Use of Lanreotide (long acting Somatostatin analogue) in Congenital Hyperinsulinism (CHI)

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Overview

• Introduction – CHI and Lanreotide

• Aim

• Methodology

• Preliminary results

• Summary
Introduction

• Congenital hyperinsulinism (CHI) - commonest cause of recurrent & persistent hypoglycaemia in infants & children

• Inappropriate secretion of insulin from the pancreatic β-cells in relation to the blood glucose concentration

• Clinical presentation - symptomatic hypoglycaemia soon after birth & require large amounts of intravenous dextrose infusions to maintain normoglycaemia
Complications

- Increased risk of brain injury due to lack of both glucose & ketones.

Treatment

- Intravenous therapy/dietary therapy
- Pharmacotherapy – Diazoxide; Glucagon and Octreotide; calcium channel blockers (eg, nifedipine).
  New medications like **Lanreotide** (long acting Octreotide - Somatostatin analogue)
- Surgery – near total pancreatectomy – if not responsive to pharmacotherapy.
Diffuse disease
Histological and/or physiological abnormalities in \(\beta\)-cells throughout the pancreas

Focal disease
A focal lesion (adenomatous islet-cell hyperplasia, focal nodular adenomatosis), rest of the pancreas normal

Genetics of CHI - ABCC8, KCNJ11, GLUD1, GCK, SCHAD, HNF4A, SLC16A1, UCP2, HNF1A
Islet of Langerhans

Schematic representation of the anatomic relationships in an islet of Langerhans. The insulin-producing B cells (in blue) are in the center closest to the blood supply and are surrounded by the glucagon-producing alpha (α) cells (in orange). On the outside are the delta (δ) cells (in yellow), which make somatostatin, and the PP cells (in green), which make pancreatic polypeptide.
Lanreotide

- Octreotide - long-acting analog of somatostatin, which has inhibitory effects on the release of insulin from pancreatic β-cells.
- Lanreotide is an octapeptide analogue of natural somatostatin.
- Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions.
- Lanreotide has high binding affinity for human somatostatin receptors (SSTR) 2 and 5, and a reduced binding affinity for human SSTR 1, 3 and 4.

Used in:
- acromegaly
- treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.
Lanreotide use in CHI


  2 children (4 and 4.5 years) treated with a once-monthly injection of a long-acting somatostatin analogue.


  Use of the very-long-acting somatostatin analogue lanreotide autogel in 6 patients with CHI – reduced overall risk for hypoglycemic episodes (odds ratio 0.38) significantly.


  10 paediatric patients with HI unresponsive to diazoxide and treated with s.c. octreotide were included.
Adverse effects

- Rarely allergic type reactions / local reactions at the site of injection
- Gastrointestinal side effects include anorexia, nausea, abdominal pain, bloating, flatulence, loose stools.
- Suppression of growth and thyroid hormones
- Decrease gallbladder contractility and bile secretion leading to cholestasis, hepatic dysfunction and gall stones.
- Blood flow to the splanchnic circulation is decreased by octreotide – hence to be used cautiously in babies at risk of necrotising enterocolitis.
- Rare adverse effects - include bradycardia, malabsorption of vitamins A, B12 and D, and alopecia.
Aim/Objectives

• To understand the pharmacodynamics of lanreotide given every 28 days in children with CHI - change of 4 times a day octreotide injections to once 4 weekly lanreotide injection

• To understand somatostatin receptor expression in islets
Materials and Methods

- Ethical approval obtained from NRES (National Research Ethics Services) committee and GOSH R&D department

- Parent and children (5-10 years and > 11 years) information sheet and their consent form.

- Children >3.5 years of age – on daily octreotide injections or on diazoxide with side effects.
Methods – For lanreotide therapy (used in children >3.5 years)

- Continuous blood glucose monitoring (CGMS), baseline bloods, USS gall bladder before starting lanreotide therapy

5 day admission
- Lanreotide injection – ametop or emla cream applied

- Pain score chart
- Monitor vitals
- Blood glucose monitoring
Methods – For lanreotide therapy (used in children >3.5 years)

• Blood samples of lanreotide

• Height and weight on admission and then every 6 months

• Plan given to wean octreotide/diazoxide

2nd admission (for 1 night) – 4 weeks after the 1st injection

• Wean and stop octreotide/diazoxide night before 2nd dose of lanreotide.

• Blood glucose monitoring
Methods – For lanreotide therapy (used in children >3.5 years)

Follow up:

- Routine laboratory tests and ultrasound liver and gall bladder every 6 months

- Quality of life (QoL) survey – during 1\textsuperscript{st} injection and at 6 months

- CGMS at the end of 1 year of treatment

- Those on bolus/continuous feeds overnight - to gradually reduce feeds and stop after 3 doses of lanreotide injection.
RESULTS
Case – 6.5 years

- Diagnosis: CHI (negative genetics)

- Treatment: Octreotide 22mcg/kg/day 4 times a day

- Feeds: 3 bolus feeds during daytime and continuous feeds overnight (fast tolerance max 4 hours)

- Started on Lanreotide – stopped Octreotide before the 2nd dose of Lanreotide

- After 6 months of therapy – have come off continuous feeds and bolus feeds – fast tolerance 14 hours
Summary

Preliminary data has shown that
- Lanreotide has been found effective in treatment of children with congenital hyperinsulinism – improved QoL
- So far 13 children has been started on Lanreotide

Adverse effect so far:
- One child had loose stools initial few months – then settled.
Future Plan

- Continue to recruit patients for lanreotide
- Follow up
- Immunohistochemistry – receptor expression in islets
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