linked to the medication administered.

Diabetic ketoacidosis in response to epinephrine is a significant complication to a standard component of the critical care pharmacy. While this complication appears to be uncommon, the incidence of diabetes in the United States is increasing (7) which suggests that more patients will be at risk. Additionally, the previously reported case demonstrated that epinephrine can induce ketoacidosis in a patient with type 1 diabetes. This patient had features of both type 1 and type 2 diabetes. She had positive glutamic acid decarboxylase antibody (> 30 U/mL; reference interval < 1.0 U/mL) consistent with type 1 diabetes. But she had risk factors for type 2 diabetes including obesity with a BMI of 30.7 kg/m² and a family history that included multiple family members (including her brother) with non-insulin-treated diabetes. She also had evidence of ongoing endogenous insulin production; she did not develop ketoacidosis during a 1-month period when she took no insulin 1 year prior to this episode, and her c-peptide level was low normal (0.83 ng/mL; reference range 0.80–3.85 ng/mL) 8 months after this episode. Thus, this case demonstrates that a much larger population of patients with diabetes who may still have endogenous insulin secretion are also at risk for ketoacidosis during treatment with catecholamines. Additionally, while in the previously documented case the patient reported taking intermediate-action insulin prior to presentation, the possibility remains that the insulin was not accurately dosed, administered, or reported. In the present case, the long-acting insulin was administered by hospital staff, eliminating any uncertainty and making it clear that ketoacidosis developed despite the presence of long-acting insulin. While both reported cases involve epinephrine administration for anaphylaxis, epinephrine is also used in many other situations including for hemodynamic support in shock. As a result, critically ill patients with diabetes receiving epinephrine infusions may also be at risk for ketoacidosis and acute decompensation. Although the only reported cases of this event both involve epinephrine, norepinephrine is also a strong α-adrenergic agonist and is very commonly used for hemodynamic support in critically ill patients. Based on the mechanism postulated above, patients with diabetes mellitus receiving large doses of catecholamines should be monitored for the development of diabetic ketoacidosis.

**Patient consent**

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient.

**Author contribution statement**

Drs Brenner and Kleinman gathered patient data, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Manzo and Bembea reviewed and revised the manuscript. Dr Cooke consented the patient for publication, gathered patient data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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