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Interpreting insulin immunoassays during investigation of apparent spontaneous hypoglycaemia and insulin overdose

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Abstract

We report two cases of hypoglycaemia; one with apparently spontaneous hypoglycaemia and one with presumed insulin overdose. In both cases insulin concentration was normal when measured with the Roche immunoassay, but elevated when remeasured with the Advia Centaur immunoassay and a diagnosis of hypoglycaemia secondary to insulin analogue administration was made. These cases highlight that physicians need to understand the binding characteristics of the insulin immunoassay they use.

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Severe hypoglycaemia can cause seizure, loss of consciousness and even death. Distinguishing whether hypoglycaemia is insulin-dependent and, if so, whether hyperinsulinaemia is exogenous or endogenous is critical in the diagnostic work-up of such patients. It is crucial to obtain simultaneous measurements of insulin and C-peptide during an episode of hypoglycaemia to differentiate between endogenous and exogenous hyperinsulinaemia. We report two cases of hypoglycaemia where the diagnosis was initially obscured by low cross-reactivity between insulin analogues and the commonly used Roche insulin immunoassay (Roche Diagnostics Australia Pty Ltd, NSW, Australia). These cases illustrate that an understanding of insulin assay binding characteristics is essential to arrive at a correct diagnosis.

Case 1: A 48 year old woman was admitted to hospital after a generalised seizure. She initially regained consciousness, but then became drowsy with a finger prick blood glucose level (BGL) of 2.0 mmol/L. The patient was administered 50 mL 50% dextrose intravenously and symptoms improved. She had two previous presentations to hospital with suspected hypoglycaemia, but had remained euglycaemic throughout a prior 72 h fast. Other medical history included seizures and/or pseudoseizures, diet-controlled type 2 diabetes, hypercholesterolaemia, chronic back pain and gastro-oesophageal reflux. Her medications were sodium valproate 400 mg twice daily, controlled release morphine sulphate 30 mg daily and esomeprazole 40 mg daily. The patient reported no contact with other persons with diabetes or diabetes medications.

The patient was admitted for a 72 h fast. After 24 h fasting the patient became drowsy and plasma glucose fell to 2.6 mmol/L, but symptoms and plasma glucose improved spontaneously without intervention (Table 1). On day 3 of the fast she became unresponsive with a finger prick BGL of 1.9 mmol/L. Fifty mL of 50% dextrose was administered intravenously after bloods were collected. Laboratory plasma glucose was 2.6 mmol/L. Despite suppression of beta hydroxybutyrate indicating insulin-like activity, insulin (Roche) and C-Peptide (Advia Centaur, Siemens Healthcare, Vic., Australia) concentrations were low during hypoglycaemia (Table 1). Plasma sulphonylurea screen was negative, morning cortisol was 698 nmol/L and insulin-like growth factor-1 was 21 nmol/L (7–25 nmol/L). Computed tomography scan of the chest and abdomen did not reveal a mass lesion.

As administration of an insulin analogue was a differential diagnosis, insulin concentrations were re-measured using another immunoassay (Advia Centaur, Siemens Healthcare). This revealed higher insulin concentrations during hypoglycaemia, but similar insulin concentrations during euglycaemia (Table 1), suggesting a diagnosis of factitious hyperinsulinaemia secondary to administration of an insulin analogue. The patient denied insulin administration, but she has not been readmitted to our Hospital with hypoglycaemia in the 3 years since these laboratory results were discussed.

Case 2: A 74-year-old woman who was well the night prior to admission was found unconscious in bed. Past medical history included type 2 diabetes and interstitial lung disease. The patient's usual medications were insulin aspart/isophane 22 units twice daily (NovoMix 30, Novo Nordisk Pharmaceuticals Pty Ltd., NSW, Australia), metformin 500 mg nocte and prednisone 6 mg daily. Paramedics recorded an undetectable finger prick BGL and administered 1 mg glucagon intramuscularly and commenced intravenous 10% dextrose. On arrival to hospital the Glasgow coma score was 4 and pupils were equal but slow to react to light. There was no subcutaneous depot of insulin palpable. Venous blood gas glucose was initially 14.6 mmol/L, but it fell to 1.6 mmol/L three hours later. The patient was intubated and intravenous dextrose infusion and hydrocortisone were administered. Despite this, glucose level dropped to 3.5 mmol/L five hours after admission. Serum insulin (Roche) at this

Table 1 Biochemistry results from case 1

	Time (hours)	Glucose (mmol/L)	Insulin (mU/L) Roche	Insulin (mU/L) Advia	C-peptide (pmol/L)	βOH butyrate (mmol/L)
Day 1	0804	5.7	11		1082	0.2
	1835	5.6	5.3	5.4	503	
Day 2	0500	**2.9**	**0.6**	**34**	<100	0.13
	0645	**2.6**	**0.5**	**33**	<100	0.11
	0820	**3.1**	**0.5**	**24**	<100	0.19
	1800	4.6	7.0	7.2	384	0.19
Day 3	0900	5.1	4.2	4.5	391	0.61
	1640	**2.7**	**<0.5**	**32**	<100	0.14
	1730	**2.6**	**<0.5**	**24**	<100	0.17
	1850	11.3		29	321	0.20

Bold values highlight periods of hypoglycaemia with discordant results using the two insulin assays. βOH butyrate, beta hydroxy butyrate

Table 2 Cross-reactivity between insulin analogues and insulin immunoassays

Assay	Glargine	Detemir	Aspart	Glulisine	Lispro
Roche (Roche Diagnostics)	+	–	–	–	–
Advia Centaur (Siemens)	+++	+	+++	–	+++
IMMULITE 2000 (Siemens)	++	+++	++	–	++
ARCHITECT (Abbott)	+++	++	+++	+	+++

–, <10% cross-reactivity; +, 10–25% cross-reactivity; ++, 25–75% cross-reactivity; +++, >75% cross-reactivity. Adapted from references 2, 8 and 9 with permission.

time was 5.5 mU/L and C-Peptide (Advia Centaur) was 68 pmol/L, levels not consistent with endogenous hyperinsulinaemia.[1] Plasma metformin was <1 mg/L and insulin antibodies were not detected.

As insulin overdose was suspected, serum insulin was retested with another assay (Advia Centaur). This revealed a markedly elevated insulin of >300 mU/L, consistent with insulin overdose with an insulin analogue. Intravenous glucose was weaned and ceased two days after admission and an insulin infusion was subsequently required to treat hyperglycaemia. However, the patient did not regain consciousness and died five days after admission.

Discussion

Endogenous insulin comprises two polypeptide chains; an A chain with 21 and a B chain with 30 amino acids. Insulin analogues are structurally similar to human insulin with only minor alterations, predominantly at the carboxy-terminal of the B chain. Insulin aspart has a single substitution of aspartic acid for proline at position B28, while the amino acids at positions 28 (Pro to Lys) and 29 (Lys to Pro) of the B chain are reversed in insulin lispro.[2,3] Insulin glulisine also has an amino acid substitution at the carboxy-terminal end of the B chain (Lys to Glu at B29) and also one at the amino-terminal end (Asp to Lys at B3).[4] These amino acid substitutions reduce hexamer formation, resulting in rapid absorption after subcutaneous injection, a faster onset and shorter duration of action. Insulin glargine has a glycine substituted for asparagine at A21 and two additional arginine residues at the carboxy-terminal of the B chain, resulting in slower, more prolonged absorption than regular insulin and a longer duration of action.[2] Insulin detemir also has a longer duration of action resulting from a fatty acid side chain linked to the amino acid at position B28.[5]

Insulin is usually measured by immunoassays that use the sandwich technique. However, the site of antibody binding varies for different assays and influences detection of insulin analogues. As one of the antibodies in the Roche immunoassay is directed against the carboxy-terminal region of the B chain, it does not detect insulin aspart, lispro, detemir or gluisine.[2,6] Although insulin glargine also has a modification at the carboxy-terminal end of the B chain, it undergoes biotransformation in human serum to metabolites M1 and M2 and the M1 metabolite binds to the Roche assay.[6,7] In contrast, the antibodies in the Advia Centaur immunoassay are directed against a different region of the insulin molecule. Therefore, it recognises insulin aspart, lispro, detemir and glargine, but not glulisine, because of the additional amino acid substitution at the amino-terminal end of the B chain.[6] Table 2 compares the cross-reactivity between insulin analogues and several insulin immunoassays used in Australia.[8,9]

The high analytical specificity of the Roche insulin immunoassay for endogenous insulin and lack of cross reactivity with several insulin analogues is noted in the Roche Product Information. However, there have been case reports of hypoglycaemia, predominantly in the paediatric literature, in patients with known diabetes treated with insulin analogues where the cause of hypoglycaemia was not initially clear.[10,11] These cases expand the clinical scenarios where an understanding of insulin assay binding is required for the correct diagnosis. Case 1 had apparently spontaneous hypoglycaemia. In this setting, the underlying cause is usually suggested by measurements of insulin and C-peptide during hypoglycaemia.[1] Our case highlights the need to be aware of insulin assay binding sites in this context, an issue that is not discussed in Endocrine Society Clinical Practice Guidelines.[1] Case 2 demonstrates that unawareness of the binding characteristics of the Roche immunoassay may prevent detection of severe hyperinsulinaemia during an overdose with an insulin analogue sufficient to cause prolonged loss of consciousness and death.

In conclusion, an understanding of insulin assay binding sites is critical when assessing apparently spontaneous hypoglycaemia and presumed insulin analogue overdose. Endocrinologists, Emergency and Critical Care physicians and Chemical Pathologists need to be aware of the binding characteristics of the insulin assay they use.

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Acute kidney injury is under-recognised and under-reported in hospitalised patients in Australia

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Abstract

Acute kidney injury (AKI) in hospitalised patients is associated with adverse outcomes; however, it remains unrecognised and under-reported. A total of 48 045 serum creatinine results from 8129 tertiary hospital inpatients were reviewed. The prevalence of AKI was 4.33%. Mortality was significantly higher in patients with AKI (16.76%) compared to those without AKI (1.88%, $P < 0.001$). Documentation of AKI in discharge summaries was poor.

Acute kidney injury (AKI) in hospitalised patients is strongly associated with adverse outcomes, including increased mortality.[1–3] It has been hypothesised that AKI in hospitalised patients is both a reflection of a critically unwell patient as well as an independent determinant of poor outcomes.[4] Early intervention for AKI may improve outcomes; however, referral to inpatient nephrology services prior to the initiation of dialysis is under-utilised.[5,6] This may be because early stage AKI is unrecognised by ward medical staff or the presence of advanced age and extensive comorbidities in many of these patients complicates decision-making.[5,7] Recently, it has been recognised that the severity and duration of AKI in hospitalised patients is a risk factor for the development of chronic kidney disease[8,9] and current guidelines recommend that these

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