CASE REPORT

Dilemma of diagnosing sulphonylurea overdose in children: deliberations and considerations before reaching a diagnosis

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SUMMARY

A 15-year-old non-diabetic Caucasian girl presented with sudden onset of seizures, unrecordable blood glucose readings and acute renal failure. She denied any medication ingestion and no other precipitating factors were encountered for this acute presentation. She was treated with intravenous glucose infusion and hydrocortisone injection. Investigations showed a non-ketotic hypoglycaemia with high C-peptide and insulin levels. It took several days and multiple investigations to establish the exact cause of her persistent hypoglycaemia before it was concluded to be secondary to gliclazide overdose in a suicide attempt by the young girl. She made a complete recovery in a week with no apparent lasting neurological or renal impairment.

BACKGROUND

Sulphonylurea is a group of oral hypoglycaemic agents acting by promoting direct secretion of insulin from the pancreatic beta cells even when the glucose concentrations are well below the threshold for glucose-driven insulin release.¹ As a result, it can mimic the findings of hyperinsulinism-induced hypoglycaemia that is inappropriately high insulin and C-peptide suggesting endogenous production of insulin rather than exogenous insulin administration in which C-peptide levels would be low. In our patient, the lack of evidence of an insulinoma aided our diagnosis of possible sulphonylurea intoxication. Intoxication with sulphonylurea is associated with profound and prolonged hypoglycaemia refractory to dextrose treatment more so within the paediatric and elderly population.² Sulphonylurea overdose has also been reported previously to cause profound neuroglycopenic response without autonomic or adrenergic responses.^{3,4} Herein, we report a 15-year-old girl who presented with acute onset of persistently severe non-ketotic hypoglycaemia. A hypoglycaemic drug as the cause of hypoglycaemia was considered on the basis of the biochemical findings together with the lack of evidence of insulinoma and development of acute kidney injury (AKI). A gliclazide overdose was confirmed by the detecting presence of the drug in urine. By way of this case study, we would like to highlight the importance of systematically ruling out causes of non-ketotic hypoglycaemia and looking for evidence of unusual causative agents causing a combination of

hypoglycaemia and renal failure. We would also like to reiterate the importance of executing the core skills in taking a thorough psychosocial history in adolescent patients and using the pertinent cues from the history and clinical examination to consider suicidal ideation and attempt at the top of the list of differential diagnosis.⁵

CASE PRESENTATION

Our patient is a fit and healthy 15-year-old Caucasian girl who presented to the emergency department (ED) with sudden onset of generalised tonic seizures secondary to profound hypoglycaemia (figure 1). She was living with her mother, step-father and three stepsiblings. We were unable to elucidate an obvious cause of this hypoglycaemia from the history given by the patient and her carers. The night before presentation, she had gone to bed feeling 'livid and nauseous' but had no other adrenergic symptoms such as hunger, anxiety, palpitations or sweating. In the early hours of the morning of her admission, her mother found her in bed unconscious and stiff with frothiness in her mouth. In the ED of the local district general hospital, her capillary blood glucose was recorded to be 'low' on the bedside glucose monitor. She was haemodynamically stable and required no resuscitation other than 2 mL/kg of intravenous 10% dextrose bolus to stabilise blood glucose levels. By the afternoon, she had made a complete recovery and was discharged home. She re-presented on the same evening to the ED with another episode of generalised seizure and unrecordable blood glucose and was treated with intravenous hydrocortisone, subcutaneous glucagon and 2 mL/kg 10% dextrose. Subsequently, she was admitted to the paediatric ward for ongoing management and investigations. On admission, her Glasgow coma score was 6/15, heart rate 80/min, oxygen saturation 99% in air, respiratory rate 20/min and blood pressure 125/82 mm Hg. Her blood glucose on the monitor was unrecordable, which was confirmed by a laboratory measured glucose level of 0.8 mmol/L. On this occasion, a hypoglycaemia screen was sent to the laboratory prior to administering further dextrose boluses and an infusion of 10% dextrose commenced. The maximum glucose requirement to maintain normal blood glucose was 8 mg/kg/min.

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Figure 1 The 24-hour trend in bedside monitoring of blood glucose levels.

On clinical examination, she was noted to have multiple superficial lacerations to her left arm, right ankle and left wrist. Fresh lacerations with bleeding were noted on the left wrist. In view of these findings, urine was collected for a routine toxicology screen to exclude overdose with common drugs of abuse, together with a blood sample to exclude paracetamol/salicylate overdose. Results of these investigations were normal. The rest of her general and systemic examination was normal.

Further history from the family revealed that she was known to the safeguarding team for previous self-harm with the most recent episode having occurred 2 weeks prior to this admission. She had also been reported to be facing multiple difficulties with family and school. Her mother had recently suffered a stroke and was on amlodipine, omeprazole and sertraline tablets. Her stepfather was on allopurinol and naproxen tablets. There was no known family member on diabetes medication, and the patient firmly denied any substance misuse or drug overdose despite several attempts made by various health professionals at different time points to engage with her.

On day 2 of her admission, while awaiting the results of her hypoglycaemia screen, her blood pressure started to rise and she was noted to develop progressively worsening proteinuria, haematuria along with a rise in serum creatinine levels consistent with AKI stage 3 (figure 2).

In view of the clinical history, renal failure and results of the initial hypoglycaemia screen, it was felt to be important to exclude the presence of sulphonylurea. Screening for oral hypoglycaemic agents in urine was undertaken despite repeated denials of any known agents within the family home or with the extended family, which confirmed the presence of gliclazide.

This confirmed the diagnosis of deliberate drug overdose as a cause of the AKI and hypoglycaemia.

Further survey of the 'grandmother's' home was undertaken after these results were confirmed, and late maternal 'grandfather's' unused medication box was found in a cupboard, which contained his gliclazide tablets. Maternal grandmother had completely forgotten the existence of this box after her husband's death. On direct questioning and with the results of laboratory test confirming the presence of gliclazide in urine, the patient reluctantly admitted to having deliberately taken gliclazide tablets that belonged to her late grandfather, as a suicide attempt, following a disclosure with her family members of a severe trauma, which she had sustained in the past and had not divulged to any member of the family at that time with a view to not to upset her mother and siblings. She admitted that it made her extremely upset when her mother got to know of her abuse. And she did not want to face her mother being upset about her and thus decided to end her life.

INVESTIGATIONS

All investigations are summarised in table 1. Glucose was confirmed to be low (0.8 mmol/L) with analysis of 3-OH butyrate and free fatty acids indicating absent ketogenic and lipolytic response consistent with hyperinsulinism. Urinary ketones were also negative. Insulin and C-peptide levels were inappropriately elevated suggesting an endogenous source of the insulin; however, she had a normal CT scan of the pancreas. Analysis of urine by mass spectrometry (ultraperformance liquid chromatography-time of flight-mass spectrometry) indicated the presence of gliclazide as the source of the inappropriate endogenous production of insulin. Metabolic alkalosis with hypokalaemia and hypophosphataemia was noted on admission. Renal function tests revealed a progressively worsening renal failure with creatinine levels peaking at 198 µmol/L (AKI stage 3) 4 days after admission (figure 2). A synacthen test ruled out adrenal insufficiency. The rest of her biochemistry and metabolic screen was normal (table 1). A routine urine toxicology screen was negative. Table 1 shows the summary of all investigations with interpretation and reference values.

DIFFERENTIAL DIAGNOSIS

A sudden unexplained profound hypoglycaemia in a non-diabetic young adult directed us to consider the following organic causes at the first instance:

1. adrenal Insufficiency,
2. pituitary insufficiency,
3. insulinoma,

Figure 2 Trend of creatinine, urea and phosphate levels.

Table 1 Summary of all investigations

Test number	Normal values (units)	Plasma glucose	On admission	Hypoglycaemia screen					
1	3.3–6.0 (mmol/L)	Glucose	2.2	0.8					
Test number	Expected response (units)	Hypoglycaemia screen	Sample type	Result	Comment				
1	Low	C-peptide	Serum	3135	Inappropriately high (fasting reference range 298–2350)				
2	Suppressed (pmol/L)	Insulin	Serum	456.1	Not suppressed (<14 pmol/L) in response to hypoglycaemia				
3	Increase (mmol/L)	Free fatty acids	Plasma	0.3	Poor lipolytic response to hypoglycaemia				
4	Increase (mmol/L)	3-Hydroxybutyrate	Plasma	<0.1	Absent ketogenesis				
5	>550 (nmol/L)	Cortisol	Serum	>1650	Cannot interpret as hydrocortisone given in A+E				
6	>6.7 (µmol/L)	Growth hormone	Serum	29.3	Appropriate response				
7	0–50 (mmol/L)	Ammonia	48	Normal					
8	0.5–2.2 (mmol/L)	Lactate	1.8	Normal					
9	NA	Acylcarnitine profile	Plasma	Normal	No significant abnormality and normal free carnitine				
10	NA	Amino acids	Plasma	Low levels	Would normally see increased branched-chain amino acids—not seen				
11	NA	Amino acids	Urine	Typical for age	No significant abnormality seen				
12	NA	Organic acids	Urine	Normal	No significant abnormality				
13	NA	Sugar chromatography	Urine	Normal					
		Impression	Non-ketotic hypoglycaemia with inappropriately high insulin and C-peptide levels						
Test number	Normal values (units)	Capillary blood gas	0 hour	12 hours	24 hours	26 hours	36 hours	48 hours	
1	73.6–7.44 (pH)	pH	7.54	7.5	7.52	7.47	7.48	7.43	
2	4.6–6.0 (kPa)	Pco2	4.6	5.1	4.6	5.4	4.73	5.36	
3	22–26 (mmol/L)	Hco3	29.9	29.6	29.2	28.7	25.9	26.1	
4	<2 (mmol/L)	BE	6.4	6.0	5.6	5.0	2.7	1.7	
		Impression	Metabolic alkalosis—improving						
Routine biochemistry									
Normal values (units)		(serum)	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	
41–94 (µmol/L)		Creatinine	63	178	198	113	80	77	
		AKI status	1	2	3	2	1	0	
7	2.5–6.5 (mmol/L)	Urea	1.7	5.6	8.8	4.2	5.3	3.5	
1	133–146 (mmol/L)	Sodium	139	140	140	143	141	140	
2	3.5–5.3 (mmol/L)	Potassium	3.2	3.5	Haemolysed		4.5	3.8	
3	2.2–2.6 (mmol/L)	Corrected calcium	2.43	2.37	2.25	2.38	2.53	2.42	
4	0.9–1.8 (mmol/L)	Phosphate	0.3	1.1	1.4	1.5	1.3	1.0	
5	60–425 (IU/L)	Alkaline phosphatase	101	98	83	86	91	93	
6	0–55 (U/L)	Alanine transaminase	19	11	–	<6	10	–	
Normal values (units)		Urine results	Day 0	Day 1	Day 2	Day 3	Day 5	Day 7	
1		Protein (dipstick)	3+	3+		3+	1+	1+	
2		Blood (dipstick)	0	4+		1+	3+	0	
0–15 (mg/mmol creatinine)		Protein/creatinine ratio			206	238	40	24	
		Impression	Consistent with acute renal failure (protein excretion now normal—9 mg/mmol creatinine)						

Continued

Table 1 Continued

Test number	Normal values (units)	Plasma glucose	On admission	Hypoglycaemia screen		
Test number	Normal values (units)	Toxicology screen	Sample type	Result	Comment	
1	NA	Routine screen	Urine	Negative		
	NA	Paracetamol/salicylate	Serum	Not detected		
2	NA	Oral hypoglycaemics	Urine	Gliclazide	Screened by UPLC-TOF-MS and confirmed by HPLC-DAD	
3	NA	Other drugs	Urine	Cyclizine, fluoxetine, paracetamol	Screened by UPLC-TOF-MS	
		Impression	Deliberate drug overdose			
Test number	Normal values (units)	Synacthen test	Baseline	30 min	60 min	Comment
1		Cortisol	325	649	756	Performed on day 2
2		Impression	Adequate response to synacthen—excludes adrenal insufficiency			
Test number	Normal values (units)	Imaging				
1		Ultrasound abdomen	Normal		–	–
2		CT scan pancreas	Normal		–	–
		Impression	No evidence of insulinoma			

AKI, acute kidney injury; HPLC-DAD, high-performance liquid chromatography with diode array detection; NA, not applicable; UPLC-TOF-MS, ultraperformance liquid chromatography-time of flight-mass spectrometry.

4. exogenous insulin,
5. inborn errors of metabolism.

In parallel, based on the history and examination findings related to self-harm, a drug overdose was also considered in this case and urine for toxicology screen was undertaken.

The results (table 1) of all the biochemical and radiological investigations including the routine urine toxicology screen ruled out all the common causes of hypoglycaemia. The fact that the insulin was high without CT evidence of insulinoma that convinced us that it was likely to be drug overdose and the fact that the C-peptide was also raised suggested oral hypoglycaemic agent rather than endogenous insulin. The concurrent development of renal failure in our patient and our subsequent literature review confirmed the association between sulphonylurea and renal failure. Since the routine toxicology screen would not test for oral hypoglycaemic agents, we undertook an extended toxicology-screening panel using liquid chromatography-tandem mass spectrometry, which tested positive for gliclazide and confirmed the diagnosis of sulphonylurea overdose.

TREATMENT

The patient was initially treated with boluses of intravenous dextrose 10%, intravenous hydrocortisone sodium succinate 100 mg and subcutaneous glucagon 1 mg, followed by infusion of intravenous dextrose 10% for the first 24 hours. She was slowly weaned to intravenous dextrose 10% and 0.45% saline infusion over the next 48 hours that was stopped when her blood glucose levels stabilised between 5 and 8 mmol/L. Her renal failure was conservatively managed under the guidance of the tertiary paediatric nephrologists through close monitoring of her blood pressure, input/output balance and renal function. Her renal function returned to normal 10 days following admission.

OUTCOME AND FOLLOW-UP

The patient remained an inpatient for a total of 10 days for the medical management of her acute renal failure. Creatinine returned to within the normal range 8 days postadmission, and proteinuria resolved after 15 days. Subsequently, she was transferred to an inpatient psychiatry unit where she was offered psychological therapies. After 3 months, she was discharged home, along with an intense support offered in the community by her personal social worker. Follow-up 6 months after admission confirmed a complete and sustained recovery from acute renal failure. She continues to receive support from her social worker.

DISCUSSION

Our case highlights the importance of looking at the biochemical abnormalities holistically (persistent hypoglycaemia, evolving renal failure and results of the hypoglycaemia screen) along with the presentation of the patient (hypoglycaemic seizures and raising blood pressure) in trying to elucidate the organic aetiology for the acute presentation.

A biochemical picture of non-ketotic hypoglycaemia with a high C-peptide and insulin levels, normal CT scan of the pancreas, a normal ammonia, lactate, growth hormone and cortisol ruled out the possibility of an identifiable organic cause for her profound hypoglycaemia and a high glucose requirement. This led us to suspect possible overdose with a drug that is not included in the routine urine toxicology-screening panel. A concurrent rise in blood pressure and a rapid deterioration in renal function (figure 2) prompted us to explore the literature further in search of sulphonylurea intoxication as the likely

cause in view of the raised insulin and C-peptide levels. This was confirmed by the presence of gliclazide in our patient's urine sample (table 1).

A report published by Barracca *et al* in 1998 demonstrated a patient presenting with hypoglycaemia and developing acute renal failure following an ingestion of 28 g of gliclazide. He required dialysis and recovered his renal function 10 days post-ingestion.⁶ It was this case report and results of initial biochemical investigations that prompted us to pursue investigations to look for the presence of oral hypoglycaemia agents in our patient in spite of repeated denials by the patient and no history forthcoming of any member in the current family being on hypoglycaemic medications despite our direct questioning.

This was confirmed by the presence of the drug in our patient's urine sample (table 1). Although our patient developed renal failure, she did not require dialysis, which might be due to her ingestion of a relatively lower dose of gliclazide (2.2 g, 36 mg/kg) as compared with the patient described by Barracca and his colleagues. Caksen *et al* reported hepatitis, hemiplegia and dysphasia in a 14-year-old non-diabetic girl, following an ingestion of 20 mg/kg of gliclazide, which was not experienced by our patient.⁷ We also concur with the observations made by Ling *et al* and Dalan *et al*, with the absence of classical autonomic adrenergic symptoms and predominance of neuroglycopenic response in these patients.^{3 4} Our patient was found fitting in bed in the early hours of the morning and responded rapidly to a 10% dextrose bolus. She, however, later in the day, became suddenly drowsy and started fitting without displaying any prewarning signs of severe hypoglycaemia that can lead to a misdiagnosis or a delay in diagnosis as experienced by our patient. Also persistent stimulation of the pancreatic beta cells by sulphonylurea ensues continuous secretion of insulin, resulting in recurrent rebound hypoglycaemia. Hence, it is prudent to admit and closely monitor these patients for a minimum of 24–48 hours, however small the ingested dose of sulphonylurea may be.⁸ Our patient was discharged from the ED within a few hours of presentation with an acute unexplained severe hypoglycaemia without sufficient assessment, which includes an input from the paediatricians and social services. We discussed this at the mortality and the morbidity meeting and constructive feedback was provided to the ED.

Evidence also suggests that administration of glucagon has no effect on sulphonylurea-induced hypoglycaemia, rather somatostatin analogues may have a better role in reducing the rebound risk.⁹ We do concur with this observation as evident in our patient experiencing recurrent hypoglycaemic episodes despite the administration of glucagon.

An important learning point is that the pattern of biochemical abnormalities mimics those seen in insulinoma; this is due to the effect of gliclazide on pancreatic beta cells promoting insulin release. Where insulinoma is not confirmed on CT consideration of an oral hypoglycaemic agent is an important differential diagnosis. The hypophosphatemia seen in the patient is consistent with increased uptake into cells as a result of the high insulin levels which may also explain the low levels of amino acids seen. The metabolic alkalosis, which is likely to be multifactorial in origin, may also be contributing to the low phosphate (figure 2).

This case report underlines the need of a systematic approach in children presenting with unexplained hypoglycaemia and argues the need for considering deliberate drug overdose with oral hypoglycaemic agents in the differential diagnosis in certain patients, although it is rare within the paediatric population. The fact that the late grandfather was a diabetic and was on gliclazide tablets being completely forgotten by the family members

Learning points

- ▶ Gliclazide enhances the endogenous production of insulin by stimulating the beta cells of the pancreas resulting in raised insulin and C-peptide levels, mimicking the results seen in insulinoma, as opposed to normal C-peptide levels encountered in exogenous insulin overdose. Overdose with sulphonylurea being extremely rare within the paediatric population poses a serious risk of misdiagnosis or delay in diagnosis, unless the treating clinician is mindful of this cause when managing children with acute unexplained hypoglycaemia.
- ▶ A very high glucose requirement is rare in hyperinsulinism presenting in adults unless it is a malignancy. Hence, an urgent CT scan of the pancreas is warranted in all older children and adults to look for insulinoma when the glucose requirement is quite high (≥ 8 mg/kg/min).
- ▶ A deliberate drug overdose with sulphonylurea should always be considered and screened for in any patient with sudden unexplained hypoglycaemia despite their denial.
- ▶ Screening for sulphonylurea overdose should be included as a second-line test in an extended toxicology screen panel for all patients presenting with unexplained hypoglycaemia whose initial toxicology screen is negative.
- ▶ Clinicians should always have a high index of suspicion about a new autolytic attempt in adolescent patients with recent self-inflicted lesions.

emphasises the importance of actively exploring the history of diabetes in first and second-degree relatives, living or dead.¹⁰ This would have led to a correct diagnosis without the need for extensive investigations such as CT scan of the abdomen in our patient. Self-harming in young people is a growing epidemic and there appears to be a well-publicised rise in admissions following self-harm by adolescents,¹¹ especially as the numbers admitted for this reason still fall well below those that might be expected by extrapolation from population prevalences.¹² This report also highlights the importance of inclusion of sulphonylurea as a second-line test within the toxicology screen panel in all patients presenting with unexplained hypoglycaemia to prevent such serious and potentially life-threatening complications.

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REFERENCES

- 1 Bösenberg LH, van Zyl DG. The mechanism of action of oral antidiabetic drugs: A review of recent literature. *Journal of Endocrinology, Metabolism and Diabetes of South Africa* 2008;13:80–8.
- 2 Glatstein M, Scolnik D, Bentur Y. Octreotide for the treatment of sulphonylurea poisoning. *Clin Toxicol* 2012;50:795–804.
- 3 Dalan R, Leow MK, George J, *et al*. Neuroglycopenia and adrenergic responses to hypoglycaemia: insights from a local epidemic of serendipitous massive overdose of glibenclamide. *Diabet Med* 2009;26:105–9.
- 4 Ling GR, Singh K, Wong SY, *et al*. Severe neuroglycopenia secondary to severe hypoglycaemia from serendipitous overdose of gliclazide without adrenergic or autonomic response. *Diabet Med* 2009;26:1182–3.

Reminder of important clinical lesson

- 5 Cohen E, Mackenzie RG, Yates GL. HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth. *J Adolesc Health* 1991;12:539–44.
- 6 Barracca A, Ledda O, Michittu B, *et al.* Acute renal failure after massive ingestion of gliclazide in a suicide attempt. *Ren Fail* 1998;20:533–7.
- 7 Caksen H, Kendirci M, Tutuş A, *et al.* Gliclazide-induced hepatitis, hemiplegia and dysphasia in a suicide attempt. *J Pediatr Endocrinol Metab* 2001;14:1157–9.
- 8 Veitch PC, Clifton-Bligh RJ. Long-acting sulfonylureas -- long-acting hypoglycaemia. *Med J Aust* 2004;180:84–5.
- 9 McLaughlin SA, Crandall CS, McKinney PE. Octreotide: an antidote for sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2000;36:133–8.
- 10 Loo PY, Yap F. Unwitnessed sulphonylurea poisoning in a healthy toddler. *Eur J Pediatr* 2010;169:1409–12.
- 11 Rise in children hospitalised for self-harm as thousands contact Childline [Internet]. *NSPCC* 2017. <https://www.nspcc.org.uk/fighting-for-childhood/news-opinion/rise-children-hospitalised-self-harm-thousands-contact-childline/>
- 12 Muehlenkamp JJ, Claes L, Havertape L, *et al.* International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. *Child Adolesc Psychiatry Ment Health* 2012;6:10.

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