Novel treatment (new drug/intervention; established drug/procedure in new situation)

Bezafibrate to prevent relapsing pancreatitis in WAGR syndrome

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Summary

Recurrent episodes of acute, severe pancreatitis are a feature of the rare WAGR congenital anomaly syndrome. Although pancreatitis is well recognised as a life-threatening association of WAGR syndrome, treatment to prevent pancreatitis is not recommended. We report the successful prevention of hypertriglyceridaemia-associated relapsing pancreatitis in a child with WAGR syndrome with Bezafibrate. In addition to dietary fat restriction, Bezafibrate may be a useful therapeutic adjunct in WAGR related relapsing pancreatitis.

BACKGROUND

WAGR is a rare syndrome with high mortality in children. Pancreatitis is a well-recognised and life-threatening association with the WAGR syndrome. However, there are no treatment guidelines to prevent relapsing, recurrent pancreatitis in WAGR syndrome. Our experience of successful prevention of hypertriglyceridaemia-associated pancreatitis with Bezafibrate and dietary fat restriction may provide an important treatment possibility to limit mortality in this rare syndrome with a poor prognosis.

CASE PRESENTATION

A 12-year-old girl who had been previously diagnosed with WAGR syndrome presented with several episodes of acute pancreatitis over a 12-month period (figure 1). She was born with bilateral cataracts and aniridia. Genetic testing showed deletion in chromosome 11p11.2-11p13, consistent with WAGR syndrome. She underwent Wilm's tumour screening with subsequent detection and treatment of stage 1 Wilm's tumour of the right kidney at age 2 years. The patient developed obesity in early childhood, with weight $> +2.5$ SD (figure 1). At age 10 years, she underwent oral glucose tolerance testing which showed evidence of insulin resistance. At this time, high triglyceride levels (8–9 mmol/l, upper end of normal <1.5 mmol/l) were noted, while serum cholesterol levels remained within range (2.4–4.5 mmol/l). The patient's dietary fat content was reduced with satisfactory compliance with dietary restriction and consequent significant weight reduction. Weight loss was accompanied by a reduction in serum triglyceride levels (5.5 mmol/l), although remaining above the normal range (<1.5 mmol/l) at age 12 years (figure 1).

The patient suffered her first episode of acute pancreatitis with acute abdominal pain at age 12 years, following an infusion of Propofol, which was prescribed for anaesthesia for brain MRI. Further to this episode, she had seven successive episodes of pancreatitis (five with clear biochemical evidence), with no obvious triggering factor other than persistent hypertriglyceridaemia (5–6 mmol/l), despite continuing weight reduction.

INVESTIGATIONS

On biochemical testing, the patient had elevated serum amylase (>1000 U/l) and lipase (>6000 U/l) levels, consistent with acute pancreatitis. During these episodes, serum calcium and liver function tests remained normal. An interval endoscopic ultrasound scan of the pancreas showed evidence indicative of chronic calcific pancreatitis (figure 2).

TREATMENT

Although dietary fat restriction had reduced serum triglyceride levels significantly, normal values were not achieved by age 13 years. Therefore, while pancreatitis continued to recur in the presence of relatively high triglyceride concentrations (>2.5 mmol/l), Bezafibrate (200 mg twice daily) was introduced to lower serum triglyceride levels further. Following the introduction of Bezafibrate therapy, no further episode of acute pancreatitis occurred for 1 year (figure 1). At age 14 years, she had had a period of non-compliance with her fat restricted diet, coincident with one further clinical episode of abdominal pain, suggestive of pancreatitis when the serum triglyceride level was 1.8 mmol/l. Since then, compliance with dietary fat restriction and Bezafibrate have remained excellent; serum triglyceride levels have remained in the normal range and further pancreatitis episodes have not occurred.

OUTCOME AND FOLLOW-UP

Two years hence, the patient remains free of pancreatitis, while on treatment with Bezafibrate and dietary fat restriction. Her liver function blood tests have remained normal and she has not experienced any complications of Bezafibrate such as myopathy or rhabdomyolysis.

DISCUSSION

Relapsing acute pancreatitis is a recognised clinical feature of WAGR syndrome,¹ a rare congenital anomaly syndrome consisting of Wilm's tumour, aniridia, genital abnormalities and mental retardation, due to a chromosomal deletion in the short arm of chromosome 11. Acute

Figure 1 Cessation in episodes of pancreatitis coinciding with the reduction in triglyceride levels following dietary fat restriction and the introduction of Bezafibrate. Weights in kilograms are plotted on the UK 1990 weight charts (SD). Triglyceride levels are plotted as full dark circles, connected by dark lines. Incomplete dark lines represent levels following Bezafibrate use. Pancreatitis episodes are represented by arrows between 12 and 13 years of age. Bezafibrate was introduced after the last significant episode of pancreatitis.

pancreatitis can be life threatening to patients with WAGR; therefore, prevention of pancreatitis is an important consideration.

The precise aetiology of pancreatitis in WAGR remains unknown. One likely contributory factor to pancreatitis is hypertriglyceridaemia, although the cause for this is also unknown. It is recognised that a proportion of children with WAGR syndrome may be obese,² and it is possible that hypertriglyceridaemia in this child might have been secondary to obesity. Therefore, a dietary strategy to reduce energy and fat was justified. However, despite having lost weight, serum triglyceride levels remained high, although considerably below that observed initially.

Figure 2 Upper gastrointestinal endoscopic ultrasound of the head of pancreas showing multiple hyperechoic foci with postacoustic shadowing indicative of chronic calcific pancreatitis.

At age 12 years, she had had eight episodes of acute pancreatitis, the first of which was triggered by Propofol.

Dietary fat restriction and medication such as Bezafibrate to reduce triglyceride levels have been noted to be effective in adults to prevent relapses of hypertriglyceridaemia-induced acute pancreatitis.³ However, experience and data of this effect in children are lacking. While the statin group of drugs have been used more widely in children and noted to reduce triglyceride levels, case reports suggest pancreatitis may occur as a rare adverse effect.⁴ In view of the risk of pancreatitis, statins were not considered for treatment.

Bezafibrate is rarely used in children and efficacy data are not available, particularly in WAGR syndrome. The International WAGR Syndrome Association in 2007 issued recommendations for health supervision for children with WAGR syndrome,⁵ which included dietary consultation, encouraging physical activity and monitoring of blood lipids from early childhood. No recommendation was made on the use of Bezafibrate to reduce the risk of pancreatitis.

Bezafibrate is a member of the fibrate group of drugs which can reduce serum triglyceride by 30–50%. Fibrates act as synthetic ligands to peroxisome proliferator-activated receptors- α , thereby increasing lipolysis and plasma clearance of triglyceride-rich lipoproteins. Fibrates can also promote β -oxidation of fatty acids, thus reducing the availability of free fatty acids for triglyceride synthesis. Although its use is anecdotal in children, the introduction of Bezafibrate may be justified, particularly if aiming to prevent serious and potentially life-threatening acute pancreatitis in WAGR syndrome. Bezafibrate is known to have rare but significant side effects, including cholelithiasis, renal impairment, myositis, rhabdomyolysis and Stevens-Johnson syndrome; therefore the use of Bezafibrate should be carefully monitored not only for efficacy but also for safety.

Learning points

- ▶ Relapsing pancreatitis may occur in association with the rare WAGR syndrome, often in association with hypertriglyceridaemia.
- ▶ Pancreatitis may be a cause for the high mortality observed in children with WAGR syndrome.
- ▶ Hypertriglyceridaemia can be successfully treated by dietary fat restriction and Bezafibrate in WAGR syndrome, thereby preventing life-threatening episodes of pancreatitis.
- ▶ Bezafibrate may be a useful therapeutic adjunct to the prevention of hypertriglyceridaemia-associated pancreatitis in WAGR syndrome.

Competing interests None.

Patient consent Obtained.

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Diacono D, Fagbemi A, Puleston J, Banerjee I. Bezafibrate to prevent relapsing pancreatitis in WAGR syndrome. *BMJ Case Reports* 2012;10.1136/bcr-2012-006413, Published XXX

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