Cardiology in the Young (2018), **28**, 511–513
doi:10.1017/S1047951117002724

Brief Report

Recurrent hypoglycaemia in a toddler on β-blocker therapy

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Abstract Hypoglycaemia is a well-known side effect of Propranolol. We described the case of a child presenting severe and recurrent Propranolol-induced hypoglycaemia. Those episodes were not related to prolonged fasting and were associated with only mild ketosis. Thus, therapy with β blockers may not only aggravate classical ketotic hypoglycaemia but also interfere with glucose metabolism.

Keywords: Propranolol; hypoglycaemia; glucose; β-blocker; ketone

Received: 18 September 2017; Accepted: 17 November 2017; First published online: 8 January 2018

Glucose homoeostasis is essential to supply continuous metabolic fuel for the brain. It depends on many mechanisms including normal hormone secretion, adequate mobilisation of potential fuels and functionally intact enzymes, and pathways for their utilisation. Congenital or acquired abnormalities can alter those mechanisms and lead to hypoglycaemia. β Blockers are one of the well-known causes that can lead to hypoglycaemia. Although many cases of β-blocker-induced hypoglycaemia have been reported in the literature,[1–4] they rarely seem to be associated with severe and recurrent hypoglycaemia. Furthermore, they are associated with prolonged fasting. We describe the case of a 4-year-old-girl who presented atypical characteristics of Propranolol-associated hypoglycaemia.

Case description

She was born at term (2.76 kg). Her prenatal history was remarkable only for atrial extra-systoles and she had a normal cardiac ultrasound. During the first hours of life, she presented incessant tachycardia that recurred after Adenosine and was non-responsive to Digoxin and Sotalol. She was diagnosed with permanent junctional reciprocating tachycardia and started on Propranolol and Amiodarone to achieve control of her arrhythmia. Digoxin was added at 4 months of age.

She first presented to the endocrinology team at 20 months of age. She had been hospitalised for bronchiolitis 2 days previously and had been released in good clinical condition. The night before her admission she had eaten a sufficient meal and did not seem sick according to her mother. Upon awakening, she presented hypothermia, bradycardia, and an altered level of consciousness. By the time she arrived at the hospital, her serum glucose was 23 mg/dl. She was treated with intravenous glucose without further metabolic testing. She did, however, have a urinalysis that demonstrated positive urine ketones (5.0 mmol/L = moderate). She was subsequently found to be subfebrile with a temperature of 38.0°C and was diagnosed with pneumonia because of persistent oxygen needs. She was treated accordingly and discharged 2 days later.

Between the ages of 3 and 4, she presented three episodes of morning seizures. Each time she was found to have a serum glucose <18 mg/dl (see Table 1). Parents were instructed on preventive measures such as glucose monitoring and offering snacks in circumstances considered risky for hypoglycaemia such as intercurrent illness. Notably, only the second episode was associated with diminished food intake the night before. Each time she was assessed by the endocrinology team she had a normal physical examination aside from the finding of short stature (third percentile whereas midparental height was 85th percentile). More specifically, there was no dysmorphism, midline defects, hyperpigmentation,

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Table 1. Hypoglycaemia episodes

	Propranolol (mg/kg/day)	Glycaemia (mg/dl)	Serum β-hydroxybutyrate (mmol/L)	Other observations
20 months	10	23		Ketones + in urine
$3^{5/12}$ years	7.5	16	1.9	
$3^{8/12}$ years	7.5	<18	1.8	No response to glucagon challenge
$3^{11/12}$ years	5	<18	1.8	

Table 2. Metabolic work-up and critical sample

Glucose	30.6 mg/dl	Hypoglycaemia if glucose <50 mg/dl
Cortisol	1714 nmol/L	Normal response to hypoglycaemia: cortisol > 480 nmol/L
Insulin	< 14 pmol/L	Normal response to hypoglycaemia: no detectable insulin
Growth hormone	18.9 µg/L	Normal response to hypoglycaemia: GH > 8 µg/L
Free fatty acids	1.06 mmol/L (N = 0.27–0.82)	Normal response to hypoglycaemia: FFA >1.5 mmol/L
Ammonia	29.5 µmol/L	Normal < 50 µmol/L
Lactate	1.1 mmol/L	Normal < 1.5 mmol/L
Acylcarnitine, total and free carnitine	Normal	
Urine organic acids	Slight elevation of ketones	Expected during hypoglycaemia
Urine amino acids	Normal	
Plasma amino acids	Normal	

FFA = free fatty acids; GH = growth hormone.

or hepatomegaly. She, however, had a normal growth rate. On investigation, the critical sample during one episode of severe hypoglycaemia showed an appropriately elevated cortisol and growth hormone level, an appropriately suppressed insulin and normal metabolic work up with only mildly elevated ketones (see Table 2). Each episode responded rapidly to glucose boluses. During one event, a glucagon challenge was tried (0.12 mg/kg, excessive dose given by error) but it induced an insignificant rise of 14 mg/dl glycaemia. This indicated that she had appropriately consumed her hepatic glycogen while hypoglycaemic (no hyperinsulinism). Between the episodes, she was sent home with regular glucose monitoring, which revealed no hypoglycaemia – even on continuous glucose monitoring for 5 days. After the third episode, the dose of Propranolol was decreased progressively and stopped after the fourth. However, the control of her arrhythmia was sub-optimal and Propranolol needed to be reintroduced (2 mg/kg/day) for a short period before being switched for Sotalol (8 mg/kg/day), whereas Amiodarone was stopped. She had no other episode of hypoglycaemia in the 2 years following this change in therapy and is currently well on Sotalol and Digoxin.

Discussion

Propranolol is a non-selective β-adrenergic blocker agent used in many paediatric conditions including cardiac, psychiatric, and dermatologic diseases. Although it has been well studied in adults, its safety profile in children has been establish mainly based on case reports.[1–4] In these reports, profound hypoglycaemic events or seizure-related hypoglycaemia have been linked to Propranolol. Like our patient, most of the reported cases were seen in young children – between 6 months and 9 years – on prolonged Propranolol therapy.[7] Unlike our patient, most of the cases presented only one hypoglycaemic event. To our knowledge, Poterucha[2] was the only one to describe recurrence in his cohort, with three episodes being the maximum of events reported. Hypoglycaemic events have been associated with prolonged fasting periods or diminished oral intake before an overnight fast, which was not the case for the two last events of our patient and probably why we were not able to prevent them.

The mechanism of Propranolol-induced hypoglycaemia is still not completely understood. It has been suggested that by antagonising the β2-adrenergic receptor, Propranolol would interfere with epinephrine's counter-regulatory role during hypoglycaemia. Epinephrine can increase hepatic glycogenolysis and later on hepatic and renal neoglucogenesis. It does increase substrates available for gluconeogenesis in the liver, such as lactate, alanine, and also glycerol and free fatty acids.[5] Both glucagon and epinephrine are secreted at similar levels of hypoglycaemia.[6] β Blockers could also influence the insulin/glucagon balance in favour of hypoglycaemia, by impairing insulin clearance[7] and by lowering glucagon.

https://doi.org/10.1017/S1047951117002724 Published online by Cambridge University Press

Experiments in healthy subjects showed that 7 days of Propranolol use lowers the rise of glucagon during induced hypoglycaemia.[8] Interestingly, the mild ketosis observed in our patient has not been discussed in other reports about Propranolol-induced hypoglycaemia. After reviewing other case reports, we found only one author reporting mild ketosis during metabolic work-up[4] and one reporting serum β-hydroxybutyrate of 1 mmol/L[3]. Ketotic hypoglycaemia is a paediatric disorder typically associated with morning or fasting hypoglycaemia in toddlers. It has been postulated that propranolol might exacerbate ketotic hypoglycaemia. However, these patients have highly elevated serum ketones (β-hydroxybutyrate mean value of 2.3 mmol/L usually more than 2 mmol/L),[9] which does not match our findings. Interestingly, our clinical findings are in line with previous metabolic studies showing that β adrenergic blockade reduced post-hypoglycaemic rise in blood β-hydroxybutyrate by 50%.[10]

This case illustrates the β-blocker-associated hypoglycaemia in a patient considered to be at low risk. It is unusual to present such profound and recurrent hypoglycaemia in the absence of prolonged fasting. Although the pathophysiology underlying Propranolol-associated hypoglycaemia is still under investigation, the characteristics of our case seem to indicate an acute and unpredictable alteration in the glucose counter-regulatory mechanism (i.e. lower the effect of epinephrine and glucagon response, lower substrate release for neoglucogenesis). We propose that β-blocker-induced hypoglycaemia has a specific metabolic signature of moderate elevation of free fatty acids and ketones, which do not reach the expected values of classical ketotic hypoglycaemia (free fatty acids > 1.5 mmol/L and β-hydroxybutyrate >2 mmol/L). Some guidelines recommend stopping the use of Propranolol during fasting episodes to decrease the risk of hypoglycaemia.[1] This may not be an option when Propranolol is prescribed for a cardiac condition. Therefore, β blockers should be used with caution in children and hypoglycaemia should be suspected and treated promptly when a child presents with compatible symptoms.

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency or commercial or not-for-profit sectors.

Conflicts of Interest

None.

Ethical Standards

Consent for publication has been granted by the patient's family.

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