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Homicide by Insulin Administration

REFERENCE: Haibach, H., Dix, J. D., and Shah, J. H., **"Homicide by Insulin Administration,"** *Journal of Forensic Sciences,* JFSCA, Vol. 32, No. 1, Jan. 1987, pp. 208-216.

ABSTRACT: This report describes a case of homicide by insulin administration and a study of the effects of storage conditions on insulin in serum. The study revealed insulin to be remarkably stable at refrigerator temperatures. Therefore, for forensic science purposes, insulin immunoassay data are interpretable even when serum is not stored by the standard laboratory method of freezing.

KEYWORDS: toxicology, insulin, homicide, effects of storage

Cases involving the administration of insulin with the intent to harm or kill have recently come to trial in the United States [*1,2*]. The publicity surrounding insulin as a deadly weapon may invite imitation and thus increase the number of similar cases brought to the attention of forensic science specialists [*2*].

We studied the case of a hospitalized patient who died of maliciously administered insulin. The diagnosis of an insulin overdose was suspected clinically and confirmed by the evaluation of insulin and C-peptide concentrations in multiple blood specimens. Since the stability of some of the blood specimens was questioned because of suboptimal storage conditions, we studied the stability of exogenous insulin in human serum specimens stored under different laboratory conditions.

Case Report

A 59-year-old white man underwent a craniotomy for a malignant atrocytoma. Even though the tumor could not be removed completely, the patient's recovery was uneventful during the first postoperative week. He had a left-sided hemiparesis and was unable to speak; however, he was able to communicate by writing. Eight days after surgery he was moved from the intensive care unit to a regular ward room. On the same day he became progressively lethargic. He was being taken to the radiology department for evaluation when he suddenly became unconscious and had to be resuscitated. A computed axial totmography (CAT) scan of the head showed no evidence of edema or hemorrhage which could account for

Presented in part at the 37th Annual Meeting of the American Academy of Forensic Sciences, Las Vegas, NV, 12-16 Feb. 1985. Received for publication 23 Jan. 1986; revised manuscript received 6 March 1986; accepted for publication 7 March 1986.

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this sudden change in mental status. Blood taken at the time of the resuscitation revealed a low serum glucose concentration of 32 mg/dL. He was given two 50-mL ampules of 50% glucose. A second dose was given 1 h later when a repeat serum glucose was 26. Glucose was then given by continuous infusion and it was not until the following morning that the serum glucose had increased to 184 mg/dL.

The neurosurgeons were uncertain as to the cause of their patient's hypoglycemic episode and thus arranged an endocrinological consultation. The endocrinologist concluded the sudden decrease in serum glucose and the persistently low concentrations in spite of continuous replacement therapy could only be explained by an exogenous source of insulin. Blood specimens from before, during, and after the hypoglycemic episode were sent to a reference laboratory for quantitation of insulin and C-peptide. During the next four days the patient remained in a comatose state, assisted by a ventilator, until he died.

Pathologic Findings

An autopsy performed by the medical examiner revealed few findings. The brain was consistent with a postsurgical state and brain death; there was no significant edema or hemorrhage. Both lungs were focally consolidated with a pneumonic process. Careful examination of the pancreas failed to reveal any signs of an islet cell tumor. Microscopic sections confirmed the presence of residual malignant astrocytoma in the brain and bronchopneumonia. Sections of the pancreas demonstrated acute pancreatitis and, more importantly, no tumor or hyperplastic process.

The cause of death was ruled as hypoglycemia complicated by bronchopneumonia secondary to an exogenous insulin overdose. The death certificate was not signed until the results of the insulin and C-peptide assays (Fig. 1) were known. These findings supported the diagnosis of an exogenous insulin source. The death was ruled a homicide.

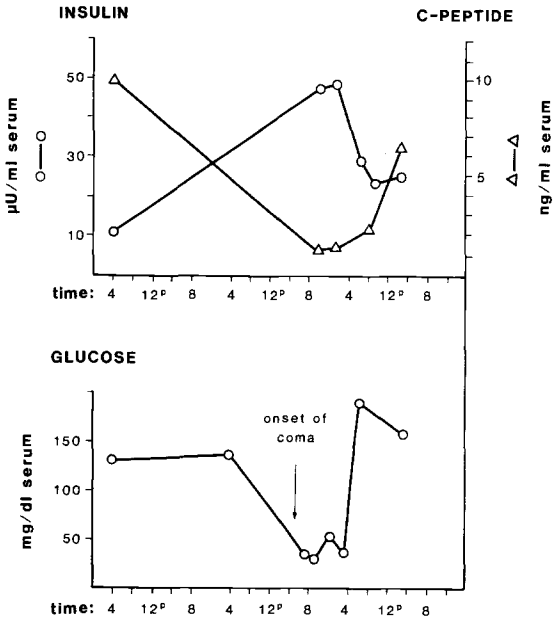

FIG. 1—*Serum glucose, insulin, and C-peptide concentrations before, during, and after the hypoglycemic episode (State Exhibit 21* [1], *redrawn).*

The Accused

The patient's wife became a suspect soon after her husband became comatose. Retrospectively, her actions were suspicious throughout her husband's hospitalization. Before her husband's death she removed all funds from his bank account. She called all funeral homes in the area to find the quickest route to cremation. Before the hypoglycemic incident, she bet hospital personnel that he would not live past the evening he became unconscious. Other facts about her marriage were also of note. She had been married to the decedent less than two months before his hospitalization. This was her tenth marriage. She had met her husband through correspondence with a "Lonely Hearts Club."

At the time of her husband's autopsy, the wife was being held by the police on the charge of driving with an expired driver's license. When the gross examination was completed, the medical examiner phoned the police department's chief homicide detective and informed him the only findings were signs of brain tumor and pneumonia. He further stated it was impossible to prove at autopsy that the death was secondary to a suspected insulin injection given five days earlier. The detective then confronted the wife by saying the medical examiner had performed an autopsy on her husband and concluded the death was due to an insulin overdose. Upon hearing this, the wife broke down and confessed that she did not mean to kill him; she only wanted to give him enough insulin to return him to the intensive care unit where he would receive better care. She stated that she had found the insulin at the nursing station on the ward and had injected the insulin intravenously, using a syringe she carried in her purse. She professed knowledge of insulin and intravenous injections because she was a licensed practical nurse.

The Trial

The trial [*1*] was held in a different county because of a change of venue. The wife's confession stood up in court; she was convicted of murdering her husband and subsequently was sentenced to 50 years in jail without parole. However, the insulin and C-peptide data were ruled inadmissable as evidence because the technologist who performed the test in California did not initial the laboratory results on the computer printout. The defense attorney was thus successful in suppressing this evidence because the chain of custody of the laboratory results was not legally acceptable.

Some details of this case have been described in a previous publication [*3*] which dealt with the management of a homicide case in a hospital environment, but they are not discussed in this paper.

Serum Insulin Studies

Studies of the stability of insulin in stored serum were conducted. Regular porcine insulin (Squibb® Novo® 100 U/mL) was added to pooled serum from normal fasting or nonfasting healthy volunteers to simulate concentrations found in case reports of surreptitious and malicious insulin administration. Insulin was diluted stepwise with sterile 0.9% sodium chloride. To prevent adsorption of insulin to glass or plastic container walls [*4*], human serum had been added to the saline (2-mL serum/L). The diluted insulin was added to a serum pool to yield concentrations approximately 2500, 300, 200, and 80 μU/mL. Aliquots were promptly frozen at $-70°C$ or incubated in disposable, clean but not sterile, vials at $4 \pm 2°C$, room temperature, or $37 \pm 2°C$ for varying times up to six days. All aliquots were then kept frozen at $-70°C$ until analysis for insulin in duplicate by a slight modification of a radioimmunoassay technique [*5*]. This method has been successfully used previously to determine human and porcine insulin in human serum [*6, 7*].

As summarized in Fig. 2, a significant loss of the various concentrations of added insulin did not occur at 4°C storage. The slight variability of the data shown here is indigenous to

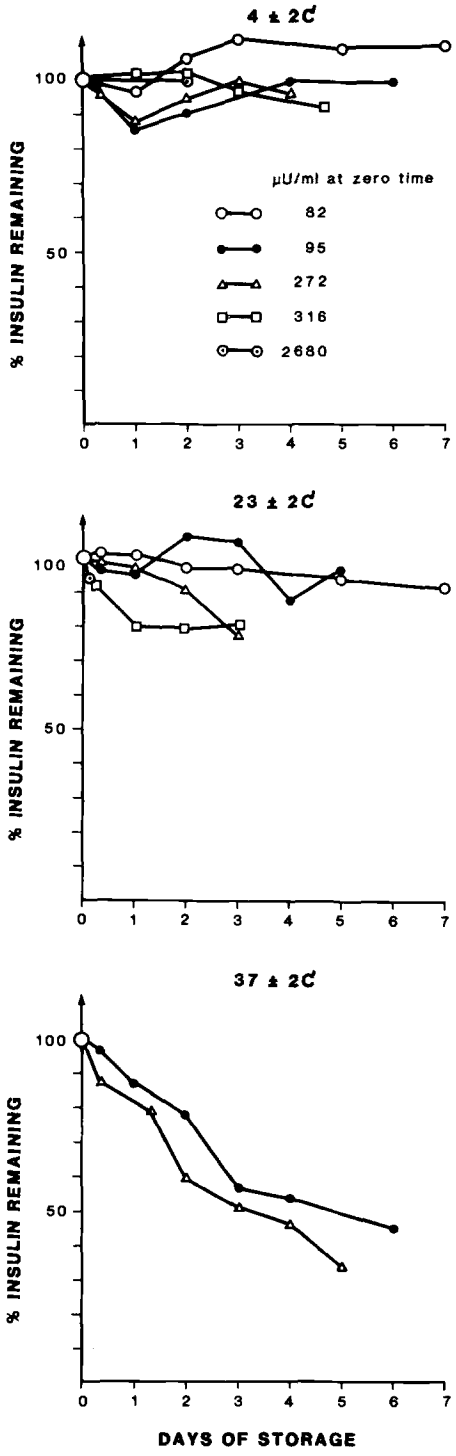

FIG. 2—*Stability of insulin in serum stored at 4 ± 2, 23 ± 2, and 31 ± 2°C. The concentrations of insulin remaining after 24, 48, 72, and 96+ h are not different from those at zero-time for storage at 4°C (p = 0.11, 0.27, 0.50, 0.25) and at 23°C (p = 0.16, 0.06, 0.08, 0.10), respectively.*

the assay and in keeping with immunoassays of peptide hormones. Thus, there is no significant degradation at refrigerator temperature over four to five days, although most (60 to 70%) is lost at 37°C in four to five days. At room temperature, the stability of insulin is less predictable. These results show that insulin determinations for forensic science purposes are not invalidated by storage of serum at refrigerator temperatures.

Comment

Circulating insulin is the major regulating hormone of blood glucose [*8*]; it facilitates the entry of glucose into tissues. Supraphysiological quantities of insulin move glucose into storage tissues, lowering blood glucose to concentrations insufficient for normal brain function, resulting in varying degrees of coma, sometimes convulsions, and occasionally in permanent brain damage or death. Prolonged hypoglycemia (serum glucose less than 40 mg/dL) is a life-threatening condition. Most hypoglycemic episodes are promptly recognized and corrected by the administration of glucose to the patient if they occur in a well-known clinical setting, such as a diabetic injected with an erroneously large dose of insulin, missing a meal, or suffering from an intercurrent illness. Less common causes of hypoglycemia, such as sepsis or insulin-secreting neoplastic tumors, are usually diagnosed after costly or time-consuming clinical testing. By its very nature, surreptitious injection of insulin evades prompt diagnosis and requires a high level of clinical awareness and specific serum assays. Only rarely does the physician think of insulin as a weapon used for homicide.

This case involved a hospitalized, terminally ill man who had a craniotomy for a malignant brain tumor and unexpectedly lapsed into a sudden coma. There was no evidence of a neurosurgical complication or any other condition which could explain the sudden deterioration of the patient's condition. Hypoglycemia was unsuspected but was recognized with the help of a set of serum chemistries usually ordered for sudden onset coma. Three hundred and ten grams of glucose were administered over 10 h to normalize and maintain normal blood glucose concentrations. This dose appeared inordinately large for correction of low blood glucose levels encountered in insulin-treated diabetics or other hypoglycemic states. Many hours elapsed before there was a suspicion that a large dose of insulin was causing the problem.

In a series of 15 cases with intentional insulin overdoses, Stapczynski and Haskell [*9*] demonstrated a direct relation of the insulin dose (1) with the quantity of glucose needed for correction of the hypoglycemia, (2) with the length of glucose administration, and (3) with the rate of glucose infusion expressed as g/h. This relationship spans a wide range, 100 to 1000 U insulin, doses many fold larger than commonly contained in single injections for the treatment of diabetes mellitus. Table 1 lists 21 cases of surreptitious and malicious insulin injections for which more detailed data are available. Serum insulin concentrations ranged from 12 to 40 600 μU/mL.

A second lead not immediately considered by the medical team of the present case was the profession of the patient's wife. As a licensed practical nurse, she had access to insulin and was well aware of the effects of overdosage. Many of the cases listed in Table 1 also involved health care professionals.

The postmortem examination, performed on the day of the patient's demise and five days after the onset of the hypoglycemic episode, confirmed the absence of other conditions known to cause prolonged hypoglycemia. Care was taken to search for neoplastic tumors or hyperplastic tissues capable of secreting insulin at pancreatic and extrapancreatic sites. Pancreatic insulinomas which have come to surgery have been reported to vary from 8 to 0.6 cm in diameter [*10*]. The smaller lesions, thus, may easily escape the unaware examiner.

Medical laboratories commonly store remnant serum specimens for several days to permit retesting if the validity of test results is questioned. In this case, when a malicious administration was deemed to be likely, seven sera were retrieved and submitted to a commercial

TABLE 1—*Cases reported with surreptitious or malicious insulin administration.*

Senior Author	Reference	Serum/Plasma Glucose, mg/dL	Serum/Plasma Insulin, μU/mL	Serum/Plasma C-Peptide, ng/mL	Years of Age	History	Source of Insulin
Sturner	*23*	25–50	2 000		32[a]	suicidal	
Dershewitz	*24*	10	184		3 1/2[a]	child abuse	
Scarlet	*12*	32	646	0.86	20[a]	surreptitious	nurse
		39	5 067	0.56	41[a]	suicidal	nurse's aide
		25	4 600	4.41	20[a]	heroin addict	medical technican
		20	2 640	1.6	4	child abuse	nurse
		19	1 036	0.58	27[a]	surreptitious	
Schneider	*25*		500[b]		47	suicide	nurse
			28[b]		34	suicide	nurse
Stellon	*26*	4.5	300	0.0005[c]	16[a]	surreptitious	diabetic mother
Bauman	*27*	30–40	500	<0.1	67	inadvertant injection	hospital
Bauman	*28*		1 000	low	1	child abuse	diabetic brother
			2 500	low	1 1/2	child abuse	
Bauman	*29*	27	40 600	2.0	[a]	malicious	
Murray	*13*	18	4 200	1.0	22[a]	surreptitious	diabetic sister
Bauman	*15*	24	93	0.25	21[a]	surreptitious	nurse
		30	1 029	0.25	27[a]	surreptitious	nurse
		28	79	0.90	33[a]	surreptitious	nurse
		40	1 021		12[a]	surreptitious	diabetic sister
Couropmitree	*30*	17	3 305[d]	0.7	49	surreptitious	diabetic
Huddle	*31*	16	12	<0.3	21	surreptitious	diabetic

[a]Female, others were male.
[b]Cardiac blood from autopsy seven days post mortem.
[c]Picomol/mL.
[d]Extractable insulin.

laboratory for radioimmunoassay of insulin and C-peptide. These results and the serum glucose data are summarized in Fig. 1.

Insulin is synthesized by the endocrine pancreas and stored there as proinsulin [*8*]. Proinsulin itself has little glucose lowering activity. At the time of release, it is split into equimolar quantities of active insulin and a remnant molecule C-peptide which has no known biologic function. Insulin has a short halflife in the circulation of 5 to 10 min, while C-peptide is degraded at a slower rate resulting in a longer halflife and relatively larger circulating concentrations [*7*]. Both the normal pancreas and insulin-secreting neoplastic tumors secrete insulin and C-peptide [*8*]. In contrast, exogenous injected insulin does not contain C-peptide [*8*]. Thus, high circulating insulin and low C-peptide indicate the presence of exogenous insulin, as seen in Fig. 1. In the specimen obtained before the hypoglycemic episode and in the last specimen, both insulin and C-peptide were found, indicating the presence of endogenous insulin. During the time of abundant exogenous insulin and hypoglycemia, endogenous insulin production was suppressed as expected. Circulating glucose, operating through a negative feedback mechanism at the pancreas, is the predominant regulator of insulin secretion. The usefulness of the combined use of these assays in distinguishing between hypoglycemic episodes secondary to endogenous and exogenous insulin has been demonstrated repeatedly [*11–13*]. Both assays and their reagents are readily available commercially.

There are other causes of surreptitious hypoglycemia not caused by insulin, but attributable to secretagogue drugs such as tolbutamide or chlorpropamide, which are commonly used in the treatment of diabetes mellitus. These agents stimulate the secretion of endogenous insulin by the pancreas and enhance the action of insulin in the peripheral tissues. If the use of these secretagogue drugs is not considered, insulin and C-peptide assays are potentially misleading. The investigation of this form of surreptitious or malicious hypoglycemia includes demonstration of the drug in the circulation by specialized assays [*14*].

Bauman and Yalow [*15*] chose another approach to the differentiation of endogenous and exogenous insulin in human serum. The vast majority of insulin used for treatment of diabetes mellitus is porcine, bovine, or a mixture of both. Human insulin is prescribed infrequently [*16*]. The investigators used as an assay reagent a guinea pig antibody that does not distinguish between human, porcine, and bovine insulin, and also an antibody isolated from serum of diabetics treated with animal insulin. The latter antibody "crossreacted with human insulin much more weakly than with either porcine or bovine insulin" [*15*]. Their study clearly identified eleven cases of exogenous insulin administration with these species-specific assays. These procedures are solely research tools.

In a few highly specialized situations, particular caution is indicated in the interpretation of data of insulin assays. Patients previously exposed to exogenous insulin, such as insulin-treated diabetics, may have circulating antibodies which compete with the reagent antibody and, depending on the individual assay technique, may simulate high or low insulin concentrations [*17*]. However, anti-insulin antibodies do not cross-react in the C-peptide assays; therefore determination of C-peptide under these circumstances is not affected. Another possible source of confusion to be considered is cross-reaction of high circulating proinsulin in insulin or C-peptide assays. Gabbay et al. [*18*] reported a kindred with 18 members affected by an autosomal dominant defect of insulin synthesis evident by asymptomatic hyperproinsulinemia. Third, Benson et al. [*19*] described a group of Asian subjects with endogenous fasting hyperinsulinemia and hypoglycemia. The C-peptide concentrations were low, however, there was no reason to suspect interference by exogenous insulin. The high insulin levels are readily explained on the basis of circulating insulin autoantibodies which are an expression of autoimmune disease. Sudden release of active insulin from these autoantibodies have been thought to cause hypoglycemia in these patients. Most of the more than 85 cases described so far have occurred in Japan, have evidence of an autoimmune disease, or give a history of exposure to medicinal drugs [*20*]. Careful investigation, including procedures so far available only as research tools, may be required to unravel these most uncommon and complex situations.

We studied the stability of insulin in serum stored under standard laboratory conditions, at 4, 23, and 37°C. According to published test procedures for insulin and other peptide hormones, all specimens should be stored in the frozen state to preclude possible deterioration of the analyte before assay [*21,22*]. This recommendation is fully justified for clinical tests and research protocols when specimens are collected specifically for such assays. It also lends itself to challenge the validity of insulin assay data of specimens stored under conditions other than the frozen state. To our knowledge, the effect of various storage conditions on exogenous insulin in human serum has not been systematically studied. Findings of our study indicate that insulin is fairly stable at 4°C and at room temperature, and largely degraded at 37°C over four to five days (Fig. 2). Eighty to ninety-five percent of the insulin is recoverable after six days at 4°C. Since surreptitious or malicious administration of insulin may not be suspected until days after the onset of hypoglycemia, the determinations of insulin in sera stored refrigerated at 4°C are valid.

Similar studies of the stability of endogenous insulin have been reported. Kubasik et al. [*32*] examined the effects on endogenous insulin in human serum. They found no degradation at 4°C and approximately 25% degradation at room temperature over seven days when compared with storage in the frozen state. Their data are given as means of twelve specimens

analyzed in triplicate, and thus offer no measure of the variability of individual specimens and of the assay reproducibility. Reimers et al. [*33*] studied the effect of storage on endogenous insulin in canine serum and reported similar stabilities. Thus, there is no evidence to suggest that endogenous and exogenous insulin differ in stability.

Our data indicate that insulin assays can be performed on specimens which have not been collected and stored under optimal conditions. While the assay results may not yield the exact insulin content at the time of specimen collection, they nevertheless serve to verify the diagnosis of insulin excess.

Acknowledgments

The authors wish to thank Mike Peters for technical assistance and Betty Payne for typing the manuscript. The work was supported in part by the Research Service of the Veterans Administration.

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