

GERIATRIC PATIENT WITH REPETITIVE HYPOGLYCAEMIC EPISODES

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Hypoglycaemia is one of the significant hospitalization reasons in elderly patients with diabetes mellitus. Concerns should increase in admission of such a case in the emergency room owing to a number of associated disorders which may contribute to the undesired consequences. An eighty-year-old diabetic woman who was on glimepiride therapy was brought to the emergency unit because of repeated episodes of hypoglycaemia. She was having Alzheimer's disease leading to forget the usual dose she was receiving that also gives rise to double the pill together with skipping the snacks. Age related changes in pharmacokinetics and the potential for adverse effects and drug interactions due to polypharmacy leading to interactions and less adherence to receive the right dose at the right time should also be considered when choosing appropriate pharmacological therapy. Geriatric patients require special considerations related to delayed response of counter-regulatory hormones to hypoglycaemia and associated conditions must be taken into consideration for a successful management program.

Key words: Diabetic, glimepiride, hypoglycaemia, geriatric.

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INTRODUCTION

Hypoglycaemia is one of the significant hospitalization causes in patients with diabetes mellitus who are on antidiabetic medication (1). Even though the risk of hypoglycaemia is less in type 2 diabetics than in patients with type 1 diabetes mellitus, when it occurs during sulfonylurea use especially in the elderly, may prolong more than expected and may associate with a higher mortality rate (2). The tendency of hypoglycaemic episodes are increased in geriatric patients (3). Below a patient with Alzheimer's disease who was investigated due to repetitive episodes of hypoglycaemia will be presented and possible reasons will be discussed.

CASE

An eighty-year-old lady was brought to our emergency department in the afternoon because of confusion and disorientation. Her relatives informed the emergency team that she did have the same clinical picture in the same day during very early hours

of the morning and hypoglycaemia was diagnosed at another hospital and she was discharged soon after glucose perfusion. She was on glimepiride 2mg for three years but was known to be diabetic for about fifteen years. A couple of years ago she was put on donepezil after Alzheimer's disease was diagnosed at another health centre. She had transient ischemic attack two years ago and experienced hypoglycaemia that did not happen again after she was advised to quit metformin 850mg slow releasing tablets that she was receiving twice daily.

She was not responding to verbal stimuli and plantar reflexes were unresponsive during admission. Blood pressure, heart beat, ECG, and other physical examination results were all within normal limits except for the body temperature which was 35.5 °C (checked for twice). After the initial blood sample was drawn, 5% dextrose in water solution was started for perfusion. Her blood glucose was 27mg/dl.

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Table 1. Laboratory values during admission

WBC	8.4K/ μ L (4.1-10.9)
Creatinine	0.8mg/dl
RBC	4.49M/ μ L (4.20-6.30)
Cholesterol	128mg/dl
Haemoglobin	11.4g/dl (12-18)
LDL-Cholesterol	37.2mg/dl
Hematocrit	36.1% (37-51)
Triglyceride	69mg/dl
MCV	86.2fl (80-97)
HDL-Cholesterol	73mg/dl
MCH	27.2pg (26-32)
AST	20U/L
RDW	14.7% (11.5-14.5%)
ALT	27U/L
PLT	234 K/ μ L (140-440)
ALP	97U/L (50-136)
GGT	16U/L (5-85)
Na	137mmol/L
K	4.2mmol/L
Glucose	27 mg/dl
HbA1c	6.3%
Insulin	40.85 μ IU/ml (1.90-23)
C-peptide	1.8ng/ml (1.1-5.0)

The patient's mental status improved after the glucose perfusion. Laboratory findings are given in Table 1. Taking into consideration of the patient's age, associated illnesses such as hypertension, hyperlipidemia, cerebrovascular disease, depression and Alzheimer's disease and two hypoglycaemic episodes in the same day, our team convinced the patient and her relatives to shift her to the service of internal medicine department for further evaluation.

While she was having glucose perfusion under close glucose monitorization, patient had a glycaemic level of 55mg/dl. Low level of blood glucose level gave rise to increase of the glucose concentration from 5% to 10%. So the new plan was administration of 200gr glucose in 2lts of water continuously and daily. Other drugs such as aspirin 80mg, an angiotensin converting enzyme (ACE) inhibitor which may sensitize patient to endogenous insulin were all discontinued not to let any contribution to another hypoglycaemic episode. On that day glycaemia was ranging from 183mg/dl (the lowest) to 280mg/dl (the highest). On the third day perfusion concentration of the solution was decreased to 5% as the highest level of 350mg/dl was reached. The next couple of days were uneventful with the levels between 141 and 235. In the initial sample when the glucose level was 27mg/dl, insulin level was 40.85 μ IU/ml (1.90-23) and C-peptide was 1.8ng/ml (1.1-5.0).

As the proinsulin level could not be detected at our institute, we started to investigate for 72h fasting test for possible endocrine tumor under close glucose monitorization, frequent visits and daily electrocardiograms (ECGs).

Fasting was discontinued after 56h due to patient's and relatives' desire. However hypoglycaemia did not occur during this period. Blood glucose was even not below 160mg/dl. Patient was discharged from the hospital informing her and her relatives for frequent snacks, diet contents and regular home blood glucose checking. Regarding with the condition of patient, relatives were also advised to give the medications on time and not to let her take them herself alone as she may double the dose or have it even if she skipped her meals. She was discharged from the hospital after informing her relatives and recent caregiver how important it was to supervise her medication administration.

DISCUSSION

The most common cause of hypoglycaemia in adults is insulin treatment in the management of diabetes (4). However neither our patient nor anybody close to the family were on insulin therapy for the glycaemic control. Further assessment of the initial blood sample also ruled out exogenous insulin administration.

Although very rare in the literature for a patient to experience coexisting insulinoma and type 2 diabetes mellitus (5), one of the presumptive diagnosis of our patient was also insulinoma as C-peptide was 1.8 that was more than 0.2, and the insulin glucose ratio was over 0.3 ($40.85 / 27 = 1.51$) from the blood sample that was drawn initially. Proinsulin was not detected because of lack of assay in our or another unit nearby. However, results and ratios -even though may support the presumptive diagnosis of insulinoma-, may also be possible in case of sulfonylurea overdose. Serum sulfonylurea level could not be detected in our laboratory. 72h fasting test is reported to be the best method to rule out insulinoma (6). Investigators estimated that the termination of the fasting test after the hypoglycaemia became evident within 24h in 65% of the patients with insulinomas and approached to 93% after 48h [6]. In our patient test was terminated after 56h because of patient's and her relatives' concern. Glucose level was 165mg/dl when the test was quitted.

Diabetes management in the elderly necessitates more attention for increasing

number of illnesses which may associate with polypharmacy leading to interactions and less adherence to receive the right dose at the right time. Age related changes in pharmacokinetics and the potential for adverse effects and drug interactions should also be considered when choosing appropriate pharmacological therapy (7). Polypharmacy may not only increase the number of complications such as liver or kidney failures but also contribute to hypoglycaemic episodes which may trigger serious events like myocardial infarction or stroke, as well (3, 8-10). Reduced awareness of hypoglycaemia and altered release of counterregulatory hormones makes the geriatric patient more susceptible to hypoglycaemic events (11). The incidence of symptomatic hypoglycaemia in sulfonylurea-treated patients varies between 0.2 to 1.8 per 1000 patients' years (3, 12). Although it was reported that new sulfonylureas such as third generation glimepirides did cause less hypoglycaemia (13), in a recent study which was carried out by the members of German Diabetes Association, severe hypoglycaemia was emphasized even in very small doses of glimepiride such as 0.5mg, and infusion of 308 ± 256 g (104-862g) iv glucose over 43 ± 16 h period (24-65h) might be required in glimepiride-treated patients (14). Our patient was receiving 2mg of the same drug and an average amount of 200g daily glucose infusion was performed for about 72h.

However, if the patient is also having a condition like Alzheimer's disease she may forget how often her medication is or sometimes skip the meals even though the hypoglycaemic agent is already in the circulation.

While trying to find out the offending agent for hypoglycaemia, drugs that the patient was having should also be questioned such as ACE inhibitors, sulphonamides, aspirin and other NSAID's, alcohol abuse, over dosage of oral antidiabetics and of course insulin. The patient was receiving low dose aspirin and ACE inhibitor, and on the 5th day of her stay in the hospital, she remembered that she had two more pills of glimepiride even though prescription was once daily only. She did not feel herself well that morning with a loss of appetite leading to skip her meals. While the liver enzymes and creatinine levels were normal, glomerular filtration rate (GFR) found was 55ml/minute. In a study 67% of cases experiencing hypoglycaemic episodes were having creatinine clearance less than 80ml/min (8).

In NHANES III, it has been estimated that GFR was less than 60ml/min for the body surface in patients with type 2 diabetes mellitus who were over 65-years-old (15).

Long acting sulfonylureas may lead to hypoglycaemia especially in the elderly. They should be encouraged to spend more than a couple of days in the hospital after the initial therapy is done at the emergency unit so as not to experience another episode. Recent studies appear to emphasize short acting sulfonylureas instead of long acting ones to control glycaemic levels (16). Hospitalization will provide proper diagnosis, patient education, review the multi-drug regimens and even consider additional conditions as in our case as well.

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