Management of Insulinoma using the drug Octreotide
A Case Report and Literature Review

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Case

- A 40-year-old, Spanish-speaking male presented to a local hospital with persistent hypoglycemia (low blood sugar). NKDA.
- Relevant past medical history includes insulinoma
- Current home medications include hydrochlorothiazide (HCTZ) 25 mg PO daily and octreotide 75 mcg SC 4 times daily
- Emergency Room Course
  - Patient received 2 bolus injections of 25 g of 50% dextrose, 2 doses of SC glucagon, and after receiving IV continuous infusion of 10% dextrose, blood glucose raised to above 70 g/dL
- Hospital Course
  - Patient was admitted and SC octreotide was resumed, but patient reported severe headache soon after the evening and bedtime doses, and began to refuse the octreotide injection
  - Blood glucose was around 60 g/dL despite adequate intake

- Pharmacy team was asked to contribute to the therapy of this case
  - Is the headache related to the octreotide administration?
  - Can a long-acting formulation be used instead?

Insulinoma[1,2,3]

- Rare, pancreatic tumor; incidence of 4/million individuals per year[1-2]
- **Hypersecretion of insulin and thus leading to hypoglycemia**[1]
- > 90% occurs in intrapancreatic sites, 90% solitary, and 90% benign
- Extrapancreatic insulinomas are extremely rare (< 2%)

- **Clinical signs and symptoms**:
  - Persistent hypoglycemia (blood glucose < 50 mg/dL; reference range 70-110 mg/dL)[1]
  - 26% of symptoms appear early morning before breakfast[3]

  - **Neuroglycopenic symptoms**: Visual disturbances, altered mental status with or without confusion, coma, behavioral changes, seizures[1]
  - **Sympathetic Adrenergic symptoms**: Diaphoresis, tremor, palpitations[1]
- Delay in treatment can lead to permanent brain dysfunction[3]

Diagnosis:

- Variability of symptoms adds to the difficulty of diagnosis
- Classic diagnosis is based on the **Whipple's Triad**[1-2]:
  - Plasma glucose < 50mg/dL
  - Neuroglycopenic symptoms
  - Prompt relief of symptoms after glucose administration

  - **Non-Invasive Imaging:** Transabdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)[2]
  - **Invasive Imaging:** Endoscopic ultrasonography (EUS) and Arterial stimulation venous sampling (ASVS)[2]

Treatment[1,2]

- Surgical resection is the treatment of choice[2]
- **Medical Management** to normalize blood glucose prior to surgery, those not candidates for surgery (e.g. multiple insulinoma, unresectable malignant insulinoma, patients whom surgery is contraindicated, or patients refusing surgery)[2]

Table 1: Medical treatments for Insulinoma[1]

Major Therapeutic Options		Comments	Max. dose
Diazoxide	Benzothiadiazine; inhibits insulin release from β-cells	Initiate 150-200 mg given twice-thrice daily	400 mg/day
Octreotide Lanreotide	**Somatostatins analogs;** decreases plasma insulin level & raises blood glucose	Initiate 50 mcg given twice-thrice daily	1500 mcg/day
Adjuvant Therapy		**Comments**	
Phenytoin	Inhibits insulin release from β cells	At maintenance, 300-600 mg daily	
Verapamil	Calcium channel blocker	Given either alone or in conjunction to with frequently used medications to control symptoms	
Propranolol	β adrenergic blocker		
Glucocor-ticoid	Raises blood glucose		

Octreotide[4,5]

A cyclic octapeptide that belongs to a class of drugs that are synthetic somatostatin (SST) analogues[4]

- A more potent inhibitor of insulin and growth hormone; binds to SST receptors 2 and 5 with high affinity[4]
- Inhibition of insulin secretion from insulinoma can reduce episodes and/or duration of hypoglycemia[5]
- Inhibition of growth hormone can decrease insulinoma size, resulting in less secretion of insulin[5]

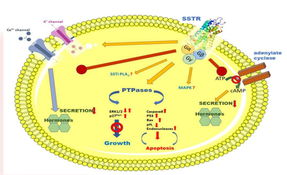

Figure. SSTR-based potential downstream pathways and signaling cascades leading to the modulation of hormone secretion, cell growth, and apoptosis[6]

Adverse Drug Reactions (ADR)[12]

- **Gastrointestinal** (34% - 61%): diarrhea, nausea, abdominal pain, gallbladder issues (typically mild/moderate and self-limiting)
- **Cardiac**: Bradycardia (25% w/acromegaly), conduction irregularities (10%) and arrythmias (9%)
- Hypoglycemia (3%) and Hyperglycemia (16%)
- Itching (18%)
- Pain at injection site (7.7%)
- **Headache and dizziness (6%)**

ADR reported based on other medical indications and off-label uses

Review of Clinical Case Reports

- Many studies exist on using somatostatin analogs for a variety of functioning pancreatic neuroendocrine tumors (pNET), but no randomized, multi-centered, prospective studies are published on its use for insulinoma.
- A retrospective study of over 3 decades in China (1984 to 2017) with one patient receiving 9 courses of somatostatin analogue, which resulted in alleviated hypoglycemic symptoms.[7]
- A 68 years old male with insulinoma received 0.1 mcg of octreotide BID for 1 month, prior to surgery to control hypoglycemic episodes, with success.[8]
- Two Japanese elderly females with insulinoma also received octreotide. Both had successful normalization of blood glucose.[9]
  - Subject 1 (76 YO) was initiated on 50 mcg daily by subcutaneous route for over a year with no further episode of hypoglycemia;
  - Subject 2 (85 YO) was initiated at 100 mcg subcutaneous daily due to the concurrent hypoglycemic coma. This individual recovered but gradually required a dose reduction to 75 mcg, 62.5 mcg and a final daily dose of 50 mcg for 3 years due to the development of hyperglycemia.

No data available on headache related to use of octreotide

No current clinical data for the use of long-acting octreotide formulation in insulinoma

- Vezzosi et al reported the treatment of 17 subjects with octreotide for insulinoma in Europe[10]
  - Female (82%), mean age 53 years (range 18 – 78 years)
  - All subjects with identified location(s) of tumor(s), and 94% with benign tumors (mean tumor size 19 mm)
    - 14/17 (82%) subjects received a short course of octreotide (octreotide response testing), with 8 subjects (47%) showing adequate response
    - 10/17 (59%) subjects subsequently received octreotide treatment; doses not detailed
    - 8/10 (80%) demonstrated symptom relief, with duration of pharmacotherapy ranging from 8 days to 8 months
  - Similar response rates to a previous 21 subjects (data not reported)
  - Adverse drug reaction was not reported
  - No concurrent use or previous use of other therapy of insulinoma was reported

Patient Disposition
- Patient agreed to be adherent to 4 times daily of SC octreotide
- Headache was managed with alternating acetaminophen and ibuprofen; psychosomatic causes were suspected
- Patient was discharged home and had not returned to hospital

Short Acting vs. Long Acting Octreotide Formulations[11]

Products	Octreotide acetate (Sandostatin)	Octreotide acetate LAR (Sandostatin LAR)
Formulations	Solution	Powder for suspension (with microsphere polymer)
Route of Administration	Subcutaneous	Intramuscular (Intragluteal)
Administration Personnel	Medical professional or Self	Medical Professional Only
Frequency	Twice to Thrice daily	Monthly
Half Life	100 minutes	NR*
Absorption	100%	~2/3 of SC solution
Strengths	50, 100, 200 mcg/mL	10, 20, or 30 mg/mL

* NR, not reported; steady state reached after 3 injections (at 4-week intervals)

CONCLUSION

- Insulinoma is a very rare condition that manifests as persistent, symptomatic hypoglycemia, and its management can be challenging
- Surgical removal of the insulin-secreting tumors is preferred, but is not feasible in this case
- Several pharmacologic options are available for insulinoma, all are off-label uses
  - Diazoxide PO and octreotide SC; supportive care
- A review of the medical literature revealed that
  - Insulinoma had been rarely identified in Europe and Asia
  - Individuals of any age could be affected by insulinoma; the prevalence appeared to be higher in older females
  - No randomized, prospective clinical trials for any therapy for insulinoma had been performed, likely due to the rarity of the condition
  - Several case reports, documenting the effectiveness of using octreotide in the management of insulinoma, were available; however, one should be aware of publication bias
  - Data on appropriate dosing and duration of octreotide treatment were limited
  - Hyperglycemia could occur during octreotide therapy; the use of long-acting formulation and headache could not be substantiated

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