Capivasertib-induced diabetic ketoacidosis in a patient with stage IV breast cancer: A case report

Payton Mueller, PharmD, Wellstar MCG Health, Augusta, GA, USA

Zoanne Harlas, PharmD, BCCCP, St. Joseph's/Candler Health System, Savannah, GA, USA

John Carr, PharmD, BCPS, BCCCP, St. Joseph's/Candler Health System, Savannah, GA, and University of Georgia College of Pharmacy, Athens, GA, USA

Purpose: Capivasertib is a selective pan–protein kinase B (AKT) inhibitor for hormone receptor–positive breast cancer. Cellular phosphoinositide 3-kinase and AKT activity plays an important role in glucose homeostasis. Additionally, AKT has a role in regulating hepatic glycogenolysis and glucose uptake via glycogen synthase kinase-3. Previous studies have found the incidence of hyperglycemia with capivasertib to be 13% to 49%.

Summary: We report the case of a 74-year-old female with capivasertib-associated diabetic ketoacidosis (DKA) with evidence of extreme insulin resistance. The patient was started on capivasertib for stage IV breast cancer and experienced hyperglycemia 8 days after resuming the medication. Her initial blood glucose level was 632 mg/dL, with an anion gap of 29 mEq/L and a pH of 7.22. She was managed according to the institution's DKA protocol with a peak insulin infusion rate of 130 units/h (1.76 units/kg/h). The patient's blood glucose level improved after 40 hours on the continuous insulin drip, and she was discharged after 10 days with a prescription for sliding scale insulin and the instruction to discontinue capivasertib.

Conclusion: This case report provides evidence of extreme insulin resistance in a patient treated with capivasertib. Guidance on the management of acute hyperglycemia secondary to capivasertib is not currently established, and further research on optimal management of these acute crises is needed.

Keywords: capivasertib, diabetic ketoacidosis, hyperglycemia, insulin resistance, phosphoinositide 3-kinases, protein kinase B

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Endocrine therapy in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor is the preferred first-line treatment option for patients with metastatic hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer.[1] Treatment options for disease progression on endocrine therapy and a CDK4/6 inhibitor are less clear. Protein kinase B (AKT) plays a key role in the phosphoinositide 3-kinase (PI3 K)/AKT pathway, which is commonly activated in HR-positive/HER2-negative advanced breast cancer. Inhibition of the PI3 K/AKT pathway can cause adverse events such as hyperglycemia, rash, stomatitis, diarrhea, nausea, and fatigue.

Capivasertib is a potent, selective pan-AKT inhibitor and has been shown to improve progression-free survival in combination with fulvestrant for patients with HR-positive advanced breast cancer who have had disease progression with aromatase inhibitor therapy with or without CDK4/6 inhibition.[1] It is currently approved for the treatment of patients with tumors positive for PI3 K/AKT, AKT1, and phosphate and tensin homolog (PTEN) alterations.[2]

An analysis of the CAPItello-291 study evaluating adverse events with capivasertib found that 16.9% of

Address correspondence to Dr. Mueller (Payton.mueller@cuw.edu).

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patients in the capivasertib/fulvestrant group developed hyperglycemia compared to 4% of patients in the placebo/fulvestrant group. Additionally, only one case of diabetic ketoacidosis (DKA) was reported in the capivasertib/fulvestrant group (0.3%).[1] The median time to onset of hyperglycemia in this analysis was 15 days. Risk factors for hyperglycemia included a body mass index of 30 kg/m^2 or higher and a history of diabetes mellitus. Previous studies have cited the incidence of hyperglycemia with capivasertib as being between 13% and 49%.[3-8]

Tyrosine kinase inhibitors have been associated with hyperglycemia due to decreased insulin sensitivity.[9] A previous case report detailed capivasertib-induced DKA in a patient without a history of diabetes mellitus.[10] In this case, the patient developed persistent hyperglycemia with blood glucose concentrations of 600 to 700 mg/dL for 48 hours despite treatment with continuous intravenous (IV) insulin after starting capivasertib and fulvestrant 10 days before. The patient was treated with IV fluids and insulin therapy starting at 0.1 units/kg/h and titrated according to the institution's DKA protocol. The patient's course was complicated by renal failure. Ultimately, the patient and the family decided against further invasive interventions and pursued comfort care. Here we report the case of a 74-year-old female with capivasertib-associated DKA with evidence of insulin resistance that required off-protocol management.

KEY POINTS

- In previous studies, capivasertib, a selective pan–protein kinase B (AKT) inhibitor for hormone receptor–positive breast cancer, has been associated with hyperglycemia.
- This case report summarizes the presentation of a 74-year-old female with capivasertib-associated diabetic ketoacidosis with evidence of extreme insulin resistance that required off-protocol management.
- Guidance on the management of acute hyperglycemia secondary to capivasertib is not currently established, and further research on optimal management of these acute crises is needed.

Case report

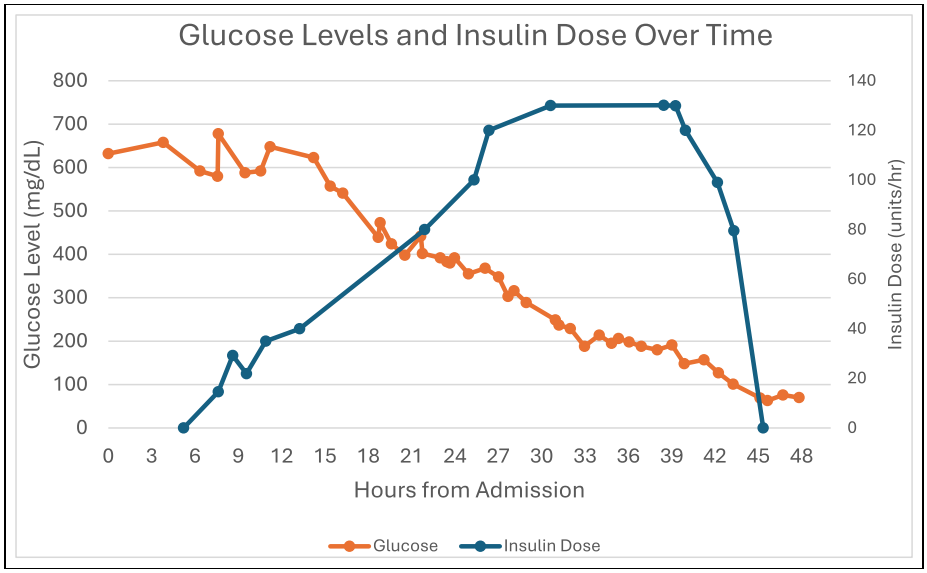
A 74-year-old female with a medical history significant for stage IV breast cancer, hyperglycemia secondary to chemotherapy, and diet-controlled type 2 diabetes presented with dizziness, lightheadedness, and hyperglycemia after recently resuming capivasertib therapy for stage IV breast cancer 8 days before admission. The patient also reported xerostomia, polydipsia, and altered mental status in addition to blood glucose readings of 400 to 500 mg/dL on her home glucose monitor. As part of her chemotherapy regimen, the patient was prescribed capivasertib 200 mg twice daily for 4 days per week in addition to fulvestrant. She was also prescribed metformin prophylactically for hyperglycemia but had not been taking it due to previous intolerance. She was not taking any additional medications for diabetes before her hospitalization, and, according to available records, she had not been prescribed insulin previously. The patient had previously been instructed to hold capivasertib for 22 days after her blood glucose concentration at an oncology visit was 436 mg/dL. She denied any additional symptoms at that time. The hyperglycemia resolved by her next oncology appointment, and capivasertib was resumed at the same dose without metformin prophylaxis, with instructions to monitor her blood glucose at home. This reinitiation of capivasertib aligns with information available in the package insert.[11] The patient had taken capivasertib as prescribed before presenting to the emergency department. She had taken a dose the morning of her hospital presentation and was on day 3 of her scheduled doses.

Upon arrival, the patient had a blood glucose concentration of 632 mg/dL with an anion gap of 29 mEq/L and pH of 7.22. She was started on an insulin drip at 0.1 units/kg/h (7.4 units/h), titrated according to the institution's DKA protocol. However, due to the insulin requirements exceeding the protocol's maximum, the protocol was amended by the attending physician with input from the clinical pharmacist to meet the patient's needs. Capivasertib was also held at the time of admission, and the patient was admitted to the intensive care unit. The patient's blood glucose concentrations and insulin titration are summarized in Figure 1. The insulin infusion rate peaked at 1.76 units/kg/h (130 units/h) approximately 9 hours after therapy initiation. The patient's anion gap closed approximately 26 hours after the insulin infusion was started. The patient's blood glucose concentrations improved after approximately 40 hours on the continuous insulin infusion, and she was transitioned off of the insulin drip to sliding scale insulin but ultimately required only one administration approximately 3 days after the insulin drip was discontinued. Although high-dose insulin has been proposed as a potential cause of cardiac arrhythmias, no cardiac sequalae were observed at any time during this patient's hospital stay.[12] She was discharged after 10 days with a prescription for sliding scale insulin and was instructed to discontinue capivasertib. The patient missed her follow-up oncology visits after hospitalization and died approximately 1 month after hospital discharge following a cardiac arrest.

Discussion

Hyperglycemia is a known adverse effect of capivasertib. Cellular PI3 K and AKT activity plays an important role in controlling glucose

Figure 1. Summary of the patient's blood glucose level (orange line) and insulin infusion dose (blue line) over time from admission.



homeostasis.[13] Animal models have shown that inhibiting these pathways can block adipocyte insulin-dependent glucose uptake and regulation. Additionally, AKT has a role in regulating hepatic glycogenolysis and glucose uptake via glycogen synthase kinase-3. The hyperglycemia associated with PI3 K/AKT inhibitors is an on-target effect that would necessitate proactive management.

This report details capivasertib-induced DKA and extreme insulin resistance in a patient with a history of diet-controlled diabetes. This case is unique due to the patient's persistent hyperglycemia despite high doses of continuous IV insulin exceeding the institutional maximum rate. Additionally, after the initial hyperglycemia resolved, the patient's glucose concentration remained controlled using minimal insulin therapy. This is consistent with a hypothesis of decreased insulin sensitivity attributable to capivasertib. The effects of capivasertib resulting in reduced cellular insulin uptake and increased hepatic glycogenolysis and gluconeogenesis are similar to the metabolic derangements that lead to DKA.[14] The risk factors for presence and severity of capivasertib-induced hyperglycemia are unclear, but the patient's comorbid diabetes mellitus before initiation of the medication likely increased the risk for more severe instances of hyperglycemia. Under these circumstances, relatively mild physiological stressors could induce metabolic shifts culminating in DKA. The combination of preexisting insulin resistance due to type 2 diabetes mellitus and the pathological increase in counter-regulatory hormones that occurs in DKA, along with the reduction in cellular insulin uptake caused by PI3 K/AKT inhibitors, likely resulted in the phenotype of extreme insulin resistance observed in our patient. The timeframe of persistent hyperglycemia, lasting for approximately 48 hours during insulin therapy, is consistent with a previously published case report on capivasertib-induced DKA and the half-life of the drug.[10,11] According to the Naranjo adverse drug reaction probability scale, it is probable that the development of DKA was related to resumption of capivasertib.[15]

Saturation of insulin receptors and their downstream effects has been proposed in some cases as a potential limitation to extreme doses of insulin.[16,17] The dose-response relationship of insulin has been characterized in healthy individuals, with a peak response observed at an insulin infusion rate of approximately 0.1 units/kg/h or slightly higher.[18] It is not known how insulin receptor saturation or peak effect might vary under different clinical circumstances, such as in critical illness, DKA, or type 2 diabetes mellitus. Further, the effects of PI3 K/AKT inhibitors likely alter this dynamic. Although a precise insulin dose cannot be identified at which a ceiling effect will occur, it is quite plausible that such an effect was occurring in our patient. This notion is further supported by the diminishing returns achieved by steadily increasing the insulin dose and the prolonged duration of DKA relative to the median time to resolution reported in the literature.[19]

Recommendations for the management of hyperglycemia have been published, but no guidelines or consensus recommendations currently exist for the management of PI3 K/AKT inhibitor–induced DKA.[20,21] In cases of DKA, we suggest discontinuation of the offending agent and prompt management of DKA according to guideline recommendations, including a

continuous insulin infusion managed according to guideline recommendations or institutional protocol.[14] Clinicians should anticipate the possibility of insulin requirements that exceed typical doses required for management of DKA. As such, if the institutional protocol involves a fixed-dose insulin infusion rather than a titratable infusion, clinicians should consider allowing the dose of insulin to be increased if needed. When considering high doses of insulin, clinicians should account for the possibility of a ceiling effect and consider stopping dose titration when no further meaningful benefit is achieved by up-titration. Under such circumstances, supportive care consistent with guideline recommendations should be provided. Close monitoring of blood glucose levels should be continued for the duration of the insulin infusion, as insulin requirements are likely to fall dramatically as the PI3 K/AKT inhibitor is cleared.

This report highlights the importance of blood glucose monitoring in patients being treated with capivasertib and provides insight on the management of capivasertib-induced hyperglycemia refractory to standard care. Currently, there are no clear recommendations on the management of hyperglycemia associated with capivasertib; however, some experts have suggested the use of metformin as initial therapy for chronic hyperglycemia. Use of insulin or sulfonylureas has been reported, although a theoretical concern that this would undermine the effectiveness of the PI3 K/AKT inhibitor has been suggested.[13] Others have proposed the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors; however, this should be considered with great caution and reserved for patients for whom metformin has failed.[22] Given the risk of euglycemic DKA, appropriate monitoring and patient education on the signs and symptoms of DKA would be paramount. Clinicians incorporating an SGLT2 inhibitor into therapy for this purpose should consider educating patients on the use of urine ketone tests and incorporating this as a component of the monitoring strategy, as the risk of euglycemic DKA in patients on PI3 K/AKT inhibitors is theoretically elevated. All patients on capivasertib therapy should have regular blood glucose monitoring, and, if hyperglycemia occurs, a dose reduction or discontinuation of capivasertib therapy may be necessary. Ultimately, guidance on the management of acute hyperglycemia secondary to capivasertib is not currently established, and further research on optimal management of these acute crises is needed.

Data availability

No new data were generated or analyzed in support of this article.

Disclosures

The authors have declared no potential conflicts of interest.

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