Hypoglycaemia documented with real-time continuous glucose sensing in a case of ‘dead in bed’ syndrome

Najeeb Waheed
FRCP, Consultant Diabetologist, Hereford County Hospital, Hereford, UK

Muhammad Butt
FRCP, FHEA, Consultant Diabetes & Endocrinology, Peterborough City Hospital, Peterborough, UK

Colin Dayan
FRCP, Professor of Clinical Diabetes & Metabolism, Director, Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, UK

Correspondence to:
Dr Najeeb Waheed, Consultant Diabetologist, Diabetes Centre, Hereford County Hospital, Union Walk, Hereford HR1 2ER, UK; email: najeebwaheed@yahoo.com

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Abstract
The objective of this observational case report was to present the first case consistent with the ‘dead in bed’ syndrome in which hypoglycaemia has been documented by real-time glucose monitoring at the time of death.

We report the case of a 41-year-old male with type 1 diabetes. Diagnosed at age 14, he had poor glycaemic control during his teen years and suffered from severe hypoglycaemia unawareness. His diabetes was complicated by nephropathy, neuropathy and retinopathy. He was last seen alive and well by the family seven days before he was found dead in bed with his insulin pump and sensor in situ. The last recorded interaction between the patient and the pump system was seven days previously with evidence of prolonged hypoglycaemia around the time. Post-mortem examination showed no specific cause of death.

The findings in this case report are consistent with the hypothesis that hypoglycaemia is a precipitant of the ‘dead in bed’ syndrome in diabetes and indicate that the presence of low glucose alarms does not provide complete protection against such an event. Copyright © 2013 John Wiley & Sons.

Key words
dead-in-bed; hypoglycaemia; real-time glucose monitoring

Introduction
In 1991, Tattersall and Gill described a newly-reported syndrome of sudden nocturnal death in young patients with type 1 diabetes, which subsequently became known as the ‘dead in bed’ syndrome. The syndrome remains rare with the number of deaths of this kind being estimated at 2–6 per 10 000 patient years. For a typical large secondary care service covering a population of 10 000 patients with diabetes, this represents 2–6 deaths per year or approximately 6% of all deaths in patients with diabetes aged less than 40 years.

Clinical reports suggest that nocturnal hypoglycaemia is a likely pre-requisite of the event, but that the death is sudden and probably caused by cardiac arrhythmia with no evidence of a traumatic seizure. Hypoglycaemia itself has been documented to cause premature ventricular contractions, QTc prolongation, atrial arrhythmias and ischaemia ECG changes, but not sustained ventricular arrhythmia, possibly because such patients did not survive.

There is now extensive evidence that insulin-induced hypoglycaemia can cause an acquired form of long QT syndrome and, during experimental hypoglycaemia, the QTc interval can increase by a mean 60–80 ms from baseline in healthy individuals and diabetic patients without autonomic neuropathy. In addition to QTc prolongation during hypoglycaemia, QT dispersion (the difference between the longest and shortest QT interval on a 12-lead ECG) increases. Hypoglycaemia, particularly when seen in the setting of cardiac disease, creates multiple changes that are proarrhythmic.

It has generally been assumed that death in this syndrome is secondary to hypoglycaemia precipitating a sudden cardiac event. The diagnosis of hypoglycaemia is difficult to confirm after death as glucose levels, even in the vitreous humour, fall rapidly post-mortem. Hence, high vitreous levels exclude, but low levels do not prove, ante-mortem hypoglycaemia. Furthermore, hypoglycaemic events are common in insulin-treated patients including nocturnal hypoglycaemia, but rarely result in sudden death and, indeed, limited episodes of hypoglycaemia are often accepted as an inevitable consequence of tight glycaemic control. Tannenberg et al. reported the case of a young man who died in an undisturbed bed while
wearing a continuous glucose monitor without real-time capability. Download of the monitor demonstrated hypoglycaemia prior to death.

Here we report a case consistent with the ‘dead in bed’ syndrome in which the patient died while wearing a continuous glucose monitor with real-time reporting, providing further direct evidence that hypoglycaemia is associated with this syndrome and indicating that alarm functions linked to real-time monitoring may not provide complete protection against hypoglycaemia-associated death.

Case history and examination
A 41-year-old man was found dead in an undisturbed bed with a continuous glucose monitoring device in situ in March 2010. He had a history of type 1 diabetes diagnosed in 1982 at the age of 14 with poor glycaemic control during his teenage years.

His diabetes was complicated by proliferative retinopathy requiring retinal photocoagulation, nephropathy (proteinuria and creatinine of 140μmol/L) and peripheral neuropathy complicated by previous osteomyelitis of the left toe. He also suffered from severe hypoglycaemia and hypoglycaemia unawareness resulting in three road traffic accidents with head and shoulder injuries. He began continuous subcutaneous insulin pump therapy in 2005 and linked continuous real-time glucose monitoring in June 2009 (with the Medtronic Paradigm Real-Time system). His recent HbA1c had been 7.9% (63mmol/mol). He lived alone and was last seen alive and well by his family seven days before being found dead in bed with no signs of violent injury.

Investigation
The post-mortem download of his glucose monitoring device and insulin pump is shown in Figure 1, displaying frequent hypoglycaemic episodes over the nine-day period. On day 9, he became hypoglycaemic at around 16.00 hrs and temporarily stopped and then restarted his pump. Despite alarms from the continuous glucose monitor (black squares), he became more hypoglycaemic. At 17.00 hrs he gave two 10 unit insulin doses while still hypoglycaemic and this was the last recorded interaction between the patient and the pump/sensor system.

Figure 1. Post-mortem downloads of the patient’s insulin pump and sensor. Figure 1A shows the data for a 10-day period. No insulin doses or interaction with the pump or sensor are recorded after 17.30 hrs on the 9th day and this is the presumed time of death. Figure 1B shows the data in detail for the day, indicating that the patient became hypoglycaemic around 16.00 hrs and temporarily stopped and then restarted his pump. Despite alarms from the continuous glucose monitor (black squares), he became more hypoglycaemic. At 17.00 hrs he gave two 10 unit insulin doses while still hypoglycaemic and this was the last recorded interaction between the patient and the pump/sensor system.
The exact date and time of death are uncertain. He was found dead in an undisturbed bed seven days later. Food from a delivery earlier that day was found unused in the fridge and his computer showed the last access to be on the afternoon of the day (shown in Figure 1b). Post-mortem examination revealed generalised signs of early decomposition therefore consistent with death several days before his body was discovered. There was no evidence of any traumatic injuries. The examination showed a single, narrowed, but not occluded, coronary artery. The only other abnormal autopsy findings were renal cortical scarring consistent with diabetic nephropathy, and pulmonary oedema. Neither post-mortem histological assessment of the major organs nor blood or urine toxicological analyses indicated an unequivocal cause of death.

Discussion
This is a case of death in type 1 diabetics with a real-time continuous glucose monitor in situ.

We believe the circumstances of the current report are consistent with the syndrome of ‘dead in bed’ as, contrary to the patient’s usual severe hypoglycaemic episodes (often associated with violent behaviour), the patient was found in an undisturbed bed. The administration of two doses of insulin while hypoglycaemic prior to death most likely represents confusion during hypoglycaemia as is the switching on and off of his pump prior to this.

Deliberate overdose of insulin seems unlikely as the patient had displayed no previous evidence of low mood and the doses given were modest and typical of his pattern of evening meal dosing (one bolus and one as a ‘square wave’ bolus). Why this particular event precipitated sudden death remains a key issue, and in his case may be related to his single narrowed coronary artery. We note that it remains possible that the hypoglycaemia is circumstantial and not directly causative.

There are some differences between the clinical details in our case and that reported by Tanenberg et al., as he had poorer glycaemic control (HbA1c: 7.9% [63mmol/mol] vs 6.4% [46mmol/mol]), and both micro- and macrovascular complications, whereas the reported case had no diabetes-specific complications. Our patient was prone to unpredictable hypoglycaemic episodes and not just the nocturnal hypos as in the reported case, and the timing of death was more accurate in the reported case.

It is of particular concern that, despite repeated alarms, the real-time system was unable to avert the tragic outcome in our case. Previous studies with real-time monitoring have shown improvement in HbA1c but not necessarily a reduction in severe hypoglycaemia episodes, a trial specifically in hypoglycaemic individuals is currently underway. Whether this is due to patients ignoring the alarms in the hypoglycaemic state, developing tolerance to them because of frequent previous episodes or responding inappropriately and illogically to the alarm while hypoglycaemic, as appears to be the case in our patient, is not clear. However, studies particularly targeted to understanding patient behaviour under these circumstances are required to improve outcomes, and the link in newer systems between hypoglycaemia and pump shut-off seems a very valuable development. It is likely that, as the use of continuous glucose monitoring becomes more widespread, additional cases will be reported and increase our understanding of the ‘dead in bed’ syndrome.

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