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A Case of Surreptitious Glargine Overdose Confirmed by Insulin Pharmacokinetic Time Curves

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RUNNING TITLE:

Insulin Cross-reactivity in Glargine Overdose

ABSTRACT

Case: A 49-year-old man presented with recurrent altered conscious state suggestive of encephalitis. This was followed by an episode of severe hypoglycaemia requiring protracted intravenous glucose administration. Comparing the pharmacokinetic time curves of serum insulin levels on two insulin immunoassays with different insulin analogue cross-reactivity allowed the likely diagnosis of surreptitious glargine overdose to be made rapidly.

Discussion: The differing insulin analogue cross-reactivity of serum insulin immunoassays, in this case the Abbott ARCHITECT and Roche Elecsys, allows the presence of insulin analogue to be detected. Through comparison of time curves the characteristic signature of the specific causative insulin analogue can be identified. This information confirms surreptitious insulin overdose in a timely manner, therefore avoiding the expensive and time-consuming investigations required to exclude alternate causes of severe hypoglycaemia.

Keywords: insulin, immunoassay, pharmacokinetics, hypoglycaemia

Case

The differential diagnosis for acute profound hypoglycaemia includes surreptitious or malicious insulin overdose, which can be difficult to identify in the absence of prescribed insulin or psychiatric illness. We report a case where surreptitious subcutaneous injection of high-dose insulin glargine (Lantus®, Aventis Pharmaceuticals) was determined to be the most likely toxicologic aetiology of

protracted hypoglycaemia through the use of two insulin immunoassays with different cross-reactivities to synthetic insulin analogues.

Presentation

A 49-year-old man was admitted to a rural hospital with bradyphrenia and bradykinesia. He had no medical history including of psychiatric or neurologic disorders and took no regular medications. His symptoms resolved following two days of empiric treatment for presumed infective encephalitis. Over the following months he re-presented four times with drowsiness and confusion, each time recovering over 3-5 days following intravenous methylprednisolone. At each of these presentations he was transferred to the same tertiary institution where extensive investigations including biochemistry, brain MRI, electroencephalography and lumbar puncture were non-diagnostic. A presumptive diagnosis of seronegative autoimmune encephalitis was made and sodium valproate, mycophenolate mofetil, and prednisolone commenced.

Five months following the initial presentation the man re-presented with drowsiness and dystonic posturing. Random blood glucose (BG) levels were 6-7 mmol/L until 8.00pm on day 4 when it measured 1.1 mmol/L in the setting of tachycardia (120 beats per minute), diaphoresis, and reduced consciousness. Hypoglycaemia persisted despite intramuscular glucagon and a continuous infusion of intravenous 50% dextrose. He was transferred to tertiary intensive care where continuous intravenous 10% dextrose was required for 160 hours to manage recurrent hypoglycaemia.

Investigations

Investigations at the time of hypoglycaemia revealed a markedly elevated insulin concentration (356.8 mIU/L) with undetectable c-peptide (< 0.03 nmol/L) (Figure) on the ARCHITECT analyser (Abbott Laboratories, Abbott Park, Illinois). Over time both plasma insulin concentration and the intravenous dextrose requirement to maintain euglycaemia fell. Insulin antibodies and sulphonylurea screen were negative. Combined with the undetectable c-peptide level, these results suggested exogenous insulin administration, which given the time course of hypoglycaemia would have occurred during admission to the rural hospital. However, following an internal investigation of medication charts and dispensing records at both hospitals and the ambulance service, no evidence of insulin prescription, administration, or irregularity between stock and dispensing records was found. No insulin injection site was detected on physical examination and no other members of the patient's household had diabetes or were prescribed insulin or sulphonylurea medications. Of note, no hypoglycaemia had been detected during previous presentations.

As surreptitious insulin administration was suspected, samples were re-analysed on the Elecsys (Roche Diagnostics, Indianapolis, Indiana) immunoassay, which has an absent to low cross-reactivity with synthetic insulin analogues. This result was significantly lower than the Abbott assay (13.2 vs 88 mIU/L) (Figure). The c-peptide level was undetectable, consistent with the previous result. Urine was unavailable for the confirmation of glargine metabolite, however, urine samples from preceding admissions had tested positive for benzodiazepines when these had not been administered by the ambulance service nor prescribed to the patient. Our patient and their spouse firmly denied self-administration of insulin despite knowledge of the laboratory results and declined forensic referral. After discharge, his anti-epileptic and

immunosuppressant medications were weaned and he remains well with no further episodes of hypoglycaemia or altered conscious state.

Discussion

Following cleavage from proinsulin, circulating human insulin comprises two polypeptide chains that are 21 (A-chain) and 30 (B-chain) amino acid residues in length. Insulin analogues used in diabetes management include aspart, lispro, glulisine, glargine and detemir, which all have B-chain carboxy-terminal modifications(1). Thus, sandwich immunoassays designed specifically to detect endogenous human insulin that target the B-chain carboxy-terminal have low cross-reactivity with insulin analogues while those targeting different epitopes exhibit high cross-reactivity(1). In vitro studies using insulin analogue diluted in aqueous bovine serum albumin have been performed on various automated insulin immunoassays. The ARCHITECT assay has been shown to be non-specific for human insulin, its cross-reactivity with insulin analogues at a concentration of 100 mIU/L was measured as 75% (aspart), 100% (lispro), and 83% (glargine) (2). By contrast, the Roche assay has been found to be specific to human insulin and, uniquely among such assays, does not detect aspart, lispro, or glargine analogues (cross-reactivity < 0.2% at a concentration of 100mIU/L)(3). In vitro spiking of the parent drug, however, does not permit cross-reactivity assessment of insulin analogue metabolites formed in vivo. This is particularly important for insulin metabolites that have long circulating half-lives and can activate the insulin receptor.

 Glargine is a long-acting insulin analogue that is formed by the substitution of glycine for asparagine at position 21 on the A-chain and the addition of two arginine residues to the B-chain carboxy-terminal. It is normally injected subcutaneously where it forms a depot that is absorbed over 18-24 hours. On entering the circulation, glargine

is rapidly metabolised by serum carboxypeptidases, first by proteolytic cleavage of the B-chain terminal arginines to form 21^A-Gly-insulin, (denoted M1), and then by cleavage of the now-exposed threonine to form 21^A-Gly-des-30^B-Thr-insulin (denoted M2)(3)(4). The M1 metabolite predominates though both are functionally active(1). There is some inter-individual variability in the rate of conversion seen in biotransformation studies, which is likely determined by genetic differences in carboxypeptidase activity, but conversion is rapid with one study of 69 individuals finding 46-98% conversion of glargine to M1 by 30 minutes(4). Given its B-chain equivalence with endogenous insulin, M1 is detected by assays that target the B-chain carboxy-terminal while M2 is not. The most comprehensive study of immunoassay cross-reactivity with insulin analogues to date was consistent with previous analyses and quantified both M1 and M2 cross-reactivity(1). At a 100mIU/L concentration (60mIU/L for glargine metabolites) this study detected the following cross-reactivities for the ARCHITECT assay: aspart 67%, lispro 87%, glulisine 7% glargine 108%, M1 114%, M2 109%. For the Roche assay cross-reactivities were: aspart <0.2%, lispro <0.2%, glulisine <0.2%, glargine <0.2%, M1 23%, M2 <2%.

The very high insulin concentrations with suppressed c-peptide on the ARCHITECT assay during the period of hypoglycaemia was consistent with administration of an insulin analogue other than glulisine, the only analogue not significantly detected by this assay. The far lower, but inappropriately measurable, insulin concentration on the Roche assay is most clearly explained by the presence of the glargine M1 metabolite since this assay displays 23% cross-reactivity for M1 with human insulin whereas all other insulin analogues and M0 glargine are not detected(1). Hypoglycaemia duration and carbohydrate requirements in our case paralleled those of

previously reported glargine overdoses(5)(6)(7). Prolonged hypoglycaemia of up to 120 hours is typical with large glargine overdoses where the ‘depot effect’ prolongs absorption well beyond 18-24 hours(8). In our patient, 140 hours after initial hypoglycaemia detection when the administered glargine and its metabolites would be cleared from circulation, insulin concentrations measured by the Abbott and Roche immunoassays were almost identical (Figure).

Clinical implications

This case highlights the complementary information provided by insulin concentrations measured concurrently on insulin-specific and non-specific immunoassays when evaluating suspected insulin toxicity. The differing pharmacokinetic time curves between the two immunoassays not only flagged the presence of an insulin-like substance with variable cross-reactivities, the pattern suggests glargine as the culprit. This technique returns results within 24 hours, a more rapid turn-around than the relatively inaccessible insulin radioimmunoassay, or the insulin antibody assay used to exclude insulin autoimmune hypoglycemia. With the Australian release of Toujeo® (glargine 300 units/mL), a glargine overdose of 450 units can be readily achieved with a single injectable device, potentially leading to more severe and prolonged hypoglycaemia. Furthermore, in institutions that measure insulin on the Roche analyser, particularly in the setting of an aspart or lispro insulin analogue overdose, plasma assessment during a hypoglycaemic episode will return an undetectable c-peptide and insulin level. These results might mislead the clinician to erroneously investigate for non-islet cell tumour hypoglycemia.

Rapid identification of the presence of an insulin analogue responsible for hypoglycaemia allows the treating clinician to discuss the likelihood of exogenous

insulin administration with the patient or to formally confirm the suspected insulin analogue used, thus abrogating the need to perform extensive investigations for other aetiologies. Furthermore, this information allows the time course of recovery to be predicted. Concurrent use of insulin-specific and non-specific immunoassays can thus expedite appropriate patient care.

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FIGURE CAPTION:

Figure: Pharmacokinetic time curves of the two insulin immunoassays and glucose concentrations from the time of admission. No hypoglycaemic episode (plasma glucose concentration < 3.9 mmol/L) was recorded after 106 hours.