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CASE REPORT

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Accidental Insulin Overdose*

ABSTRACT: Exogenous insulin has been used for many years to treat diabetes mellitus. Due to the complex nature of insulin therapy, there have been numerous accidental overdoses by these patients. Unfortunately, in other instances, insulin has been used as an agent for suicide and homicide in diabetics as well as nondiabetics. Presented here is a fatal case of accidental insulin overdose in a nondiabetic. Following the case presentation, we review insulin pharmacology and the methods of diagnosing insulin overdose postmortem. In any case of insulin overdose, a comprehensive scene investigation to document the amount and type of insulin used, along with information revealing the source of the insulin is critical. In addition, a complete autopsy, including appropriate laboratory studies, is needed to make a diagnosis in these cases. Proper attention should be given to collection and storage of blood samples, as these specimens often yield the strongest evidence of insulin overdose.

KEYWORDS: forensic science, forensic pathology, death, overdose, insulin, autopsy, accident

Exogenous insulin has been used for many years to treat diabetes mellitus. Over the years, there have been numerous accidental overdoses by these patients. In other instances, insulin has been used as an agent for suicide (1–7), by both diabetics and nondiabetics. More rarely, insulin has been utilized in homicides (8–13). A shared finding in a vast majority of these cases is ready access to insulin, whether by medical condition or by occupation. The number of insulin overdoses, though, far outnumbers actual fatalities, as the mortality rate of insulin overdose has been reported to be 21–27% (1,14). Interestingly, the amount of insulin used seems to be independent of morbidity and mortality (1,14–16), while the level and duration of the hypoglycemia does influence outcome (1). Making a postmortem diagnosis of insulin overdose can be a difficult task and necessitates a thorough scene investigation, adequate laboratory samples and testing (3), as well as close attention to tissue pathology. Presented here is a fatal case of accidental insulin overdose in a nondiabetic. A synopsis of the pharmacology of insulin and a summary of the diagnostic criteria for insulin overdose are discussed.

Case Report

An 82-year-old white male, postoperative day 12 from incarcerated hernia repair, was transferred to the hospital's rehabilitation unit for care of continuing medical problems. Diagnoses on transfer included pulmonary embolus, improving pneumonia, esophagitis, decreased mobility, and urinary retention requiring intermittent catheterization. The patient's past medical history was also significant for coronary artery disease with four bypass surgery, abdominal aortic aneurysm with graft repair, and emphysema. The patient's condition was slowly improving and he remained in the rehabilitation unit.

Eight days later, the patient's nurse entered his room to check on him and to flush his PICC (peripherally inserted central catheter) line as was ordered every 8 h to prevent the line from becoming plugged.

The flushing process was to involve injection of the line with 5 mL of saline followed by 1 mL of heparin. The line had 2 ports, a brown port which was previously plugged and was no longer being flushed, and a white port that the nurse flushed without problem. When the nurse left the room, the patient was doing well with no complaints. One hour later, the patient was noted to be in distress and a "Code Blue" was called. During the code, a rapid blood sugar was found to be low and the physician ordered one ampule of D50 (50% dextrose) to be given. At this time, the white port, patent 1 h earlier, was found to be plugged and a new IV site had to be used to administer medication and fluids. Blood glucose was 13 mg/dL 2 h and 25 min after the PICC line flushing and 33 mg/dL 4 h and 45 min after the flushing (normal range 64–105 mg/dL). Four more ampules of D50 were given before the blood glucose normalized later that morning. The patient's clinical course became substantially worse following this event and he died three days after the incident. The body was released to a funeral home and the body was embalmed.

On the following day, the patient's primary care physician reviewed the laboratory data, questioned why the patient had the hypoglycemic event, and ordered insulin levels on blood samples taken during the code (Table 1). The testing on blood obtained 2 h and 25 min after line infusion revealed an insulin level of 297.5 μIU/mL (normal range 0–22.7). Only after this information was obtained, was the coroner notified and the case further investigated.

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TABLE 1—*Serum total insulin levels reported in μIU/mL (normal range 0–22.7).*

Time After Infusion	Insulin Level
2 h, 25 min	297.5
7 h, 10 min	11.6
13 h, 10 min	6.8

Autopsy, limited by previous embalming, performed two days after death revealed findings consistent with the patient's past medical history of severe cardiopulmonary disease, including atherosclerotic coronary disease, cardiomegaly (570 g), pulmonary emphysema, and multiple surgical scars. Examination of the pancreas revealed no masses or lesions. The remainder of the autopsy was unremarkable. Further laboratory testing on a blood sample stored from the time of the code included a C-peptide level of 0.9 ng/mL (normal range 1.1–4.6 ng/mL). The cause of death was determined to be insulin overdose with cardiopulmonary disease as an underlying contributing factor.

An internal investigation by the hospital and a police investigation were conducted to detect the cause of this incident. Internal investigation by the hospital found that insulin (100 units/mL), heparin, and saline containers were together on top of the medication cart in the patient's unit, and that sometimes the nurse caring for this patient would pre-draw heparin and saline for line flushes at the beginning of each shift. Additionally noted, the heparin and insulin bottles had a similar size and shape (Fig. 1), and each was labeled with a patient's name which could cover the name of the medication. It was deemed that the patient mistakenly received a dose of insulin that could have ranged from 100 units if mistaken for 1 cc of heparin, to 500 units if mistaken for 5 mL of saline. No reason or evidence of malicious administration could be found by either investigation. With this information, the manner of death was ruled accidental.

Discussion

Insulin is a major regulatory hormone that serves to lower the serum concentration of glucose. A proinsulin molecule, consisting of a two peptide chain molecule (insulin) linked by a connecting peptide (C-peptide), is synthesized in the beta cells of the pancreas. Rising serum glucose, along with other regulatory amino acids and hormones (17), causes proteolytic cleavage of the proinsulin molecule and yields the active insulin molecule and the inactive C-peptide in a 1:1 ratio (17). At this point, the active molecule binds with receptors on insulin-sensitive tissues including muscle, adipose, and liver. It stimulates glucose uptake in muscle and adipose, and suppresses hepatic glycogenolysis and gluconeogenesis. Hepatic production of glucose can be completely inhibited at levels as low as 50 uIU/mL (17). The plasma half-life of insulin is only 5–8 min (3). Insulin is degraded by red-cell proteolytic enzymes, the kidney, and the liver. C-peptide, which is degraded primarily by the kidneys, has a half life of 10–20 min (3). This results in a slightly higher circulating level than that of insulin.

The half-life of insulin, as well as its hypoglycemic effect, can be altered by several factors. First, insulin clearance will be delayed if a patient has impaired hepatic or renal function, as may occur with diabetes (17). A single, large dose may in itself lead to delayed absorption due to a pooling effect (17). Site of injection plays an important part in absorption as areas of high blood flow have faster absorption rates than those with less blood flow. The same is true when the body is under stress. With exercise, an increase in blood flow will lead to faster mobilization of insulin while shock will decrease mobilization (2). Also, repeated injection may cause a local lipohypertrophy that could further delay absorbtion (18). Additionally, patients previously exposed to exogenous insulin can develop antibodies to the drug. These antibodies bind to the insulin molecule that can not only delay degradation, but also lead to falsely high or low insulin values (8). For this reason, both free and total insulin levels can be measured. In nondiabetic individuals the

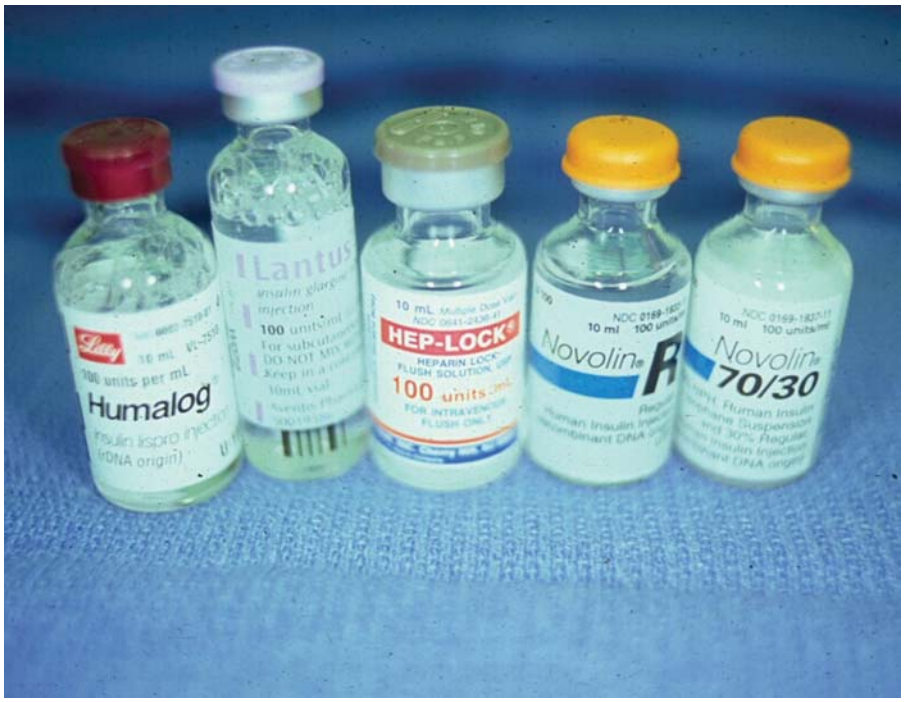

FIG. 1—*Picture showing four different insulin vials surrounding a heparinized saline flush vial (center). Notice all vials are similar in size and shape.*

TABLE 2—*Summary of types of insulin and their pharmacokinetics (19).*

Insulin Type	Preparation	Onset (h)	Peak (h)	Duration (h)
Rapid	regular, lispro	0–1	1/2–5	6–8
Intermediate	NPH, lente	1–2 1/2	4–15	24
Slow	ultralente	4–8	10–30	>36

TABLE 3—*Factors increasing endogenous insulin levels (20).*

Post-prandial state
Thyrotoxicosis
Acromegaly
Cushing's Disease
Pancreatic insulinoma

values should be the same, while in diabetics the total insulin level can be much higher than the free, active insulin (8).

Multiple brands and types of commercially produced insulin are available. Generally, there are three main types of insulin: rapid acting, intermediate acting, and long acting. Knowing the onset, peak, and duration of the various types of insulin can be helpful in an overdose scenario (Table 2). This illustrates the need for a thorough scene investigation in potential overdose cases.

A major difference between commercial insulin and endogenous insulin is the absence of C-peptide in commercial preparations. With a large dose of exogenous insulin, one would expect an elevated insulin level and a suppressed C-peptide level. The suppression is due to a negative feedback system that stops the cleavage of the proinsulin molecule following detection of the active insulin molecule in the bloodstream. It should also be recognized that C-peptide levels can be suppressed independently with alcohol or thiazide ingestion and in certain metabolic disorders (20). C-peptide levels are also decreased after suppression tests such as 2-deoxyglucose, diazoxide, and epinephrine (20). Factors that cause increased production of endogenous insulin (Table 3) will result in elevated insulin and C-peptide levels.

Additionally, the hypoglycemic effect of all types of insulin, endogenous and exogenous, can be potentiated by other pharmaceutical agents as well as alcohol. Widely documented correlations have been made between insulin and monoamine oxidase inhibitors (MAOIs) (2,16,21), while other agents including barbiturates (2), beta blockers, salicylates, tetracyclines, fenfluramine, and clofibrate have also been implicated (21). This demonstrates a need for a full toxicology screen in any case where insulin overdose is suspected (2).

Considering the difficulty of making a diagnosis of hypoglycemia postmortem (2,22), the interpretation of insulin and C-peptide levels becomes a crucial aspect of making a diagnosis of insulin overdose. While insulin has been recovered in vitreous (3) and bile (7), serum levels remain the standard for analysis and interpretation. As stated before, an elevated serum insulin level along with a suppressed C-peptide level is virtually diagnostic of exogenous insulin administration. Lethal insulin levels have been highly variable (1), and no standard exists to date. In the case of a diabetic individual, one might also order insulin antibody levels and free and total insulin levels, as opposed to just total insulin.

The technique of choice for measuring insulin levels is radioimmunoassay (RIA) (23). In this method, ^{125}I-labled insulin competes with insulin from a patient's serum sample for binding to an insulin antibody on a testing tube (23). A gamma counter is then used to determine the amount of ^{125}I-labeled insulin bound to the tube (23). This value can then be used to determine the patient's insulin level by using a calibration curve obtained from plotting the results of known standards (23). Peripheral blood is preferred as blood samples from the right heart have much higher insulin levels than peripheral blood (22). All samples should be placed in red-top serum separator tubes, spun down, and frozen as soon as possible. Samples for insulin and C-peptide levels are also valid in green-top plasma tubes, when spun down and frozen as above. Samples in purple-top EDTA tubes are not valid for analysis, nor are hemolyzed samples as these specimens will have falsely elevated values (23). Also, it should be noted that some insulin antisera have some cross-reactivity with proinsulin that can lead to falsely elevated insulin values (23). This would only be a concern in individuals with high circulating proinsulin levels, such as diabetics and patients with islet cell tumors (23). This cross-reactivity is not seen with C-peptide (23). A summary of how much serum is required for insulin antibody (Ab), insulin free and total (F&T) and C-peptide along with stability at different temperatures is provided in Table 4. Previous reports have mentioned other suggested preparations, so it is advised to contact the laboratory that will be performing the testing to confirm their requirements (3).

TABLE 4—*Summary of recommendations for laboratory testing (20). Recommendations from the Associated Regional and University Pathology (ARUP) laboratories.*

Test	Amount (min)	Ambient	Refrigerated	Frozen
Insulin Ab	0.5 mL (0.1)	2 days	7 days	3 months
Insulin, F&T	2.0 mL (1.1)	2 h	7 days	3 months
C-peptide	0.5 mL (0.3)	not stable	not stable	1 week

Autopsy findings in cases of insulin overdose are often unremarkable (3). In cases involving nondiabetics, locating needle punctures can be of use though difficult if a high gauge needle was used. Immunohistochemistry can be used to detect whether insulin is present in an injection site. This method has been used in both homicide (9) and suicide (4) cases. Close attention also should be given to the pancreas and gastrointestinal tract to rule out insulinoma, as these can be quite small and hard to detect (8). In cases of prolonged hypoglycemia, neuropathology can show selective destruction of neurons, without necrosis, which affects the entire cerebral cortex while sparing the cerebellum (10).

Conclusion

Although insulin overdose is still a somewhat rare occurrence in cases of suicide and homicide, increased numbers of cases have been reported in the world literature in recent years. Whether this increase is due to an increased awareness and quality of postmortem investigations, or a true increase in the number of occurrences is not clear. Still, it has been speculated that many insulin-related deaths in diabetics have been misclassified or missed entirely, when they actually represented suicides (2). One reason for this discrepancy is that many deaths in known, complicated diabetics are often written off as accidents when, in reality, the death was a suicide. Many coroners and medical examiners may want to avoid the stigma of a suicide when there is reasonable belief that the deceased may have accidentally overdosed on their prescribed medication. While this is reasonable, one must consider the increased occurrence of major depression in diabetic individuals as a whole, and that poorly controlled diabetics have a higher rate of major depression than well controlled patients (24). Additionally, many cases may not be attributed to insulin at all due to inadequate scene investigation,

TABLE 5—*Summary of procedures for autopsy cases in which insulin overdose is a possibility.*

Scene Investigation	Autopsy	Laboratory Studies
• Collect all medicine containers and syringes	• Locate and excise potential injection sites (especially in a nondiabetic) • IHC of injection sites for insulin, if warranted • Collect appropriate blood samples and store them accordingly (peripheral blood, serum-separator tube, frozen for most tests) • Careful examination of pancreas for insulinoma • Routine histology	• Routine toxicology • Routine vitreous electrolytes • Total insulin and C-Peptide in a nondiabetic • Free and total insulin, C-peptide, and anti-insulin antibodies in a diabetic

autopsy, or laboratory testing. These circumstances necessitate a thorough evaluation in cases of potential insulin overdose (Table 5). A comprehensive scene investigation to document any amount and type of insulin used, along with information revealing the source of the insulin is crucial. In addition, a complete autopsy, including appropriate laboratory studies, is needed to make a firm diagnosis in these cases. Special attention should be given to properly collecting and storing blood samples, as these specimens often yield the strongest evidence of insulin overdose.

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