Metformin therapy for diabetes in Prader–Willi syndrome

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Children with Prader–Willi syndrome (PWS) are commonly obese and have an increased risk of developing insulin resistance, hyperinsulinaemia and non-insulin-dependent diabetes mellitus (NIDDM). The conventional management of NIDDM associated with PWS includes dietary control and behavioural modification. Oral hypoglycaemic drugs such as sulphonylurea drugs have often been used but these tend to cause weight gain rather than weight loss. The biguanide metformin has the potential advantage of reducing appetite, but its place in PWS is uncertain.

CASE HISTORY

The patient, whose parents are Egyptian, was delivered at 36 weeks by caesarean section because of breech presentation and polyhydramnios. At birth he weighed 3.6 kg and was found to be hypotonic with bilateral undescended testes; he required nasogastric tube feeding for the first 4 days of life. Subsequently he showed developmental delay with moderate learning difficulties and special educational needs. After failure to gain weight in the neonatal period, his weight accelerated to well above 97th centile in early childhood as a result of excessive appetite and obsessional eating habits. His height was maintained along the 50th centile.

At 13 years of age, polydipsia and polyuria developed. Random glucose was 24.6 mmol/L without ketonuria. He was clinically obese and weighed 95 kg (body mass index 41.5 kg/m^2). Since diet manipulation for glycaemic control proved difficult, metformin 500 mg once daily was initiated. The medication was well tolerated and was increased to 500 mg twice daily. Over the four months of metformin treatment, a 20 kg weight reduction was observed along with improvement of glycaemic control (capillary finger prick blood glucose 10–14 mmol/L). Formal assessment of glycaemic control with HbA1c has not been possible because of the patient's reluctance to have venepuncture.

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COMMENT

Diabetes mellitus occurs in up to 14% of patients with PWS[1] and the incidence of abnormal glucose tolerance increases after 15 years[1]. In most cases the diabetes is non-insulin-dependent (type 2) and the high rate of NIDDM may be aetiologically linked to the morbid obesity and associated insulin resistance. Other possible explanations for the development of diabetes mellitus in PWS include reduced number of insulin receptors on target cells[2], reduced beta-cell response to glucose stimulation and increased hepatic insulin extraction and insulin clearance[3].

Treatment of NIDDM associated with PWS may be difficult since most children exhibit obsessive food-related behaviour with impaired satiety response[4]. Diet control and behaviour therapy tend to be unsuccessful. Specialized group home placement therapy with diet restriction, a monitored exercise programme and a structured environment have proved effective in weight and glycaemic control[5]. However, many PWS children with NIDDM have been treated with insulin for glycaemic control, which in itself may lead to further weight gain. This may also be true of sulphonylureas, the oral hypoglycaemic agents used in the paediatric age group. To our knowledge, therapy with biguanides such as metformin has not been reported in children. Metformin improves glycaemic control by inhibiting hepatic gluconeogenesis and increasing peripheral insulin sensitivity. Additionally, it has anorectic properties that enhance weight loss independently of its glucose-lowering effect[6], and these may be especially advantageous in PWS. Side-effects at low doses are infrequent; the rare complication of lactic acidosis with metformin usually arises in patients with renal impairment, which causes accumulation of the drug. Low-dose metformin deserves consideration in PWS with NIDDM, when the need is for improved glycaemic control together weight reduction.

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