Oral quinine-induced hypoglycaemic seizures

J Elliott, A Mackie, C Dibden, A Blumsohn, F Creagh*

ABSTRACT

A patient with type 1 diabetes mellitus was admitted for investigation of hypoglycaemic seizures. His past medical history included a combined pancreas and kidney transplant, but by the time of admission both organs had failed. As his renal function deteriorated leg cramps were problematic, and so oral quinine had been prescribed. Despite reducing his insulin doses, his glycaemic control became more erratic. His plasma quinine concentration was typical of that expected in high dose intravenous treatment of malaria. On ceasing oral quinine therapy his hypoglycaemic seizures stopped.

This case highlights that in cases of unexplained hypoglycaemic attacks, in patients with some residual endogenous insulin secretion, oral quinine must be excluded as a possible cause. Copyright © 2010 John Wiley & Sons.

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KEY WORDS

hypoglycaemia; quinine; seizures

Case report

A 30-year-old male patient developed type 1 diabetes at the age of 22 months and underwent a combined pancreas and kidney transplant at age 27. Initially, both organs functioned well (creatinine 162µmol/L and HbA_{1c} 5.7%), but approximately 18 months post-transplant his pancreas started to fail. Insulin was recommenced and up-titrated to a dose of Levemir 8 units bd with NovoRapid 6 units bd. His renal function declined from 30 months post-transplant, to the point when dialysis was recommenced some six months later (creatinine 760µmol/L). His past medical history included proliferative diabetic retinopathy, hypertension, osteoporosis, and Charcot's arthropathy of his right ankle.

Three months after dialysis was reinitiated, he was admitted to hospital following a hypoglycaemic seizure, at which time the capillary blood glucose reading was 1.3mmol/L. This was the first such hypoglycaemic seizure since he was seven years old. He had experienced increasingly frequent hypoglycaemic episodes during the preceding few weeks and had been reducing his insulin, to a point at which he was injecting 2–4 units of Levemir per day. Despite this dose reduction his home blood glucose measurements continued to be erratic and ranged from 1.3–22.5mmol/L. He had five nocturnal hypoglycaemic seizures (between 2 and 5 am) over a seven-week period. During one such hypoglycaemic episode, plasma glucose was measured at 1.7mmol/L; simultaneous insulin and C-peptide levels were 79.3pmol/L (16–67) and 483pmol/L (364–1655) respectively.

Amongst 13 regular medications, he was taking quinine sulphate 300mg nocte, which had been recommenced for leg cramps at the time his renal function was declining. (The other medications were aspirin, amlodipine, losartan, doxazosin, folic acid, alfacalcidol, omeprazole, domperidone, tacrolimus, prednisolone, Venofer, and NeoRecormon. There had been no recent dose changes to any of his medications.) Plasma quinine concentration was measured at 5.7mg/L (analysed at Sheffield Teaching Hospitals NHS Trust, Clinical Biochemistry, using HPLC with fluorometric detection). Of note, the usual dose of quinine in malaria treatment is 10mg/kg tds, and the therapeutic range is 3–7mg/L. On ceasing quinine treatment his home blood glucose measurements were immediately less erratic, and severe hypoglycaemic episodes leading to seizures ceased. Insulin injections were cautiously reintroduced and up-titrated to Levemir 12 units daily in divided doses. Of note, he had not experienced any of the other features of quinine toxicity, e.g. tinnitus, visual disturbance, headache, rash, fever, hypotension or abdominal pain.

Discussion

Hypoglycaemia is known to occur in malaria and is complicated by intravenous quinine therapy causing hyperinsulinaemia.[1] Intravenous quinine is also known to cause lower plasma glucose and higher plasma insulin in healthy individuals (mean plasma quinine 4.5mg/L).[2] In both healthy volunteers and patients with type 2 diabetes, plasma glucose falls three to six hours post quinine ingestion (maximum quinine concentration 3.7mg/L).[3] The mode of action is analogous to that of glucose itself, i.e. quinine inhibits potassium conductance, causing activation of voltage-dependent calcium channels, resulting in insulin release.[4] There are a small number of case reports of oral quinine inducing hypoglycaemia, mostly in patients taking 300mg once a day for leg cramps. One gentleman with severe congestive heart failure was found to have asymptomatic fasting blood glucose measurements of 2.5mmol/L, and inappropriately high plasma insulin, which returned to normal on stopping quinine therapy.[5]

There are two cases quoted in the literature of quinine-induced hypoglycaemia which was associated with severe renal failure, as in our patient. One of these patients had a creatinine of 1730µmol/L and blood glucose of <0.8mmol/L, and was deemed to have

Jackie Elliott, MRCP, PhD
Alasdair Mackie, MD, FRCPE
Catherine Dibden, MSc, DipRCPath
Aubrey Blumsohn, PhD, FRCPath
Fionuala Creagh, MD, FRCP

Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

***Correspondence to:** Dr Jackie Elliott, Department of Diabetes, P20, Royal Hallamshire Hospital, Sheffield S10 2JF, UK; e-mail: Jackie.elliott@sth.nhs.uk

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inappropriately high plasma C-peptide and plasma insulin, in addition to a plasma quinine of 8.75mg/L.[6] In the second case, quinine was thought to be involved in causing hypoglycaemia in a patient undergoing investigation for a possible insulinoma.[7]

More recently, Kerr *et al.* described a case in which quinine caused hypoglycaemic episodes to such an extent that the patient over-compensated by eating carbohydrate, gained weight and developed type 2 diabetes, before the significance of quinine was recognised. On stopping quinine therapy the hypoglycaemic episodes resolved, the patient lost weight and a repeat oral glucose tolerance test returned to normal.[8] Another case elegantly illustrated this clinical problem by performing a 72-hour fast in a patient on quinine 325mg qds for leg cramps, and then repeating the test off quinine treatment, before reintroducing the quinine. In the initial study, the blood glucose fell to 2.0mmol/L, but on the repeat testing no hypoglycaemic episodes occurred in the 72 hours. At that point, quinine was reintroduced, and his blood glucose fell to 2.5mmol/L. Whilst hypoglycaemic, his plasma C-peptide and plasma insulin were found to be inappropriately elevated.[9]

Therefore, it is possible in our patient that, although the residual pancreatic function from the transplanted pancreas was not sufficient for him to remain normoglycaemic, it was sufficient to make him susceptible to hypoglycaemia via quinine therapy-induced hyperinsulinaemia. His plasma quinine was more typical of that expected in high dose intravenous doses, than that of low dose oral usage, probably due to accumulation effects caused by his severe renal failure.

In conclusion, there are only a few case reports of oral quinine therapy precipitating hypoglycaemia. In each case, the patient was on quinine to treat leg cramps, usually at a dose of 300mg once a day. However, to our knowledge this is the first report of oral quinine causing such severe and unpredictable hypoglycaemic attacks. Thus, this case highlights that in cases of unexplained hypoglycaemic attacks, in patients with some residual endogenous insulin secretion, oral quinine must be excluded as a possible cause.

Conflict of interest statement

There are no conflicts of interest.

Key points

- Both intravenous and oral quinine can induce hypoglycaemia, including seizures
- Quinine therapy causes hyperinsulinaemia, and therefore requires at least some pancreatic function to induce hypoglycaemia
- Even relatively small doses of quinine, such as 300mg od to treat leg cramps, can cause clinically significant hypoglycaemia, particularly in patients with renal failure

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