CASE REPORT

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Insulin As a Lethal Weapon

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ABSTRACT: This report describes the method employed to demonstrate that a fatal hypoglycemic episode was due to marked beef hyperinsulinemia. From the rate of disappearance of the circulating insulin, the most likely type of insulin preparation employed was determined along with the estimated time and probable route of occult insulin administration.

KEYWORDS: toxicology, insulin, blood

This report describes a nondiabetic patient who had a metastatic malignancy and who died after an extended period of severe hypoglycemia caused by hyperinsulinism. Differentiation between endogenous and exogenous insulin-induced hypoglycemia can be performed directly and definitively with appropriate laboratory studies [*1*]. In this study we describe the method used to demonstrate that a severe, fatal hypoglycemic episode was associated with marked hyperinsulinemia resulting from occult malicious administration of a vial of regular insulin.

Case Report

The patient was an elderly female with metastatic renal carcinoma. The patient had been hospitalized for several weeks with a pathologic fracture of the hip. No parental or oral medications were prescribed at the time of the incident. The patient was ready for discharge and awaiting placement in a nursing home when she was discovered at 1:00 a.m. to be unresponsive while lying in bed. An immediate blood glucose determination at 3:30 a.m. was 27 mg/dL. Intravenous glucose therapy was immediately begun. However, at 9:30 a.m. the blood glucose level was found to be only 2 mg/dL. The patient never regained consciousness and was pronounced dead about 16 h after she had been found comatose. Postmortem examination failed to disclose an insulinoma or a possible site of insulin injection. There was no evidence of residual malignancy.

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Methods

Blood glucose determinations were confirmed in the routine chemistry laboratory (after immediate determinations had been made at the bedside). Several plasma samples were collected at intervals and frozen for subsequent analysis.

To find the concentration and type of insulin in the patient's plasma two antisera were used [2]: one was a guinea pig antiserum that in cross-reaction does not distinguish among bovine, porcine, and human insulins, and the other was a human antiserum that cross-reacts with human insulin much more weakly than with bovine insulin. Radiolabeled (^{125}I) bovine insulin was employed as a tracer in each assay, and human and bovine insulins were used as standards. Plasma was assayed at several dilutions [3,4].

Results

At about 3:30 a.m. approximately 2½ h after the patient had been noted comatose, the plasma insulin was determined to be 40.6 units per litre (U/L) as measured with a guinea-pig antiserum, which does not distinguish between animal and human insulins. Insulin concentrations measured similarly in plasma obtained at 9:30 a.m. and 2:00 p.m. were 7.5 U/L and 0.63 U/L, respectively. A dilution curve of the patient's plasma was superposable upon standard curves for beef and for human insulin in the guinea pig assay system (Fig. 1, left). It was superposable only on the beef insulin standard curve when the human antiserum was employed (Fig. 1, right). Furthermore, plasma insulin concentrations measured with the human antiserum and the beef insulin standard were identical with those determined in the guinea pig assay system. Thus the hyperinsulinism was attributable to an animal insulin that cannot be distinguished immunochemically from beef insulin. The C-peptide levels remained suppressed at less than 2 ng/mL during the period the plasma insulin remained elevated.

The rate of disappearance of the circulating insulin in this patient was compared with the time of appearance and disappearance of insulin in the plasma of another patient who reported having taken a large dose of neutral protamine Hagedorn (NPH) insulin in a suicide attempt (Fig. 2). The highest level of circulating insulin was measured 6 h after administration of the NPH insulin, and 9 h later it was still about one third the peak concentration. In the current study, by contrast, the plasma insulin was maximal at the first sampling and subsequently disappeared with a half-life of about 2 h. This rate of disappearance is consistent with subcutaneous or intramuscular administration of regular insulin. Intravenous administration of such insulin would have resulted in a half-life for disappearance no longer than about 20 min [2].

The amount of insulin administered can be estimated from kinetic studies of the distribution of insulin. The space of distribution of insulin 30 min after intravenous administration in man of tracer amounts of insulin has been reported to average about 37% of body weight [5]. Since some receptor sites are saturated by excessive insulin but others are not [6], the space of distribution of this extremely large amount of insulin is probably somewhat less than 37% but still somewhat larger than extracellular space, 16% of body weight, as measured by small ions such as ^{24}Na and ^{82}Br [7]. The peak insulin was 41 U/L, and the space of distribution at that time was estimated to be at least 20% of body weight (50 kg). Therefore, the amount of nonhuman insulin in the body at the time of the first sampling was at least 400 U. Since the half-life for disappearance is about 2 h, the amount of insulin in the body at the time the patient was found comatose was probably at least 800 U.

Discussion

Hyperinsulinism with associated hypoglycemia is a consequence of either endogenous secretion or exogenous administration of insulin. By demonstrating with a species-specific

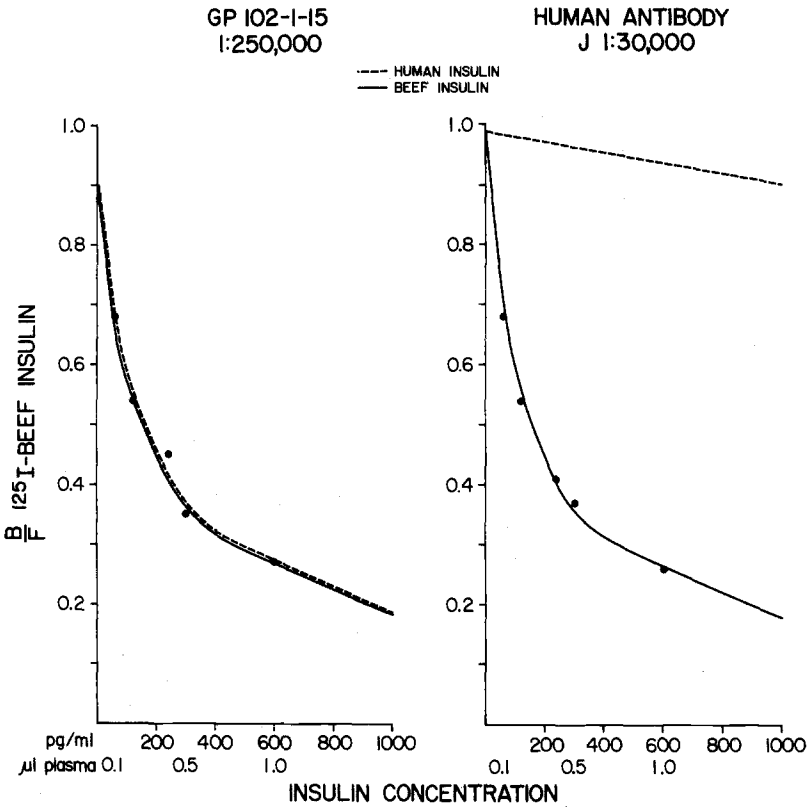

FIG. 1—*Standard curves for insulin assay. The solid lines show the standard curves for beef insulin: the broken lines are the standard curves for human insulin; the circles denote dilutions of the patient's plasma ranging from 0.1 to 1.0 µL. In the left panel a dilution of the patient's plasma can be superposed on either curve; in the right panel it can be superposed only on the beef insulin.*

antiserum that the circulating insulin was bovine, not human, in origin, endogenous insulin secretion from an insulinoma or from pancreatic secretion stimulated by an oral hypoglycemic agent was definitively excluded.

Exogenous hyperinsulinism may result from one of three causes: surreptitious self-injection, accidental injection, or occult malicious administration. Since this patient after hip fracture was immobilized in bed and did not have ready access to insulin in her hospital room, nor was she on parenteral medication, it must be concluded that she was the victim of occult malicious insulin administration. This conclusion is strengthened by the excessively elevated plasma insulin levels. The amount of animal insulin in the body at the time she was found comatose was estimated to be about 800 U. Since insulin is now routinely available in 10-mL vials containing 100 U/mL, it is most likely that the patient received most or all of a vial of a short-acting insulin subcutaneously or intramuscularly. Therefore, the time of administration is likely not to have been more than an hour before the patient was noted to be comatose. The suppressed values for C-peptide were consistent with the hyperinsulinism's resulting from exogenous insulin administration.

Radioimmunoassay provides the sensitivity and specificity for measuring and identifying the species of insulin in plasma and therefore is applicable to antemortem as well as postmortem investigations. Earlier reports [*8,9*] described the measurement by crude bioassay of pharmacologic concentrations of insulin extracted from buttock tissue at sites of

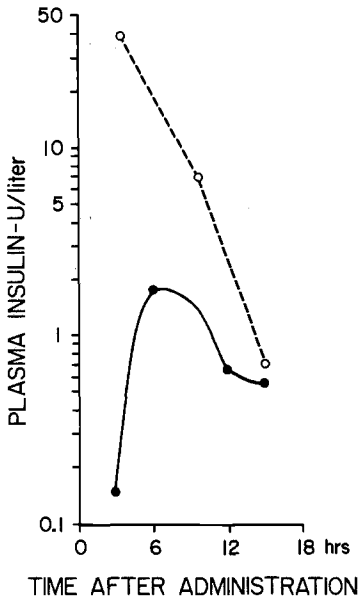

FIG. 2—*Plasma insulin as a function of time in patient known to have taken NPH insulin in a suicide attempt* (solid line) *and in the patient of the current study* (broken line). *The rate of disappearance of insulin is consistent with subcutaneous or intramuscular administration of a short-acting insulin preparation.*

hypodermic needle marks, thus proving that the death of a young woman was a consequence of malicious insulin administration. In the present case no needle marks were found at autopsy. This might be attributable to the high gauge (smaller size) needles now commonly employed for insulin administration.

Any nondiabetic patient in a hospital or nursing home setting who has an abrupt change in level of consciousness may be the subject of accidental or malicious insulin administration. Proper management includes an immediate glucose determination and immediate administration of a concentrated solution of glucose both as a diagnostic and therapeutic maneuver. This should be followed by continuous glucose administration and frequent immediate blood glucose measurements to assure that adequate therapy is maintained. Extended duration of severe hypoglycemia, as in this case, is usually fatal.

Acknowledgments

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