CASE REPORT

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Pharmaceutical Error Resulting in Fatal Diabetic Ketoacidosis

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ABSTRACT: A 41-year-old male with a 25-year history of diabetes mellitus requiring 25 to 30 units of neutral protamine hagedorn (NPH) insulin daily was found dead at home. Recent history revealed that he was well until the last four days of life when he had the onset of nausea, vomiting, and anorexia coinciding with procurement of a new bottle of insulin from his pharmacist. Pertinent autopsy findings included coronary and aortic atherosclerosis, a peptic ulcer, and diabetic glomerulopathy. Chemical analysis of the vitreous humor, including glucose (813 mg/dL) and acetone (40 mg/dL), revealed that he died of diabetic ketoacidosis. Further investigation revealed that the pharmacist had accidentally substituted regular insulin, with a duration of action of up to 6 h as opposed to 24 to 28 h, for NPH. Cultures of blood and of the regular insulin yielded no growth. Analysis of this case emphasizes the importance of obtaining a careful medical and medication history and the usefulness of vitreous electrolytes when investigating a sudden death in a diabetic.

KEYWORDS: pathology and biology, diabetes mellitus, insulin

In the investigation of an unexpected, unwitnessed death, a careful medical history, including documentation of the decedent's health and activities the last few days of life, are of paramount importance. It is important to note the type and amount of medications as these may play a major role in the death. We present a case in which careful scene investigation, medical history-taking, and postmortem vitreous chemistry enabled us to reconstruct the events leading to death and discover a pharmaceutical error, to our knowledge the first such reported case.

Case Report

The patient was a 41-year-old white male who had been an insulin-dependent (Type I) diabetic since age 16. His daily insulin dosage was 25 to 30 units of neutral protamine hage-

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dorn (NPH) insulin. He was found dead in his bedroom by family members at 4:30 p.m. He had last been seen alive 2 h previously. He had been well and his diabetes well-controlled until four days before death when, coincident with the purchase of a new bottle of insulin, he had the onset of anorexia, nausea, and vomiting, which persisted until the day of death. There was no history of hematemesis. The insulin had been kept refrigerated after purchase.

Five years before death he had been in a motorcycle accident, with loss of vision in his right eye and deafness in his left ear. Because of poor vision, family members measured his insulin for him.

Investigation of the home revealed two empty bottles of Lilly NPH beef-pork insulin and a bottle of Squibb Novo regular pork insulin containing 9 of the original 10 mL.

Autopsy Findings

Portmortem findings in this 171.5-cm (67-in.), 70.3-kg (155-lbs) man included 80% atherosclerotic narrowing of the left anterior descending and dominant left circumflex coronary arteries and severe aortic atherosclerosis. There was a 2- by 0.7-cm ulcer in the body of the stomach, but no recent or old blood in the gastrointestinal tract. At the first bifurcation of the right middle cerebral artery there was a 0.7-cm unruptured berry aneurysm.

Microscopic examination of the myocardium revealed subendocardial interstitial fibrosis, but no evidence of acute ischemia. The ulcer had a necrotic base which contained acute and chronic inflammatory cells. Within the kidneys there were diffuse and nodular glomerulosclerosis and osmotic nephrosis.

Portmortem vitreous glucose was 813 mg/dL, vitreous acetone was 40 mg/dL, urine acetone was 34 mg/100 mL, and blood acetone was 40 mg/100 mL. Cultures of the insulin showed no growth.

Discussion

In summary, this 41-year-old white male died of diabetic ketoacidosis (DKA), brought about by the inadvertent substitution of regular insulin for NPH insulin by a pharmacist. Coe found that the average vitreous to plasma glucose ratio was 0.85, and that an elevated postmortem vitreous glucose (greater than 200 mg/dL) indicates antemortem hyperglycemia. Acetone and a high glucose level in the vitreous humor prove DKA as the cause of death [*1*]. DKA, which results from lack of insulin, is characterized by metabolic acidosis with a blood pH less than 7.35, bicarbonate less than 15 mg/dL, hyperglycemia (serum glucose greater than 300 mL/dL), and ketonemia (serum ketones greater than 5 mol/L). Acidosis results from production of ketone bodies (betahydroxybutyric acid, acetoacetate, and acetone), which are strong acids, completely dissociating under physiologic conditions. Lack of insulin activates lipolysis in peripheral tissues, resulting in increased fatty acid delivery to the liver where they are converted to fatty acid coenzyme A (acyl CoA) in the hepatocytes. Unopposed glucagon activates the rate-limiting enzyme cartinine acyltransferase which catalyzes the combination of carnitine and acyl CoA to a single molecule which can enter the hepatocytic mitochondrion, where the acyl moiety is oxidized to ketone [*2*].

Unusual causes of DKA include infection (especially of the respiratory and urinary tracts), failure to take insulin, myocardial infarct, stroke, trauma, pregnancy, pancreatitis, and emotional stress. Failure to take insulin provokes DKA via unopposed glucagon, while epinephrine is the initiator in physically or emotionally stressful conditions [*2,3*].

Rarely, DKA arises in individuals with insulin resistance, characterized by lack of responsiveness to insulin in the absence of infection or stress. The usual criteria for insulin resistance, which may be immunologic or nonimmunologic, is a daily requirement of at least 200 units of insulin. Obesity (a nonimmunologic cause) is the most frequent reason for insulin resistance, with immunologic resistance usually resulting in individuals with immunoglobu-

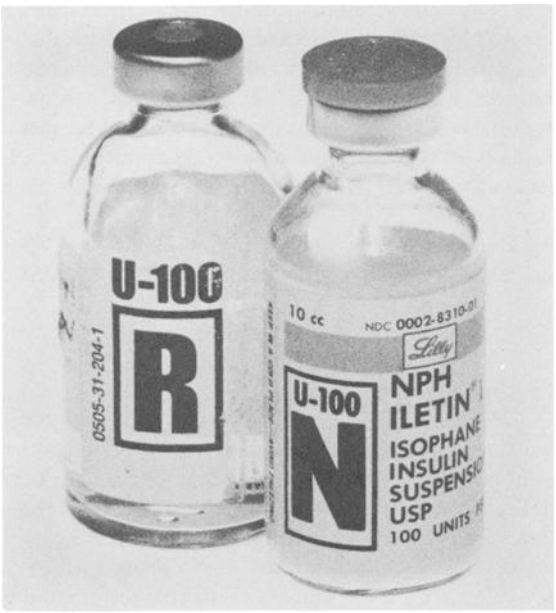

FIG. 1—*Bottle of Squibb Novo regular pork insulin* (left) *and Lilly NPH beef-pork insulin* (right). *Note their similarity.*

lin G (IgG) antibodies to beef insulin. Some insulin-resistant individuals are both obese and have anti-insulin antibodies [*4*]. Other causes of insulin resistance are the presence of hormonal antagonists of insulin (growth hormone, glucocorticoids, catecholamines, glucagon), an abnormal beta cell secretory product (an amino acid substitution in the insulin molecule or incomplete cleavage of proinsulin to insulin), abnormal coupling of the insulin-receptor complex and the glucose transport system, and insulin resistance states associated with acanthosis nigricans (characterized by severe insulin resistance, acanthosis nigricans, hirsutism, and virilism, and occurring almost exclusively in females) [*5*].

In the case presented herein, we describe the onset of DKA as a result of administration of the incorrect type of insulin. Regular insulin is detectable about 1 h after injection and lasts 6 h. NPH insulin begins to exert its effects 2 h post injection, and has a duration of 25 h [*6*]. It is apparent that for about 18 h a day of the last three days of life the deceased was without insulin. Diseases usually associated with the onset of DKA (infection, myocardial infarct, stroke, and so forth) were absent. Although there was a peptic ulcer of the stomach, there was no evidence of recent or old hemorrhage in the gastrointestinal tract, and the ulcer did not initiate DKA prior to his receiving the regular insulin. None of the causes of insulin resistance are present in this case. The decedent was of slender build (vide supra), was on the less immunogenic NPH beef and pork insulin, and the regular insulin was of porcine origin. His daily insulin dose was far below the 200 U/day usually required in insulin resistant patients. There was no evidence of elevated hormones (glucocorticoids, glucagon) either chemically or anatomically. The deceased was not female, excluding him from the category of insulin resistance associated with acanthosis nigricans. Furthermore, the development of DKA over a three-day period, when according to the family he had been in good control of his disease previously, is much more consistent with insulin lack than insulin resistance.

In the investigation of the sudden death of an insulin-dependent (Type I) diabetic, several steps must be taken: (1) determine the type and amount of insulin, and procure the bottle last used by the decedent; (2) obtain the medical history, with particular reference to the

degree of control of the diabetes, and determine whether there were recent episodes of DKA; and (3) vitreous electrolyte and ketone levels must be assayed.

Utilizing this approach and a literature review has enabled us to document, to our knowledge, the first reported case of DKA caused by inadvertent substitution of regular insulin for NPH insulin by a pharmacist. In this case, it is noteworthy that the history of poor eyesight and the fact that regular and NPH insulin bottles, even though manufactured by different companies, look alike (Fig. 1). We strongly urge the pharmaceutical industry to take steps to distinguish the different types of insulin. Suggestions include the use of colored labels, different designs on the labels, and different sized bottles. In addition, it is the practice of some pharmacies to make insulin available on shelves so that the customer procures the bottle himself. Such a practice should obviously be discontinued since the customer with poor vision may select the wrong type of insulin.

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