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Pseudohypoglycemia in a Patient on High Dose Intravenous Ascorbate for Metastatic Castration-Resistant Prostate Cancer

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Abstract

High-dose Intravenous (IV) ascorbate has been increasingly used in cancer therapy treatment. Clinicians treating patients with IV ascorbate should be aware of its effects on laboratory-based glucose measurements to avoid misdiagnosis when results indicate unexpectedly low or high glucose levels. Recently, there have been several reports of patients who within several hours of receiving IV ascorbate have had factitious hyperglycemia and hypoglycemia taken as point-of-care measurements or as part of self-management. In contrast, we report a case of factitious hypoglycemia (pseudohypoglycemia) where ascorbate was measured using a laboratory-based clinical chemistry technique. A 71-year-old Caucasian male being treated with IV ascorbate, and with no history of diabetes or metabolic disorders, had multiple laboratory reports of hypoglycemia; the patient appeared clinically stable and did not have diabetes. In this report, we discuss the cause of this pseudohypoglycemia. In patients receiving IV ascorbate, pseudohypoglycemia can occur with glucose oxidase-based testing methods, whether laboratory-based or point-of-care measurements. Consideration of the assay used, and the clinical presentation of these patients can avoid misdiagnosis and unnecessary treatment.

Keywords: Ascorbic acid therapy; Complementary therapy; Combination cancer therapy; Vitamin C

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Introduction

Integrative health practitioners have used Intravenous (IV) pharmacologic ascorbic acid therapy in cancer treatment in combination with chemotherapy in clinical studies and as a stand-alone agent [1,2]. Phase I and II trials have demonstrated the safety and potential efficacy of ascorbate in combination with chemotherapy for several cancers, including ovarian, metastatic pancreatic, glioblastoma, colon, and non-small cell lung cancer [3,4]. However, several reports indicate that high-dose IV ascorbate can factitiously alter blood glucose measurements with point-of-care testing and patient self-testing [5-12]. These reports describe patients receiving IV ascorbate who had falsely elevated (pseudohyperglycemia) or lowered (pseudohypoglycemia) blood glucose readings. Bahr et al. [5], report a case of a patient receiving IV ascorbate who was unable to register a glucose measurement on a glucose oxidase point-of-care strip following infusion. Kim et al. [7], report a patient with type II diabetes with a blood glucose concentration of 291 mg/dL according to a Self-Monitoring Blood Glucose (SMBG) device, while the patient's venous blood glucose concentration was found to be 12 mg/dL. Tang et al. [12], report ascorbic acid interference with a range of glucose oxidase-based SMBG devices, with most overreporting the levels of glucose in the sample and two underreporting the levels of glucose. These erroneous readings could lead to inappropriate glucose or insulin administration, causing severe hypoglycemia or hyperglycemia in a clinically stable patient. In contrast to point-of-care testing and patient self-testing, there have been no reports of pseudohypoglycemia or hyperglycemia with laboratory-based testing methods in patients who received high-dose IV ascorbate. Here, we present a case of pseudohypoglycemia with laboratory-based testing performed within several hours after IV ascorbate infusion.

Case Presentation

The patient is a 71-year old Caucasian male diagnosed with prostate cancer in 2008. He enrolled

Table 1: Overview of glucose determination methods and results.

Mechanism Used	Methodology Used	Instrumentation	Patient Result
Hexokinase	Abbott Clinical Chemistry	Sample analyzed *via* cuvette placed in a spectrophotometer (ARCHITECT c8000 Clinical Chemistry Analyzer)	103 mg/dL
Glucose Oxidase	VITROS® by Ortho Clinical Diagnostics	Sample analyzed on a multilayer glass slide containing reaction ingredients and in a colorimeter (Cobas c 311 analyzer, Roche Diagnostics)	42 mg/dL

Note: This table summarizes the assay kits used in the determination of blood glucose levels for the patient

in a randomized placebo-controlled clinical trial of docetaxel with or without ascorbate for metastatic castration-resistant prostate cancer (NCT02516670) in November 2017 following a treatment history of androgen-deprivation therapy, brachytherapy, and three doses of Sipuleucel-T. In May 2018, the patient entered the Open Label Extension Phase after completing cycles 1 through 8 of the study. Patients on the trial receive docetaxel (75 mg/m^2) on cycle 1 day 1 of each 21-day cycle, and IV ascorbate (1 g/kg) twice a week until progression, starting on day 1 of each cycle.

While on the Open Label Extension Phase, the patient had four reports of hypoglycemia on basic metabolic panels at his local medical facility. Despite assays measuring blood glucose levels of 28 mg/dL to 42 mg/dL (normal range, 70 mg/dL to 139 mg/dL), the patient appeared clinically stable, showing no symptoms of hypoglycemia. We investigated the relationship of the timing of these hypoglycemic events to the ascorbic acid and/or docetaxel infusions. We learned that the Basic Metabolic Panel (BMP) reported hypoglycemia only when the patient's blood was drawn within hours the IV ascorbate infusion. On non-infusion days his glucose was within normal limits.

In the most recent episode at the patient's local medical facility, his blood was drawn three hours post-infusion. This blood sample was processed for a BMP, resulting in a blood glucose result of 42 mg/dL. The same sample was processed for a Comprehensive Metabolic Panel (CMP), using a different assay later the same day, resulting in a blood glucose finding of 103 mg/dL. Table 1 presents an overview of the methodology used to determine glucose levels in our patient.

Discussion

Serum and blood glucose concentrations are typically measured *via* glucose oxidase (colorimetric method) or hexokinase (photometric method) assays (Table 1). Glucose oxidase-based assays have previously been reported to falsely indicate pseudo-hyperglycemia or hypoglycemia when performed after high-dose IV ascorbate infusion [10]. In the glucose oxidase assay, glucose oxidase converts glucose, oxygen, and water into gluconic acid and hydrogen peroxide. Peroxidase is then used to catalyze an oxidative coupling reaction between the peroxide and dye precursors, which forms a dye. The dye is measured *via* a colorimeter and directly related to the amount of glucose in the initial sample. The assay used in patient's initial blood testing employed this method. Previous reports suggest that the infused ascorbic acid may alter peroxide generated during the assay [13]. Either more or less dye is produced as an artifact, leading to falsely altered glucose measurements.

In the hexokinase method, hexokinase produces glucose-6-phosphate and ADP. Glucose-6-phosphate dehydrogenase is then added to the sample to oxidize glucose-6-phosphate, in the presence of NADP forming gluconate-6-phosphate, NADPH, and H^+. The concentration of NADPH is then photometrically determined. Due to the direct relationship to the initial amount of glucose, NADPH serves as an analogue for the amount of glucose in the sample. This method is less likely to be affected by the presence of ascorbate is not known to interact with any of the reactants or intermediates of the hexokinase-based assay.

While point-of-care or self-monitored blood glucose oxidase-based tests have been previously reported to show this ascorbate interference, there has never been a report of a confirmatory clinical chemistry lab test having an artifact like the one we demonstrate here. This suggests that confirmatory testing with the glucose oxidase assay is not a reliable method for patients receiving high-dose IV ascorbic acid due to risk of interference and that the glucose hexokinase assay should be used instead, if possible.

Conclusion

Ascorbic acid at high concentration can lead to pseudohypoglycemia in laboratory-based glucose assays that specifically utilize glucose oxidase. Pseudohypoglycemia could result in inappropriate clinical management and potential patient harm. Health care providers who have patients that are treated with IV ascorbate should be aware of this interference phenomenon and of the method of glucose analysis used in their clinical laboratory. Patients who need diabetes management while receiving ascorbate should have blood glucose levels sent to a clinical laboratory for confirmatory testing with a hexokinase assay. As patients may not volunteer that they use IV ascorbic acid treatment, health care providers should ask about it. Unless appropriate glucose assays are used, incidence of pseudohypoglycemia may increase as more patients opt to use IV ascorbic acid.

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Author Contributions

J. Gray, A. De Felice, M. Afful, K. Schultz, and C. Paller reviewed the patient's records. J. Gray, A. De Felice, and C. Paller wrote the original draft of the manuscript. M. Levine and C. Paller critically revised and edited the manuscript. M. Afful, K. Schultz, and C. Paller were involved in patient care and medical management. All authors have made significant contributions to the manuscript and have reviewed it before submission. All authors have confirmed that the manuscript is not under consideration for review at any other journal. All authors have read and approved the final manuscript.

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