

Desensitization treatment for hypersensitivity reaction to octreotide in an acromegalic patient

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Abstract Octreotide is widely used as medical therapy for acromegaly. It is known to markedly reduce growth hormone levels, improve symptoms and reduce tumor size. Common side effects include gastrointestinal symptoms, hepatobiliary disorders, dizziness, headaches, bradycardia, hyperglycemia or hypoglycemia and thyroid dysfunction. Although urticaria, allergy/hypersensitivity reactions and anaphylaxis have been noted as possible adverse reactions, there is a lack of data showing a causal relationship between octreotide and hypersensitivity reactions and there is no information on management when continued use of this medication is essential. We now report a case of a 60 year old male with acromegaly who had presented with a cutaneous hypersensitivity reaction to octreotide. In addition he failed treatment with surgery, radiation, and dopamine agonist and could no longer afford to continue treatment with pegvisomant. The patient underwent desensitization treatment for his octreotide allergy and was able to resume treatment without any further side effects. We believe this case represents the first report of successful desensitization treatment for octreotide allergy in an acromegalic patient.

Keywords Acromegaly · Octreotide · Allergy · Desensitization · Hypersensitivity reaction

Introduction

Somatostatin analogs have been considered the medical therapy of choice for patients with acromegaly. Long acting release (LAR) depot formulations of octreotide has been shown in multiple studies to normalize growth hormone and IGF-1 levels over a mean duration of 20 months by 56 and 66 %, respectively [1–7]. Overall improvement of signs and symptoms of acromegaly with depot somatostatin analogs have been reported in 64–74 % of patients [1, 3, 7–14]. Tumor shrinkage occurs in 46 and 43 % patients treated with octreotide subcutaneous and LAR formulations, respectively, of which 21 and 35 % showed shrinkage of 20–50 % [1, 2, 4–6, 9, 11, 12, 15–22].

Octreotide acetate is the salt form of the cyclic octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. It is available in a vial containing the sterile drug product along with D, L-lactic and glycolic acids copolymer, mannitol, carboxymethyl-cellulose sodium and water [23]. Information on the side effect profile of octreotide is mostly derived from manufacturer data rather than from the literature [24]. Over 50 % of treated patients report side effects, which tend to be mild in nature and dissipate over time [24]. The most common side effects include gastrointestinal complaints, pain at the injection site and biliary dysfunction that typically presents as asymptomatic gallstones or sludge. Phase three and four clinical trials also noted that 10 % or more patients developed hyperglycemia, hypothyroidism, headaches, dizziness, fatigue, influenza-like symptoms, anemia, hypertension, bradycardia and cardiac conduction abnormalities [23, 25]. Post-marketing reports, from which it is not always possible to establish a causal relationship to drug exposure, have also noted adverse effects of anaphylactic shock, urticaria, and facial edema [23, 25].

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There have been two studies that found between 17 and 25 % of ambulatory primary care clinic patients with medication reported adverse drug reactions, and more than half of these were considered serious [26, 27]. Allergic drug reactions are thought to account for approximately 6–10 % of all adverse drug reactions [28]. In an individual who has demonstrated a hypersensitivity reaction to a medication for which there are no reasonable alternative treatments, drug desensitization should be considered. Drug desensitization involves administering incremental doses of a drug at fixed intervals over a period of hours to days. This acts to convert a drug-sensitive person to a drug-tolerant state [29]. Desensitization protocols have been used most commonly for antibiotics, aspirin/non-steroidal anti-inflammatory drugs, and chemotherapy agents. Most desensitization protocols are derived ultimately from penicillin desensitization protocols [30]. There are no reported desensitization protocols for octreotide allergy.

Case presentation

The patient is a 60 year old male with a history of acromegaly who initially presented in June 2001 with pressure-like frontal headaches, increasing hand size for 3–4 years, arthralgias, hyperhidrosis and fatigue. The patient subsequently developed sleep apnea and had required extensive dental work. Formal visual field testing had revealed bilateral inferior temporal field cuts associated with blurred vision that was more pronounced on the right. Initial hormone evaluation revealed an IGF-1 level of 874 ng/ml and growth hormone levels during an oral glucose tolerance test of 44.4, 34.3, 30.2 ng/ml at baseline, 1 and 2 h respectively. MRI of the pituitary showed a 2 cm macroadenoma that demonstrated suprasellar extension, causing mass effect on the inferior aspect of the optic nerve decussation. The patient was referred to us after he underwent partial transphenoidal removal with micro-dissection of the macroadenoma on August 10, 2001. Pathology was consistent with pituitary adenoma and staining was positive for growth hormone and prolactin, but negative for TSH, LH, FSH, and ACTH.

Despite surgery, the patient had a persistently elevated IGF-1 level of 1,213 ng/ml. Repeat imaging 1 year post-operatively showed post surgical changes with residual enhancing adenoma tissue involving the pituitary infundibulum and left half of the gland. The patient was started on subcutaneous octreotide 50 mcg three times daily in May 2002. Shortly after, the patient developed a papular rash on the abdomen that spread to the arms and back associated with pruritis and some lip swelling. There was no mucosal involvement or evidence of desquamation. The severe skin reaction occurred with multiple re-challenges

confirming the association with octreotide. In light of the apparent medication allergy, the octreotide was stopped in November 2002 and his symptoms resolved within a few days. The patient was then treated with cabergoline 0.5 mg bi-weekly for a duration of 1 year, which was discontinued when it became apparent that this medical treatment was ineffective with IGF-1 remaining elevated at 882 ng/ml. Also in November 2002 the patient received radiation therapy, which was completed by March 2004. Following radiation treatment the patient was started on pegvisomant with a good clinical response. Pegvisomant was titrated up from 15 to 25 mg and the IGF-1 levels subsequently normalized, ranging between 144 and 222 ng/ml. Pegvisomant was continued until March 2010, when the patient stopped taking the medication due to inability to afford the \$2,300 monthly cost. While off medical treatment, IGF-1 levels became elevated once again, peaking at 445 ng/ml. The MRI of the pituitary in February 2009 showed an empty sella with a thickened infundibula/stalk still extending up towards the optic chiasm.

Since the patient could not continue treatment with pegvisomant, due to financial constraints, and as surgery, radiation and dopamine agonist treatments had demonstrated little success, the suggestion was made to institute a desensitization protocol for octreotide. In conjunction with the Allergy and Immunology department, a protocol was developed for desensitization. The patient was admitted on August 5, 2010 to perform the desensitization within the inpatient setting, in the intensive care unit. The patient was successfully desensitized to octreotide with the protocol illustrated on Table 1, which he tolerated with no

Table 1 Octreotide desensitization protocol

	Interval (min)	Dose of IV octreotide (mcg)
1	20	0.001
2	20	0.002
3	20	0.005
4	20	0.01
5	20	0.02
6	20	0.05
7	20	0.1
8	20	0.2
9	20	0.5
10	20	1
11	20	2
12	20	5
13	20	25
14	20	50

Repeat 50 mcg dose after 8 h

Increase dose to 100 mcg for subsequent doses, if desired

complications. The next day he was begun on subcutaneous octreotide. The patient was ultimately discharged on octreotide 100 mcg every 8 h that was later increased to 150 mcg every 8 h. By April 2011 the patient was transitioned to the long acting release formulation with the intramuscular dose increased from 20 to 30 mg monthly. IGF-1 levels trended down to 274 ng/ml at that time. The patient has denied having any associated skin reactions with the octreotide since the desensitization intervention was instituted.

Discussion

Acromegaly is an uncommon disorder characterized by growth hormone hyper-secretion associated with increased morbidity and mortality. Associated symptoms are related to either mass effect, including headaches and visual changes, or metabolic effects, including soft tissue swelling and cardiovascular complications. Treatment of acromegaly is imperative given the threefold overall mortality without treatment.

Surgical resection of growth hormone secreting adenoma is the recommended initial treatment for acromegaly. However the surgical cure rate for microadenoma is approximately 70 % and for macroadenoma only 50 % [31]. Despite its potential to provide immediate improvement of soft tissue swelling and normalization of GH and IGF-1 levels, recurrences can occur in up to 10 % of patients as well [31]. For cases of surgical failure or individuals who either are not surgical candidates or refuse surgical intervention there are medical therapeutic options available, including somatostatin analogs. The mechanism of action of Somatostatin analogs is via their effects on SSTR2 and 5 receptors expressed by GH-secreting tumors. Fewer than 10 % of patients treated with octreotide have no response [31]. Octreotide suppresses GH levels to $<5 \mu\text{g/L}$ in 70 % and $<2 \mu\text{g/L}$ in 60 % of patients [31]. Somatostatin analogs alleviate symptoms of headaches, sweating, and arthralgias, in almost 75 % of patients and result in a reduction of pituitary tumor size in approximately 40 % of patients [32–36]. Prolonged use of the analog is not associated with loss of activity even after 10 years [31].

Somatostatin analogs are well tolerated in most patients and side effects are usually short-lived.

The most common adverse events are gastrointestinal in nature, which include transient abdominal discomfort and malabsorptive diarrhea. Although an increased incidence of gallbladder sludge and stone formation has also been noted, they are not typically of clinical significance.

Other side effects include bradycardia, hypothyroidism, hyperglycemia, headaches, dizziness, fatigue, influenza-

like symptoms, anemia, hypertension and local pain injection site. One adverse reaction that is not readily noted in the literature, but was observed in our patient, is hypersensitivity reaction.

Drug allergies have either an antibody or cell-mediated immunologic mechanism with an immediate or delayed presentation [37]. There is a lack of data identifying the immunologic mechanism of octreotide hypersensitivity reaction. Desensitization is a method to reduce or eliminate hypersensitivity reaction to a drug. Desensitization protocols have been used primarily for antibiotics, aspirin, and chemotherapy agents, but none have been reported for octreotide allergy. This case demonstrates that desensitization treatment for octreotide allergy in an acromegalic patient can be safely performed and is a viable clinical option.

Conflict of interest The authors declare that they have no conflict of interest.

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