

# A rare cause of severe non-diabetic hypoglycaemia

## ABSTRACT

A 67-year old woman presented with an unwitnessed fall and decreased oral intake. She had a learning disability, hypertension, epilepsy, asthma, chronic iron deficiency anaemia, mild lymphopenia, osteoporosis and treated uterine cancer. After clinical review, she was treated for Hospital-acquired pneumonia (following a recent hospital admission) with possible aspiration. She was noted to have hyponatraemia secondary to dehydration. She was commenced on intravenous Levofloxacin and Metronidazole along with supportive care, based on antibiotic guidance due to her known allergy to penicillin. On day 3 of admission, she was found unresponsive with a capillary blood glucose of 0.6 mmol/L, which improved with 10% glucose infusion. The low blood glucose was attributed to poor oral intake. However, her serial blood sugar results demonstrated persistent hypoglycaemia for 72h needing further intravenous glucose infusions. A medication review was undertaken and Levofloxacin was discontinued. After 24hrs of discontinuation, the hypoglycaemic episode resolved. A short synacthen test showed a normal cortisol response. There were no further episodes of hypoglycaemia.

## Conclusion

As her persistent hypoglycaemia resolved on discontinuation of Levofloxacin, a diagnosis of fluoroquinolone induced hypoglycaemia was reported to MHRA. Fluoroquinolones are thought to induce hypoglycaemia by increasing the insulin release via blockade of adenosine triphosphate-sensitive  $K^+$  channels in the  $\beta$  cells of the pancreas. This effect may not be clinically evident in all patients because of physiologic mechanisms that regulate blood glucose levels. Health professionals should be aware of the potential risk of severe hypoglycaemia with the use of Fluoroquinolones which are a first or second-line treatment for common infective processes. Fluoroquinolones should be stopped immediately and switch to a non-Fluoroquinolones antibiotic if possible. In elderly patients with compromised oral intake or in those with other comorbidities, regular blood glucose monitoring should be carried out to avoid life-threatening hypoglycaemic episodes.

Keywords; Hypoglycaemia; fluoroquinolones; Levofloxacin

## Introduction

## **Nondiabetic Hypoglycaemia**

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Hypoglycaemia is a clinical syndrome present when the blood glucose concentration falls below the normal fasting glucose range. Whipple's triad should be present in cases of true hypoglycaemia: hypoglycaemic symptoms, accompanying low blood glucose concentration, and resolution of symptoms after raising the blood glucose concentration to normal.<sup>1</sup> Hyperinsulinaemic hypoglycaemia is not common in the general population, while iatrogenic or factitious hypoglycaemia is seen to be a more common occurrence among those with access to glucose-lowering agents.<sup>2</sup>

Symptoms of hypoglycaemia can be categorised as neuroglycopenic (the result of brain glucose deprivation) or neurogenic / adrenergic/ autonomic (the result of the persons perception of physiological changes caused by the sympathoadrenal discharge triggered by hypoglycaemia).<sup>3</sup>

Autonomic symptoms occur at plasma glucose concentrations of approximately 60mg/dL (3.3mmol/L) whereas neuroglycopenic symptoms occur at plasma glucose concentrations of approximately 50mg/dL (2.8mmol/L) or less.<sup>4</sup>

Hypoglycemia is relatively uncommon in people without diabetes and commonly occurs in the setting of the treatment of glucose lowering agents such as sulfonylureas or insulin.

Diagnostic values for non-diabetic hyperinsulinemia are a plasma insulin concentration of at least 18pmol/L, plasma C-peptide concentration of at least 0.2nmol/L, proinsulin concentration of at least 5.0pmol/L, beta hydroxybutyrate when the fasting plasma glucose is less than 3mmol/L.<sup>5</sup>

Hypoglycemia can be caused by insulin secreting pancreatic islet cell tumours and non islet cell tumours secreting IGF II. It can also be accidental, surreptitious, or even malicious. Hypoglycemia can occur as a result of hyperinsulinism after Roux-en-Y gastric bypass for obesity. It can also be caused by an antibody to insulin, drugs are the most common cause of hypoglycaemia. Hypoglycaemia sometimes occurs during sepsis and in other critical illnesses including renal or hepatic failure, and rarely in cortisol deficiency.

Many drugs in addition to insulin, insulin secretagogues, and alcohol have been reported to cause hypoglycaemia.<sup>6</sup> Medications causing hypoglycaemia include Insulin, fluoroquinolones, angiotensin converting enzyme inhibitors (especially captopril), beta-blockers and oral hypoglycaemic agents to mention a few.<sup>7</sup>

### *Mortality and morbidity associated with hypoglycaemia*

The immediate effect of hypoglycaemia is manifest in multiple systems including musculoskeletal (patients could have accidents, falls, fractures), cardiovascular (myocardial infarction, cardiac arrhythmias) and neurological (seizures, coma and cognitive dysfunction).<sup>8</sup> There is increased in-hospital and post-admission mortality risk in patients with blood glucose levels of <3.0mmol/l (70mg/dl), with and without insulin therapy when compared to those without hypoglycemia.<sup>9</sup>

Hypoglycaemia promotes platelet aggregation, decreases partial thromboplastin time, lowers platelet count, increases fibrinogen and factor VIII in type 1 diabetes patients. These alterations on the coagulation cascade-related factors could have significant effects on the cardiovascular system, contributing to major vascular events such as myocardial infarction or stroke. The hypoglycaemic state also causes lengthening of the corrected QT interval and increased QT dispersion during cardiac repolarization which leads to life threatening arrhythmias such as ventricular tachycardia or sudden death with ventricular fibrillation.<sup>10</sup>

Hypoglycaemia is commonly encountered in the treatment of diabetes with glucose-lowering medications, but there are other less common causes which can lead to significant morbidity. Therefore awareness of such causes, their diagnosis and prompt treatment is important to prevent sequelae of prolonged hypoglycaemia that may result in irreversible neurological or cardiac sequelae.

We report a case of Levofloxacin induced hypoglycaemia. Levofloxacin is widely used to treat different types of bacterial infections and its potential risk of causing hypoglycaemia is significant to avoid its related effect on morbidity and mortality.

### **Case Report**

A 67-year-old woman presented with an unwitnessed fall and decreased oral intake. She had a background of learning disability, hypertension, epilepsy, bronchial asthma, chronic iron deficiency anaemia, chronic mild lymphopenia, osteoporosis and previously treated uterine cancer. Her regular medications were oxybutynin, folic acid, ferrous fumarate, phenobarbitone, paracetamol, buprenorphine patch

and senna. At the time of admission, she was resident with her mother in a house with carers going to see her times a day. She used a walking frame and sometimes a wheelchair.

After clinical review, a provisional diagnosis of hospital acquired pneumonia (following her recent hospital admission) was made. Her clinical condition was complicated with suspected aspiration along with hyponatraemia secondary to dehydration.

Her chest x-ray showed persistent radio-opacification in the right lung zone. She was to be allergic to Penicillin. Our hospital antibiotic guideline for Hospital Acquired Pneumonia and Aspiration recommended treatment with Levofloxacin and Metronidazole. She was commenced on intravenous levofloxacin 500 mg 12 hourly and metronidazole 500 mg 8 hourly along with supportive care. Her CURB-65 score was 2 (Blood pressure 96/45 mmHg and Age- 67 years).

On Day one, her random venous blood glucose was noted to be 7.1 mmol/L. She was not known to have diabetes. On day 3 of admission, she was found to be unresponsive with an elevated Early warning score (4), capillary blood glucose was found to be 0.6mmol/L, which improved with an infusion of 10% glucose. The low blood glucose was attributed to poor oral intake. Her serial blood sugar monitoring continued to demonstrate persistent hypoglycaemia, requiring further doses of intravenous glucose.

A medication review was undertaken, and levofloxacin was discontinued. After 24hrs of discontinuation, the hypoglycaemic episode resolved. The nursing and medical staff expressed concern about her food intake and a possible risk of compromised nutrition. She was reviewed by our swallowing assessment team and she was placed on puree diet.

Her serial capillary blood glucose is shown in figure 1. A short Synacthen test showed normal cortisol response (At 0min - 262nmol/l, 30mins- 467nmol/l).

She was observed for hypoglycaemia during the remainder of her inpatient stay with serial capillary blood sugar monitoring and no further hypoglycaemic episodes were observed. Hence, a diagnosis of levofloxacin induced hypoglycaemia was considered, and no further investigation was undertaken.

## Discussion

The Federal Drug Administration in the USA published a review of reports from Adverse Event Reporting System and the medical literature between 1987-2017, in which fluoroquinolones are said to have

caused about 67 cases of life-threatening hypoglycaemic coma including 13 deaths and 9 permanent disabling injuries. Most of these cases were associated with levofloxacin.

Its hypoglycaemic effect is found to occur more in the elderly and those with diabetes using an oral hypoglycaemic agent or insulin.<sup>11</sup> Fluoroquinolones have insulin secretagogue actions and have been shown in studies on rat islet cells, to induce hypoglycaemia by increasing the insulin release via blockade of adenosine triphosphate-sensitive K<sup>+</sup> channels in the  $\beta$  cells of the pancreas. This effect may not be clinically evident in all patients because of physiologic mechanisms that regulate blood glucose levels.<sup>12, 13</sup>

An experiment assessing the effects of three fluoroquinolone derivatives- Levofloxacin, Gatifloxacin and Temafloxacin demonstrated dose-dependent stimulation of insulin secretion and inhibition of pancreatic beta-cell ATP -sensitive K<sup>+</sup> channel activity. In a reconstituted system, Gatifloxacin and Temafloxacin inhibited Kir6.2 Delta C26 channels, which function in the SUR unit, indicating direct action of the drugs on the Kir6.2 subunits. These findings indicate that the stimulation of insulin secretion by inhibition of pancreatic beta-cell K(ATP) channels gives the fundamentals of the hypoglycaemia caused by certain fluoroquinolones.<sup>14</sup> Gatifloxacin was taken out of the market on September 2<sup>nd</sup>, 2008 due to its association with potentially fatal blood sugar problems.<sup>15</sup>

While the hypoglycaemic actions of many commonly used medications may not cause clinical hypoglycaemia *de novo*, they may cause hypoglycaemia in association with factors that facilitate and contribute to the risk of drug-induced hypoglycaemia. They include restricted food access, age, liver disease and renal disease.<sup>16</sup> Our patient had no demonstrable evidence of reduced counter-regulatory hormones such as hypothyroidism or hypoadrenalism.

We believe that the combination of reduced food access and the insulin secretagogue action of quinolones acted in synergy to contribute to our patient's hypoglycaemia.

## Conclusion

Health professionals should be aware of the potential risk of severe hypoglycaemia in acutely ill patients with the use of frontline line antibiotics such as Fluoroquinolones which are treatment of choice for common infective processes. Glucose monitoring

should be a part of safety surveillance when using these medications in elderly patients who are not having good oral intake or in those with other comorbidities, regular blood glucose monitoring should be carried out, when a Fluoroquinolones is used, to avoid life threatening hypoglycaemic episodes.

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Table 1 Results of Investigations:

Full Blood Count:

Parameters	31/07/20	04/08/20	05/08/20	14/08/20	Reference Ranges
Hb	72	82	79	66	(115-165)
Wcc	10.1	3.9	2.6	4.0	(4-10)
Plt	251	182	188	215	(150- 410)
Hemat	0.224	0.267	0.249	0.221	(0.36-0.46)

Mcv	80	86	83	97	(27-32)
Neu	9.2	3.2	1.6	3.0	(2.0-7.0)
Lymph	0.3	0.3	0.4	0.4	(1.0-3.0)
CRP	15	51	43	23	(0-5)
Na	122	130	128	135	(133-140)
K	5.6	4.9	4.7	4.5	(3.5-5.3)
Urea	6.5	4.4	2.6	3.5	(2.5-7.8)
Creatinine	66	57	55	57	(55-100)
eGFR	83	>90	>90	>90	

Figure 1: Capillary Blood Glucose:

