CASE REPORT

Hypoglycaemia begets hypoglycaemia

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SUMMARY

Drug-induced (insulin/insulin secretagogue) hypoglycaemia is the most common cause of hypoglycaemia particularly in the elderly. It is estimated that hypoglycaemia of any severity occurs annually in 5–20% of patients taking antihyperglycaemic agents. Although these hypoglycaemic episodes are rarely fatal, they can be associated with serious clinical sequelae. The half-life for most sulfonylurea medications is 14–16 h; they can cause severe, prolonged hypoglycaemia. It is important to recognise, prevent and treat hypoglycaemic episodes secondary to the use of antihyperglycaemic agents. Patient education has become focused on minimising hyperglycaemia but emphasis must be placed on minimising even minor subclinical hypoglycaemia because it will contribute to a vicious cycle of hypoglycaemia begetting hypoglycaemia. Ten per cent dextrose is recommended for the reversal of all hypoglycaemic episodes rather than the conventional 50% dextrose. Octreotide can be an option for recurrent and relapsing hypoglycaemia in an acute setting.

BACKGROUND

The results of the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) prove that near normoglycaemia is clearly in the patient's best interest.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials showed that strict control of blood sugar inpatients with type 2 diabetes doubled the risk of severe hypoglycaemia from 1.5% (standard care) to 3% (strict care). DCCT (insulin) and UKPDS (insulin or oral agents) also showed that intensive glucose control therapy increased the risk of hypoglycaemia by twofold to threefold, particularly in the elderly.

Population-based data indicate that the overall event rate for severe hypoglycaemia (requiring the assistance of another individual) in insulin-treated type 2 diabetes is approximately 30% of that in type 1 diabetes. However, because there are a greater number of individuals with type 2 than type 1 diabetes, and because most people with type 2 diabetes ultimately require treatment with insulin, most episodes of iatrogenic hypoglycaemia occur in people with type 2 diabetes, more so in the elderly with cognitive impairment.

Around 50% of older people with diabetes are asymptomatic. In addition to traditional microvascular and macrovascular complications seen in younger people, older people with diabetes are at risk of developing atypical complications or geriatric syndromes such as cognitive dysfunction, depression, disability, falls, persistent pain and

urinary incontinence. Glycaemic targets should be individualised, taking into consideration the patient's overall health and life expectancy. Older people may tolerate higher levels of blood glucose before they develop osmotic symptoms because of a higher renal threshold for glucose with increasing age. On the other hand, they may appear to tolerate lower levels of blood glucose because of diminished autonomic symptoms of hypoglycaemia leading to 'dampened down' hypoglycaemia warnings or none at all.

For older people, there are added risk factors which can lead to hypoglycaemia (box 1). Normal fasting blood glucose does not exclude the diagnosis of diabetes in a frail elderly person. Stress-induced hyperglycaemia (eg, acute infection) is common and needs to be considered for treatment.

Complexity of the care for this group often requires increased support in the community from experienced health professionals such as specialist diabetes nurses and dieticians.

It is not uncommon to see elderly diabetic patients from a nursing home background admitted with acute-kidney injury due to multiple causes and still taking oral hypoglycaemic agents; such patients do not need the much advocated 50 mL of 50% glucose repeatedly for their hypoglycaemic episodes, but early enteral feeding is the key to an early stabilisation and eventual discharge. The half-life for most sulfonylurea medications is 14–16 h, which can cause severe, prolonged hypoglycaemia.

Hypoglycaemia is a common finding in acute care settings. The causes of recurrent hypoglycaemia are multifactorial. With the advent of an aggressive lowering of HbA1c values to achieve optimal glycaemic control, patients are at increased risk of hypoglycaemic episodes. Iatrogenic hypoglycaemia can cause recurrent morbidity, sometimes irreversible neurological complications and even death, and further preclude maintenance of euglycaemia over a lifetime of diabetes.

The case described highlights the problems encountered by the medical staff in treating hypoglycaemia in such situations.

Box 1 Hypoglycaemia risk in the elderly

- ▶ Advanced age
- ▶ Other illnesses or conditions as well as diabetes
- ▶ Being prescribed five or more medications
- ▶ Chronic renal problems
- ▶ Poor nutrition
- ▶ Acute illness

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CASE PRESENTATION

A 78-year-old man was admitted from a residential home with drowsiness and 'off legs'. He was found to be hypoglycaemic with a glucose of 2.8 mmol by the ambulance crew and received oral glucogel prehospital.

He had a background of cognitive impairment, type 2 diabetes mellitus, hypertension, gout and chronic kidney disease. His diabetic medications consisted of metformin (1 g twice a day) and gliclazide (160 mg in total). The rest of his medications were paracetamol, amlodipine, doxazocin and allopurinol.

Initial observations included a blood pressure of 144/84 mm Hg; his pulse rate was 86/min and regular; saturations were 94% on air; respiratory rate was 16/min and temperature was 37.4°C.

His urine dipstick was found to be nitrite positive in A&E department and the initial laboratory bloods showed a moderate rise in inflammatory markers and an acute worsening of his chronic kidney disease with creatinine increasing from 130 to 190 mmols and a capillary glucose of 2.2 despite glucogel administration.

He was started on empirical trimethoprim for urinary tract infection and received 50 mL of 50% glucose to treat his hypoglycaemia. He was then seen by the medical team in the A&E department and transferred to the acute medical unit (AMU).

His blood glucose on AMU 4 h later was noted to be 3.3 mmol and he was given a further 25 mL of 50% dextrose that increased his capillary glucose to 14.2 mmol. During the first 48 h of admission, he received 50% dextrose four times due to rebound hypoglycaemia (glucose monitoring revealed glucose increments up to 14.2 mmol post 50% dextrose and falling to as low as 3.1 mmol in a couple of hours post 50% dextrose) and was eventually started on a 10% dextrose intravenous drip to prevent this rebound.

This pattern of fluctuating blood glucose and rebound hypoglycaemia continued for another day until he started taking sufficient food orally and his kidney function improved with treatment. He was in the hospital for a total of 5 days and recurrent hypoglycaemia was found to be one of the factors that delayed the discharge.

It is interesting to note that the patient did not manifest any symptoms of low blood glucose during this entire period.

INVESTIGATIONS

Laboratory results showed a creatine of 190 mmols (baseline of 130 mmol), a C reactive protein of 42 with normal white cell

count, microcytic anaemia with haemoglobin of 11 g/dL and a mean corpuscular volume of 76 fL. His last recorded HbA1c was 54 (mmol/mol) indicating tight glycaemic controls. A random serum cortisol was noted to be normal and the question of oral hypoglycaemic drug overdose did not arise as the patient's medications were supervised in the residential home, but measurement of specific drug levels (or insulin/C-peptide if relevant) is recommended to rule out accidental, surreptitious or even malicious hypoglycaemia (box 2).

DIFFERENTIAL DIAGNOSIS

A low-plasma glucose concentration in the absence of symptoms of hypoglycaemia suggests the possibility of shifted glycaemic thresholds, as may occur in patients with repeated episodes of hypoglycaemia or artefactual hypoglycaemia.

For patients with diabetes who may have asymptomatic hypoglycaemia due to repeated episodes of hypoglycaemia and/or hypoglycaemia unawareness, intermittent use of continuous glucose monitoring may be valuable for the detection of nocturnal hypoglycaemia or patterns of hypoglycaemia.

OUTCOME AND FOLLOW-UP

The patient's discharge back to his residential home was delayed due to episodes of recurrent hypoglycaemia and the gliclazide was switched to saxagliptin as his estimated glomerular filtration rate (eGFR) was 29 mL/min/1.73 m².

DISCUSSION

In patients with diabetes, hypoglycaemia is defined as all episodes of an abnormally low-plasma glucose concentration (with or without symptoms) that expose the individual to harm. People with diabetes become concerned about the possibility of hypoglycaemia at a self-monitored blood glucose level ≤ 3.9 mmol/L. While that value is higher than the value used to diagnose hypoglycaemia in people without diabetes, it

Box 2 Important differentials for hypoglycaemia

- ▶ Drugs (see box 3)
- ▶ Alcohol
- ▶ Critical illness
- ▶ Malnourishment
- ▶ Non-islet cell tumors secreting insulin-like growth factors
- ▶ Cortisol deficiency
- ▶ Endogenous hyperinsulinism (a β cell secretagogue or tumour).
- ▶ A functional β cell disorder, often termed nesidioblastosis, that can occur as a feature of the non-insulinoma pancreatogenous hypoglycaemia syndrome or of postgastric bypass hypoglycaemia
- ▶ Accidental, surreptitious or even malicious hypoglycaemia.

Box 3 Factors predisposing an individual to antihyperglycaemic drug-induced hypoglycaemia¹²

- ▶ Age
- ▶ Elderly in the presence of coexisting comorbid conditions
- ▶ Impaired kidney or liver function
- ▶ Adrenal insufficiency
- ▶ Gastrointestinal disease
- ▶ Lack of education on hypoglycaemia
- ▶ Lifestyle
- ▶ Alcohol consumption in the absence of sufficient energy/carbohydrate intake
- ▶ Exercise
- ▶ Missed or delayed meals
- ▶ Salicylates (>4 g/day)
- ▶ Sulfonamide and macrolide antibiotics
- ▶ Tricyclic antidepressants
- ▶ Phenylbutazone
- ▶ Warfarin
- ▶ Fibrates
- ▶ Monoamine oxidase inhibitors
- ▶ Acetaminophen
- ▶ ACE inhibitors
- ▶ β -Blockers

approximates the lower limit of the physiological fasting non-diabetic range, the normal glycaemic threshold for glucose counter-regulatory hormone secretion and the highest antecedent low glucose level reported to reduce sympathoadrenal responses to subsequent hypoglycaemia.^{1 2}

The American Diabetes Association and the Endocrine Society Workgroup on Hypoglycemia recommends the following classification of hypoglycaemia in diabetes.¹

1. Severe hypoglycaemia: An event requiring the assistance of another person to actively administer carbohydrate.
2. Documented symptomatic hypoglycaemia: An event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L.
3. Asymptomatic hypoglycaemia: Asymptomatic hypoglycaemia is classified as an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of ≤ 3.9 mmol/L.
4. Probable symptomatic hypoglycaemia: Probable symptomatic hypoglycaemia is classified as an event during which typical symptoms of hypoglycaemia are not accompanied by a plasma glucose determination.
5. Relative hypoglycaemia: Relative hypoglycaemia is classified as an event during which the person with diabetes reports typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration > 3.9 mmol/L. This category reflects the fact that patients with chronically poor glycaemic control can experience symptoms of hypoglycaemia at plasma glucose levels > 3.9 mmol/L as glucose levels decline into the physiological range.

The incidence of hypoglycaemia with use of antihyperglycaemic agents is most likely underestimated due to the altered patient awareness of symptoms and under-reporting of episodes. Few large and randomised clinical trials have compared the rates of hypoglycaemia between antihyperglycaemic agents. In addition, the frequency of hypoglycaemias is not mentioned in several publications.

A decrease in blood sugar due to oral agents may be due to skipped meals or exercise. However, concurrent illness (dehydration, etc), new onset of renal dysfunction and drug interactions (box 3) are major factors that cause oral agents induced hypoglycaemia; such events prolong the half-life of sulfonylureas.

These hypoglycaemic patients require a long period of observation (> 24 h) in the emergency department due to the prolonged action of these agents and a search for the cause of hypoglycaemia is necessary and may require a significant change of medications before discharge.

Insulin-related hypoglycaemia is relatively simple to treat; it is often due to a skipped meal/snack/exercises and is treated with 50 mL of 50% dextrose and food.

The patient may be discharged early (6 h). Giving too much dextrose will not cause an increase in insulin release or cause paradoxical hypoglycaemia (these patients do not have their own insulin to release).

Oral agents are not easy to treat and sulfonylureas are a major problem; all these agents peak up to 8 h and may last > 24 h and hypoglycaemia is seen many hours after the dose. Glyburide is more long acting than glimeperide and glimeperide.^{3 4}

Sulfonylurea and meglitinides (such as repaglinide) can cause hypoglycaemia when used in monotherapy, as both classes of agents are insulin secretagogues. The frequency of hypoglycaemic episodes with sulfonylureas tends to decrease after a few years of treatment.

The frequency of hypoglycaemia with thiazolidinediones is not significantly different from that of a placebo. No cases of severe hypoglycaemia have been reported with monotherapy with these agents.

Sulfonylurea-related hypoglycaemia is very different from the insulin induced.^{4 5} A typical patient would be an ill elderly patient from a care home for whom too much intravenous dextrose may be harmful as it promotes excess insulin release (usually after 60–120 min due to the presence of oral agents that potentiate insulin release) and the blood sugar drops, prompting further treatment with more dextrose and the cycle continues. Such a situation might require half normal saline +5% or 10% dextrose as a slow infusion to stabilise the glucose.^{5 6}

Blood sugar needs to be monitored every 2 h and the literature recommends observation for more than 24 h, and therefore it is best to keep it in between 5 and 7 mmol/L as higher levels would cause hyperinsulinaemia.

Use of glucagon is a potential problem for sulfonylurea^{7 8} associated hypoglycaemia as it takes 20 min to work and the patients may develop nausea and vomiting and be unable to eat.

Glucagon 1 mg IM/SC usually increases blood sugar by 3–12 mmol in < 60 min (intravenous dextrose is faster)^{7 8} and may not increase it enough in malnourished people due to poor glycogen reserves in the liver.

Glucagon may increase the blood sugar too much, prompting a reactive hypoglycaemia due to excessive insulin release. Paradoxically, glucagon can stimulate insulin release directly and may cause a delayed drop in blood glucose.

Octreotide may be considered as a relatively new option

The first prospective placebo-controlled study published in 2008 concluded that the addition of octreotide to standard therapy in hypoglycaemic patients receiving treatment with sulfonylurea increased the serum glucose values for the first 8 h after administration in patients.^{9–11} Recurrent hypoglycaemic episodes occurred less frequently in patients who received octreotide compared with those who received placebo.

Octreotide inhibits the release of insulin, glucagon and growth hormone. If given subcutaneously (SC), it peaks around 30 min and has a half-life of 1.5–2 h. Uncommonly, it has been used in non-overdose sulfonylurea-related hypoglycaemia (used frequently in a true overdose of sulfonylureas).

A single 75 μ g subcutaneous dose might be considered for a patient having recurrent hypoglycaemia after 50 mL of 50% dextrose, but the patient still needs to stay for at least 24 h.

The newer dipeptidyl peptidase 4 inhibitors (Saxagliptin, Vildagliptin) control the glucose parameters with comparable efficacy to other antihyperglycaemic agents, without the associated weight gain or hypoglycaemia. As incretin hormones are more active in response to higher blood sugar levels (and are less active in response to low blood sugar), the risk of dangerously low blood sugar (hypoglycaemia) is low with Saxagliptin.

The glucagon-like peptide (GLP1) receptor agonists (Exenatide, Liraglutide) offer the advantage of weight loss; they also delay gastric emptying, which is a desirable effect for controlling postmeal glycaemia but one that can be associated with nausea in some patients. No hypoglycaemia is seen with use of a GLP-1 agonist as it works only in the presence of hyperglycaemia, but hypoglycaemia can occur if its glucose-lowering effects are combined with an excess dose of sulfonylurea or insulin (Exenatide has not been approved for use by those who take insulin).

CONCLUSION

The major potential adverse effect of use of sulfonylurea agents is a hyperinsulinaemic state that causes hypoglycaemia. It may be observed during chronic therapeutic dosing, even with very low doses of sulfonylurea, and especially in older patients. Given the heterogeneity of the elderly population, which includes patients with very different functional and cognitive capacities, comorbidities and life expectancy, it is critical to make a comprehensive assessment from a biopsychosocial perspective to address the vascular risk factors integrally and to establish individually tailored targets for glycaemia control.¹³

Hypoglycaemia may also result from accidental or intentional poisoning in both diabetic and non-diabetic patients. The traditional approach to sulfonylurea-induced hypoglycaemia includes the administration of glucose and glucagon or diazoxide in those who remain hypoglycaemic despite repeated or continuous glucose supplementation.

However, these antidotal approaches are associated with several shortcomings, including the further exacerbation of insulin release by glucose and glucagon, leading only to a temporary beneficial effect and later relapse into hypoglycaemia, as well as the adverse effects of both glucagon and diazoxide.

In 1999, a revised UK paramedic training syllabus and manual were introduced and in 2000, the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) published its prehospital treatment guidelines and recommended the use of 10% dextrose for reversal of all hypoglycaemic episodes.¹⁴

Octreotide inhibits the secretion of several neuropeptides, including insulin, and has successfully been used to control life-threatening hypoglycaemia caused by insulinoma, sulfonylurea overdose or persistent hyperinsulinaemic hypoglycaemia of infancy.

In patients with hypoglycaemia without diabetes mellitus, it is important to exclude potential hypoglycaemic aetiologies like drugs, critical illnesses, hormone deficiencies and non-islet cell tumours first. In the absence of these causes, the differential diagnosis narrows down to accidental, surreptitious or even malicious hypoglycaemia or endogenous hyperinsulinism.

In patients suspected of having endogenous hyperinsulinism, as in the case above, it is useful to measure the parameters mentioned in box 4.

Insulin or insulin secretagogue treatment of diabetes mellitus is the most common cause of hypoglycaemia. The practice of hypoglycaemia risk factor reduction is paramount and can be performed by addressing the issue of hypoglycaemia, applying the principles of intensive glycaemic therapy, and considering both the conventional risk factors and those indicative of compromised defences against falling plasma glucose concentrations in persons with diabetes.

Box 4 Special tests in case of hyperinsulinaemic hypoglycaemia

- ▶ Plasma glucose
- ▶ Insulin
- ▶ C-peptide
- ▶ Proinsulin
- ▶ β -hydroxybutyrate
- ▶ Circulating oral hypoglycaemic agents during an episode of hypoglycaemia
- ▶ Insulin antibodies

Given the increased susceptibility of the elderly-to-severe hypoglycaemia and its consequences, antidiabetic therapies that minimise the risk of hypoglycaemic events should be selected.¹⁵

Learning points

- ▶ Treating hypoglycaemia in an acute setting due to insulin and oral agents creates very different challenges. Some hypoglycaemic patients require a long period of observation (>24 h) in the A&E department due to the prolonged action of these oral agents.
- ▶ The goals of treatment for hypoglycaemia are to detect and treat a low blood glucose level promptly by using an intervention that provides the fastest rise in blood glucose to a safe level, to eliminate the risk of injury and to relieve the symptoms quickly and avoid rebound.
- ▶ It is important to avoid overtreatment, since this can result in rebound hyperglycaemia and weight gain.
- ▶ Drug-induced hypoglycaemia is a major obstacle for individuals (especially in the elderly) trying to achieve glycaemic targets and a timely discharge.
- ▶ Ten per cent dextrose is recommended for the reversal of all hypoglycaemic episodes rather than the conventional 50% dextrose. Octreotide can be an option for recurrent and relapsing hypoglycaemia in an acute setting.
- ▶ Use of glucagon in an acute/prehospital setting is declining as it can paradoxically stimulate insulin release directly and may cause a delayed drop in blood glucose.
- ▶ Dipeptidyl peptidase 4 inhibitors (gliptins) should be used more often if the patient's eGFR (estimated glomerular filtration rate) is <30 mL/min/1.73 m².
- ▶ The therapeutic strategy for frail elderly patients with type 2 diabetes should be individualised and focused on improving the quality of life, assuring patient safety and avoiding the adverse effects of anti-diabetic treatment.

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