CONGENITAL HYPERINSULINISM (CHI) is an important cause of persistent and severe hypoglycemia in the neonatal, infancy and childhood periods. Octreotide, a somatostatin analogue, is commonly used in diazoxide unresponsive congenital hyperinsulinism (CHI) patients as a second line medication. The aim of this study was to evaluate the dose range, side effects and long-term follow up in a large cohort of CHI patients on multiple daily octreotide injections.

METHODS

This retrospective study was carried out in the department of Paediatric Endocrinology at Great Ormond Street Hospital for Children, London. CHI patients who were unresponsive to maximum dose of diazoxide (20 mg/kg/day) and subsequently received octreotide therapy (5-35 μg/kg/day) since November 2001 were included in the study. Patients who could not be weaned off intravenous dextrose fluids after starting octreotide therapy went on to have further investigations like pancreatic venous sampling or 18F-DOPA PET CT. Depending upon the subtype of CHI, these patients either underwent near-total pancreatectomy or focal lesion resection/partial pancreatectomy. Post-pancreatectomy, octreotide therapy was recommenced on those who continued to have hypoglycemia. The case-notes of the patients treated with octreotide between November 2001 and December 2013 were retrospectively reviewed to collect detailed clinical and biochemical characteristics on presentation, molecular genetic analysis results, requirement for pancreatectomy and doses and duration of octreotide therapy used. Baseline hepatobiliary ultrasound, thyroid function test, growth factors (insulin like growth factor 1-IGF and IGF binding protein 3-IGFBP3), and liver function tests were performed before commencing octreotide therapy. These investigations were repeated at regular 3-6 monthly intervals to identify adverse effects of octreotide therapy. Weight and height/length was measured at the time of presentation and then every clinic appointment and admission to our investigation unit.

Effects of octreotide therapy on liver function and gall bladder

Apart from mild gastrointestinal side effects such as abdominal discomfort, diarrhoea, and transient elevation of liver transaminases, no serious side effects were observed which resulted in withdrawal of treatment. Transient elevation of liver enzymes was observed in 15 patients (44.4%), which resolved within 4-8 weeks despite continuing octreotide. In total, the rate of having elevated liver enzyme in patients who had gall bladder pathology (n=49, 44.4%) and without gall bladder pathology (n=97, 47.4%) was not statistically different (p=0.694). There was no difference in the mean dose of octreotide in patients with and without elevated liver enzymes (17.78±7.45 μg/kg/day v/s 17.87±7.45 μg/kg/day; p=0.969). However median age at which octreotide therapy was commenced was significantly lower in patients with elevated liver enzymes as compared to those with normal liver enzymes (0.25 months v/s 1.5 months; p=0.046). Gall bladder pathology was observed on follow up hepatobiliary ultrasonography in 32 (31.2%) patients (gallstones – 6; gall bladder sludge – 3) (Table 2). These patients were treated with ursodiol or ursodeoxycholic acid (UDCA). There was no statistically significant difference between the mean ages of octreotide in patients with or without gallstones formation (18.87±4.7 μg/kg/day v/s 17.87±4.5 μg/kg/day respectively; p=0.655). The mean duration of developing gall bladder pathology (gallstones or sludge) on octreotide therapy was 4.3±0.6 months in 9 patients, whilst 19 patients without gall bladder pathology have been followed up for 53.6±3.9 months. Also there was no statistically significant difference between median age of commencing octreotide therapy in patients with or without gallbladder pathology (1.0 months v/s 0.9 months; p=0.783).

Effects of octreotide therapy on weight, linear growth and pubertal functions

Serial evaluation of height/SDS during follow up over a year on fast admission revealed short stature (height lower than -2 SDS) but within the target centile range for the family in 3/28 (10.7%) patients. All these three patients had familial short stature. Two of these had normal height velocity and serum and IGFBP3 levels within normal range for age and sex. The third patient with low serum IGF and IGFBP3 levels was investigated with growth hormone stimulation test and overnight growth hormone profile, both of which were normal. On comparison of serum IGF1 and IGFBP3 levels before and after octreotide therapy (range: 6 months to 9.5 years), there was no statistically significant difference in the reductions of IGF1, and IGFBP3 levels. Mean (±SD) fasting serum IGF1 SDS measured before octreotide therapy vs follow up measurement were -0.6 (±0.7) vs -0.4 (±0.6) (p=0.986) and for serum IGFBP3 SDS were -0.1 (±1.7) vs -0.5 (±1.4) (p=0.121) respectively (Figure 1). On their recent evaluation, mean BMI z-score was 1.3±0.9 (range: -1.6 to 2.6). Seven out of 28 (25%) patients had a BMI z-score > 1.5 SD.

CONCLUSIONS

This is the largest study to our knowledge evaluating long term follow up of CHI patients on octreotide therapy. We showed that most prevalent side effects were gall bladder pathology (gall stone or sludge) and transient elevation of liver enzymes. Gastroinestinal function test did not show any statistically significant suppression.