Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Amantadine Induced Severe Hypoglycemia in a Patient With Type 1 Diabetes and Multiple Sclerosis

Basem M. Mishriky, MD, Doyle M. Cummings, PharmD, FCP, FCCP, James R. Powell, MD.
EAST CAROLINA UNIVERSITY, Greenville, NC, USA.

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Introduction: Amantadine is one of the few options commonly used to treat fatigue associated with multiple sclerosis. However, in a previous trial investigating the effect of amantadine on oral glucose tolerance test results, amantadine caused a reduction in plasma glucose and glucagon levels while increasing insulin levels in healthy volunteers [1]. If amantadine can reduce glucagon levels, we hypothesized that it might also cause hypoglycemia in patients with type 1 diabetes.

Case presentation: The patient is a 34-year-old African American male who has a past medical history of type 1 diabetes and multiple sclerosis. His baseline hemoglobin A1c values ranged from 6.9% to 7.6% and his weight was 88 Kg. His insulin glargine dose was 28 units daily while his insulin lispro was 10 units before meals. For almost one year he was followed in clinic and had no episodes of severe hypoglycemia (defined as hypoglycemia requiring assistance from another person).

The patient complained about gait imbalance and fatigue from multiple sclerosis for which he was followed by a neurologist. To treat these symptoms, he was prescribed amantadine 100 mg twice daily. A couple of hours following his first dose of amantadine after eating his usual breakfast (with his sister), the patient was found unconscious by his sister. Emergency Medical Services (EMS) was called and he was found to have a blood glucose of 22 mg/dL. He was admitted to the hospital. During that admission, amantadine was discontinued, and he was discharged on insulin glargine 24 units daily and insulin lispro 10 units with meals.

Discussion: We present a case of suspected amantadine induced severe hypoglycemia. In patients with type 1 diabetes, there is a loss of the pancreatic β-cells while the α-cells are preserved [2, 3]. We hypothesize that if amantadine reduces glucagon production from the α-cells, patients would be prone to severe hypoglycemia, presumably because of the unopposed insulin action. Although it is unlikely that the severe hypoglycemia was secondary to insulin since the patient was on stable doses, it cannot be completely excluded. We recommend caution when prescribing amantadine to patients on insulin therapy particularly within the first two hours after rapid acting insulin administration. More research is needed to explore this possibility.

References: [1] Diabetes Metab Syndr Obes 2009; 2: 203. [2] Br J Diabetes Vasc Dis 2014; 14: 45. [3] Peptides 2018; 10: 54.

Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Vaginal Cabergoline: A Simple Solution to a Challenging Problem

Munder Abuaisha, MD[1], Otto Gibbs, MD[1], Rachel Bier, MD[2].
[1]ENGLEWOOD HOSP & MED CTR, Englewood, NJ, USA, [2]Endocrinology Consultants, PC., Woodcliff Lake, NJ, USA.

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Introduction: Prolactinomas is a common endocrine disorder that can be associated with significant morbidity. Generally, prolactinomas are more responsive to pharmacologic treatment than any other types of pituitary adenoma. Dopamine agonists (DA), including cabergoline and bromocriptine, are the first line of treatment in all sizes of prolactinomas and they decrease both the secretion and size of these adenomas. However, treatment remains challenging for patients who are intolerance to those medications. **Case**: We report a 32-year-old Hispanic woman who presented with secondary amenorrhea, she was found to have hyperprolactinemia of 1496 mcg/L. MRI of the brain showed a pituitary adenoma measuring 2.7 cm with sella turcica invasion and mass effect on the optic chiasma. She failed the lowest doses of oral cabergoline and bromocriptine and underwent TSS and gamma knife radiosurgery. Given her persistent symptoms (marked depression, insomnia, fatigue, short-term memory loss, and lack of concentration along with constipation) and elevation of prolactin, she was started on low dose vaginal cabergoline leading to a marked improvement of her symptoms and a steady decrease in serum prolactin. **Discussion**: Despite the availability of DA as a first-line treatment of Prolactinoma, treatment remains challenging, given the commonly reported side effects for all DA. Cabergoline is oftentimes the treatment of choice due to efficacy and favorable side-effect profile. However, intolerance to those medications can lead to discontinuation of therapy and increase morbidity. Other strategies, including transsphenoidal surgery (TSS) or radiation therapy, have been considered for the minority of patients whose adenomas are resistant to DA or who cannot tolerate these drugs. Interestingly, tolerance to DA can be improved by administering the drug intravaginally, which can have similar efficacy to the oral route and a more favorable side-effect profile. However, only a few studies assessed the effectiveness and tolerance of vaginal DAs in hyperprolactinemic patients intolerant to oral medications, little evidence supports the use of intravaginal DA to improve drug tolerance, and further studies are necessary to determine the safety and efficacy of vaginal cabergoline.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Somatostatin Agonist Conjugated to the Evans Blue Moiety Is a Superior Analog in the Diagnosis and Treatment of Tumors Characterized by High Somatostatin Receptor Expression

Shilpa Thakur, Ph.D[1], Brianna Daley, B.S[1], Orit Jacobson, PhD[1], Zhantong Wang, PhD[1], Xiaoyuan Chen, PhD[1], Joanna Klubo-Gwiezdzinska, MD,PHD. MHSc[2].
[1]National Institutes of Health, Bethesda, MD, USA, [2]NIH-NIDDK, Bethesda, MD, USA.

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Background: Radiolabeled somatostatin (SST) analogs have been proven to be effective in the diagnosis and treatment of

neuroendocrine tumors (NETs), which are characterized by high somatostatin receptor (SSTR2) expression. At present, there are several SST analogs available that differ from each other in the affinity for SSTR2 and tumor retention time. To date, only a single SST agonist -DOTA-TATE- has been approved by the FDA for imaging and treatment of NETs. Recent studies have shown that addition of Evans blue (EB) moiety to an SST agonist results in superior uptake and increased retention time within the tumors. The goal of our study was to compare the diagnostic and therapeutic efficacy of three different radiolabeled SST analogs in a tumor mice model: EB-TATE - a novel modified agonist; DOTA-TATE - an agonist and JR11 - an antagonist. **Methods:** A rat pancreatic cell line (AR42J), characterized by high SSTR2 expression, was used to create a subcutaneous xenograft mice model. The AR42J cells formed sizable tumors within two weeks post-injection. The ^{86}Y-EB-TATE, ^{68}Ga-DOTA-TATE, and ^{68}Ga-DOTA-JR11 were used to determine standard uptake values by positron emission tomography (PET) imaging. For treatment purposes, the SST analogs were labeled with ^{177}Lu to generate ^{177}Lu-EB-TATE, ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11. The mice were assigned to treatment groups based on comparable tumor volume at baseline and received two doses (0.5mCi) of the ^{177}Lu-labeled analogs one week apart. Tumor measurements were performed twice per week and the mice were euthanized if their tumor burden exceeded 2 cm at any point in the study or after 6 weeks - landmark of the end of the study. **Results:** Among the three analogs tested, the novel SST analog ^{86}Y-EB-TATE was characterized by 4.3- and 3.7- fold higher tumor uptake in comparison to ^{68}Ga-DOTA-TATE ($p<0.001$) and ^{68}Ga-DOTA-JR11 ($p<0.001$), respectively. There was no significant difference between the uptake of ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-JR11 ($p=0.9$). Consistently with higher tumor uptake on imaging, ^{177}Lu-EB-TATE-treated mice responded to the treatment with an overall 86.5±13.2% reduction in the tumor volume after two weeks post-therapy. On the contrary, despite therapy with ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11, the mice treated with these agents presented with tumor progression exceeding 2 cm and were euthanized. Consequently, the progression-free survival (PFS) was significantly longer in ^{177}Lu-EB-TATE group (24±0 days) compared with ^{177}Lu-DOTA-TATE (7.7±2.6 days, $p<0.001$) and ^{177}Lu-DOTA-JR11 (6.3±3 days, $p<0.001$). There was no difference in PFS between ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11-treated mice ($p=0.3$). **Conclusion:** EB-TATE is characterized by superior diagnostic and therapeutic efficacy in comparison to DOTA-TATE and DOTA-JR11. EB-TATE might be used as imaging and therapeutic agent in tumors characterized by high SSTR2 expression.

Adrenal

ADRENAL CASE REPORTS II

Adrenal Incidentaloma to Pheochromocytoma (Variant of Unknown Significance of Von Hippel Lindau Syndrome, VHL)

Yin Htwe Oo, MD.
DALLAS VAMC, DALLAS, TX, USA.

SUN-194

Introduction

The majority of adrenal masses are found incidentally during imaging for non-adrenal causes. Approximately 5% of adrenal incidentalomas have proved to be pheochromocytomas. The majority of incidentalomas are benign and non-secretory.

Case

A 73 years-old white male with pre-diabetes and morbid obesity has been followed by endocrine service for right adrenal incidentaloma overall several years. A 1.6 cm right adrenal nodule with 31 Hounsfield Unit was found incidentally in 2009 CT abdomen for abdominal pain. It was a lipid poor adenoma with >60% absolute contrast washout in 10 minutes. Biochemically it was non-secretory. The size of nodule was gradually increased over next seven years measuring at 1.9 x 1.6 cm in 2010 and 2.1 x 1.6 cm in 2012 but remained non-secretory. In 2015 CT scan, it was measured at 3.0 x 2.3 cm with absolute washout value of 45% and relative washout value of 34%. The size was overall stable again for next three years measuring at 3.2 x 2.2 cm in 2018 scan. Repeat plasma and urine metanephrine were about 2-folds higher than upper normal reference level in 2015 and 3-folds higher in 2017. Clinically he was asymptomatic except anxiety. He has normocalcemia. He underwent laproscopic right adrenectomy after alpha blockage with doxazosin. Pathology showed 4.5 cm pheochromocytoma with positive chromogranin and synaptophysin. Fulgent paraganglioma-pheochromocytoma comprehensive panel with negative for RET,NF1,FH,SDHB,SDHD,SDHC,SDHAF2,SDHA,MAX,TMEM127 and VHL but noted to have heterozygous VUS of VHL c.205>G(p.Arg69Gly). He has no significant family history or personal history to suggest VHL.

Discussion

In a patient with lipid poor adrenal incidentaloma, pheochromocytoma should be ruled out biochemically with either plasma or 24hr urine fractionated metanephrine. Both tests have similar specificity and sensitivity. Even with initial negative biochemical assessment, repeat screening should be performed annually based on clinical suspicion and radiology characteristics. Imaging can be performed annually or biannually to assess the stability of nodule. VHL is an autosomal dominant hereditary disease with del/dup mutation in the VHL gene and associated with multisystem tumor such as CNS or retinal hemagioblastomas, RCC, pheochromocytoma, pancreatic NET, endolymphatic sac tumor, epididymal and broad ligament cystadenoma and visceral cysts.

Learning points

Lipid poor adrenal incidentaloma needs interval biochemical and imaging follow up. The frequency of monitoring can be individualized based on clinical suspicion and radiology findings. Pheochromocytoma can be clinically silent especially if it is small, however, it can be lethal with late or missed diagnosis. This is the first published case report of c.205C>G VHL variant associated with pheochromocytoma.