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REVIEW

The predictive value of an acute octreotide suppression test in patients with acromegaly

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Abstract

Acromegaly is a rare chronic disorder that is in 95% of cases caused by growth hormone (GH) secreting pituitary tumors. Endonasal transphenoidal surgery is usually considered the first line of treatment, followed by medical therapy for residual disease. The long-acting somatostatin (SA) analogues have an important role in the medical treatment of these patients. SA exert their biological effects by activating somatostatin receptors (SSTR). The predominant types of SSTR receptors in GH-secreting pituitary tumors are subtypes 2 (SSTR2) and 5 (SSTR5). The efficacy of somatostatin analog therapy (SAT) is determined by its effect on tumor shrinkage which is reported to be between 20 and 50%. Approximately 10-30% of GH-secreting pituitary tumors are resistant to SA because of variable or reduced tumoral expression of SSTR2 or SSTR5.

In many centres a test dose (TD) of octreotide is administered before commencing SAT in order to predict the long term response to treatment. There has been a great interest in identifying factors that predict a good response to SAT. To date, several studies that have examined the relationship between the TD of octreotide and SAT. It is crucial how we define response during the OST. Nadir of GH to 5mU/l or less during the OST has an excelent predictive value for evaluation of long-term response to SAT. On the other hand, if we define response as percentage of change of GH from it's baseline values, then the OST is not usefull diagnostic test.

Key words: bariatric surgery, gut hormones, weight loss

1. Introduction

Acromegaly is a rare chronic disorder that is in 95% of cases caused by growth hormone (GH) secreting pituitary tumors. In less than 5% of cases acromegaly is caused by increased growth hormone releasing hormone (GHRH) from hypothalamic tumors, ectopic GHRH from neuroendocrine tumors (mostly lung and pancreas) and ectopic GH secretion by non-endocrine tumors. Hereditary conditions that can cause acromegaly include multiple endocrine neoplasia 1 (MEN-1), Carney complex, and McCune-Albright syndrome. The incidence is estimated to be 3-4 cases per million. The mean age at diagnosis is 40 years in males and 45 years in females. The mean duration from symptom onset to diagnosis is 5-15 years, with a mean delay of 8.7 years [1]. The majority of tumors are macroadenomas (> 10mm) with infiltration of surrounding neural structures. For pituitary adenomas endonasal transphenoidal surgery is usually considered the first line treatment followed by medical therapy for residual disease. Surgery is most successful in patients with preoperative blood GH levels below 40 ng/ml and tumors no larger than 10 mm in diameter [2]. In 40 to 60% of cases there are residual tumors after surgery [3]. The best measurement of surgical success is normalization of GH and insulin like growth factor-1 levels (IGF-1). GH should be less than 2 ng/ml after an oral glucose load. Complications of surgery include cerebrospinal fluid leaks, meningitis, or damage to the surrounding normal pituitary tissue requiring lifelong pituitary hormone replacement. Radiotherapy is recommended for patients with acromegaly and unsuccessful surgical and/or medical therapy [4]. It is usually reserved for patients who have tumor residuals. Pituitary radiation causes a gradual loss of other pituitary hormones as well. The disadvantages of radiotherapy include the time delay between radiation administration and disease remission and the risk of hypopituitarism.

The long-acting SA analogues have important role in the medical management of these patients. After transsphenoidal surgery, these agents are added as second-line therapy followed by dopamine-receptor agonists (bromocriptine, cabergoline) or GH receptor antagonists (pegvisomant). SA may be used in the first line treatment of acromegaly when patients are not fit for surgery or if the tumor is inoperable.

2. Somatostatin analogues (SA)

Somatostatin (SST), also known as growth hormone-inhibiting hormone (GHIH) is produced by the neuroendocrine neurons in the ventro-medial nucleus of the hypothalamus. It is released from the neuro-secretory nerve endings into the hypothalamo-hypophysial system through neuron axons. SS inhibits growth hormone secretion from the somatotrope cells of anterior pituitary gland. It is also released from the delta cells of the islets of Langerhans in the pancreas and from D cells in the gastrointestinal tract [5]. SST acts through a family of five G protein-coupled receptors (GPCRs), known as SSTR1 to SSTR5, to carry out its biological activities including modulation of neurotransmission, inhibition of endocrine secretion, and inhibition of cell proliferation and smooth muscle contractility [6]. SSTR2 is spliced to the SSTR2a and the SSTR2b variants that have somewhat different tissue distribution [7]. The different SSTRs are expressed throughout the central nervous system (CNS) as well as in peripheral tissues like the pancreas, stomach, and small intestine. SSTRs have been identified in tumor cell lines of different etiologies including pituitary, pancreatic, breast, and hematopoietic. In general, SSTR2 is the most common SSTR subtype found in human tumors followed by SSTR1 with SSTR3 and SSTR4 being less common [7]. The mechanism of action is inhibition of secretion and inhibition of proliferation. Among the vertebrates, there are six different SST genes that have been named SS1, SS2, SS3, SS4, SS5, and SS6. Humans only carry one SST gene. SA that are currently available include: octreotide (Sandostatin, Sandostatin LAR), lanreotide (Somatuline Depot) and pasireotide (Signifor LAR) [8].

In Croatia, only Sandostatin LAR, a synthetic octapeptide analogue of SST with a prolonged duration of action is approved for the treatment of acromegaly. Octreotide inhibits GH secretion and IGF-1 in 55-70% of patients and results in a decrease in tumor size in 30% of patients [9]. Octreotide and lanreotide have also been successfully used in patients with acromegaly caused by non-pituitary tumors. SA are sometimes used to shrink large tumors before surgery [10]. Medical treatment is considered as adjuvant therapy in patients with residual disease after surgical debulking. First-line treatment with SA is considered in patients with macroadenomas that have a poor chance of surgical cure because of extrasellar extension, such as cavernous sinus invasion, in patients who refuse surgery, or in patients that have substantial surgical risk [11]. The octreotide LAR, synthetic SST, binds to SSTR 2, 3 and 5 and inhibits the release of 5-hydroxytryptamine (5-HT) and the secretion of IGF-1, insulin, glucagon, secretin, gastrin, pancreatic polypeptide (PP), vasoactive intestinal peptide (VIP), GH and motilin [12]. Octreotide suppresses GH secretion from the pituitary gland and from GH-secreting adenomas. It decreases GH binding to hepatocytes and it inhibits hepatic IGF-1 production. Most importantly, it controls tumor growth. The available SA are octreotide and lanreotide.

Octreotide and lanreotide have the greatest affinity for receptor

subtypes 2 and 5, with their affinity for subtype 2 being about 10 times higher than for subtype 5 [13]. Approximately 10-30% of GH-secreting pituitary tumors are resistant to SA because of variable or reduced tumoral expression of SSTR2 or SSTR5 [14].

Octreotide is available in subcutaneous and intramuscular administration. The octreotide LAR is delivered with an intramuscular injection in polymeric microspheres and is administered intramuscularly at 4-week intervals. For subcutaneous (SC) octreotide, the initial dose proposed is 50 μg injected subcutaneusly three to four times per day with a maximal dose of 1.5 mg per day. Lanreotide is another long-acting SSA and is available in two forms:

a sustained release formulation (Somatuline LA), which is injected intramuscularly every ten to fourteen days, and an extended release formulation (Somatuline Autogel in the United

Kingdom, or Somatuline Depot in the U.S.), which is administered subcutaneously once a month [15]. The most frequent side effects of SA are diarrhoea, abdominal discomfort, nausea, and flatulence. These gastrointestinal side effects are related to the inhibition of pancreatic exocrine secretions. In up to 30% to 60% of the patients octreotide causes gallstones by inhibiting cholecystokinin secretion [16]. Because ocreotide can induce diabetes, regular blood glucose controls are recommended after SA initiation. Patients may also experience episodes of hypoglycaemia because of glucagon inhibition. In addition, hypothyroidism may occur because of the possible suppression of thyroid-stimulating hormone.

3. Acute octreotide suppression test (OST)

In many centres, a test dose (TD) of octreotide is administered before commencing somatostatin analogue therapy (SAT) in order to predict long-term response to treatment. This is important in order to prevent unnecessary medical costs and side effects in patients that do not respond to SA. There has been great interest in identifying factors that predict a good response to SAT. To date, there have been several studies that have assessed the relationship between the TD of octreotide and SAT treatment but there is a lack of accepted guidelines for judging the response [17].

Lamberts et al. studied the effect of long-acting somatostatin analog SMS 201-99 on mean GH levels in 10 patients with acromegaly during 2 years of therapy [18]. SMS 201-995 was administered for 16-108 weeks in a dose of 200-300 μg daily for 2 or 3 sc injections. The authors compared GH levels after acute administration of 50 μg SMS 201-995 before the start of therapy with mean 24-h GH concentrations after 16-108 weeks of treatment with long-acting SA, finding a significant correlation between these values [18].

Lamberts et al. were the first to investigate the predictive value of the OST (administration of 50 μg Sandostatin) and the mean 24h GH response after chronic therapy with Sandostatin [19]. This study included 15 patients with acromegaly who were treated with 200–300 μg octreotide per day for 96 weeks. Their results showed a positive correlation between mean GH levels after the OST and mean 24 h GH levels after long-term therapy.

Colao et al. reported results of OST in 68 patients with acromegaly [20]. GH response was measured after administration of 100 μg octreotide. The response was assessed by determining the mean of GH samples collected at 2 – 6 h after octreotide. GH decrease greater or equal to 50% of baseline was considered a positive response and GH was considered normalized when decreased less than or equal to 5 μg /L. Among 38 patients who responded to the test, 20 had a normalization of GH and IGF1 levels during long-term therapy. Eight patients who didn't respond to the test also had normalization of these hormones during long-term therapy. TD had a positive predictive value (PPV) of 43% and negative predictive value (NPV) of 78% for achieving normalization of GH during long-term octreotide treatment. The authors concluded that the acute test is not adequate tool for identifying patients' responsiveness to long-term octreotide administration.

Karavitaki et al. concluded that the OST is a reliable tool for the selection of patients with active acromegaly prior to commencing therapy with long-acting octreotide (Sandostatin LAR) and long-acting lanreotide (Somatulin Autogel or Somatuline LA) [21]. This study reported the relationship between the TD and SAT in 30 patients in whom GH was measured for 6 h following 100 μg s.c. octreotide. Patients in whom GH values during the test fall < 5.25 mU/l in case of LAR treatment or 6.05 mU/l in case of lantreotide treatment had a 92-94% chance of subsequently achieving normal GH levels after 6 months of treatment. Their results also recorded that nadir GH levels were positively correlated with pretreatment GH and IGF1 values.

Biermasz et al. assessed the acute response of serum GH levels to intravenous administration of 50 μg octreotide in 98 consecutive patients with active acromegaly [22].

In order to evaluate the efficacy of chronic therapy serum GH and IGF1 were measured 3-6 months after initiation of octreotide-LAR treatment. The results showed that intravenous octreotide reduced GH to concentrations < 5 mU/L in approximately 50% of consecutive patients with active acromegaly. In patients with baseline GH levels below 50 mU/L, intravenous

octreotide reduced GH to < 5 mU/L in 77% of cases. The test, using a GH level of < 5 mU/L, had a positive and negative predictive value of 100% for prediction of GH suppression to below 5 mU/L during long- term octreotide-LAR treatment. For predicting the response of IGF-I during long-term treatment, the test performed with a sensitivity of 73% and a positive predictive value of 73%. The authors concluded that the OST predicted a good response to chronic octreotide-LAR treatment.

Gilbert et al. showed the results of a TD (50 μg sc octreotide) in 33 patients with acromegaly who were subsequently treated with depot SAT [23]. The aim of the study was to determine the predictive value of the nadir GH and the mean GH following an octreotide TD for patients with disease remission following depot SAT. Remission was defined as a mean GH < 5 mU/l (< 2 μg/l). The results showed that a nadir GH < 5 mU/l demonstrated 80% sensitivity and 83% specificity in predicting remission with depot SAT while a nadir GH < 10 mU/l demonstrated 100% sensitivity and 56% specificity. The authors concluded that nadir GH following an octreotide TD is useful in predicting disease remission with depot SA.

De Herder et al. studied whether an acute test using a subcutaneous dose of 50 μg of octreotide had any predictive value for long-term IGF-I normalization with Sandostatin LAR.

[24]. Twenty four patients with active acromegaly were studied. They applied 2 relative (> 50 or 75% fall) and 2 absolute criteria (nadir GH <1.1 or <2 μg /l) in their analysis. In this study, normalization of serum IGF-I was the only criterion for disease control with medical treatment. During the OST, 75% decrease in GH had a sensitivity of 73% and a specificity of 77% for predicting normalization of serum IGF-I with Sandostatin LAR therapy. The authors found that 23% of patients with at least 75% decrease GH in the acute test were successfully controlled with long-term Sandostatin LAR therapy (showed normalization of serum IGF-1). Also, 31% of patients who did not showed GH suppression to levels <1.1 μg /l, or 25% of the patients who did not demonstrate GH suppression to levels <2 μg /l were successfully controlled with long-term Sandostatin LAR. The authors concluded that OST is not necessary prior to Sandostatin LAR therapy.

Pokrajac et al. also reported the value of the octreotide TD (5 mcg sc) in predicting IGF-I response to SAT in 47 patients with acromegaly [25]. In this study the best predictor of normalisation of IGF-1 was a GH nadir of < 5 mU/l after the TD. During long-term SAT, 12% of patients had elevated IGF-1 despite a GH nadir <5 mU/l, while 15% of patients had normal IGF-1 and elevated GH. This confirmed that baseline GH and nadir after a TD are highly predictive of good response to SAT. Also, the higher the baseline IGF-I, the less likely IGF-1 will normalize with treatment. The authors explain that regardless of the test results, no patient should be excluded from treatment with SAT.

Balcere et al. concluded that OST has poor predictive value to predict a response to long-term lanreotide and octreotide treatment [26]. They assessed the acute response of serum GH after administration of 100 μg octreotide in 12 patients with acromegaly. Positive response was defined with > 50% GH decrease and target GH < 2 ng/ml during the test. Fifty-eight percent of patients showed good response (> 50% GH decrease) and 42% of them reached target GH < 2 ng/ml during the subsequent SSA therapy. Between patients who had moderate GH decrease (30 - 50%) one reached normalisation of IGF1. Also patients with small GH decrease (< 30%) reached target (GH < 2 ng/ml) during the chronic SAT [26].

Lindsay et al. aimed to investigate accuracy of the OST for chronic response prediction in 23 patients [27]. They compared GH response during the test with GH levels after 3 years of SAT treatment. Sixteen patients with nadir GH of 10 mU/l or less achieved GH < 5 mU/l after 3 years of therapy. Three out of 7 patients with nadir GH > 10 mU/l received external pituitary irradiation and therefore achieved GH < 5 mU/l at 3 years. The authors concluded that poor response to a test dose (GH > 10 mU/l) of sc octreotide can predict the need for adjuvant therapy if there is active disease after surgery [27].

Vizner et al. assessed the acute response of serum GH levels to a sc administration of 50 μg octreotide in 42 patients with active acromegaly [28]. OST lasted 6 hours and blood samplings were obtained at 1-hour intervals. Seventy-three percent of patients showed reduction in GH values below 5 ng/ml, while 11.9 % of patients showed suppression more than 50%. Maximal suppression was recorded in the first two hours of testing. Authors concluded that OST is useful in selecting patients for long-term treatment with SA.

In our Department, OST is performed prior to surgery and also postoperatively if there is a sign of residual tumor confirmed with MRI imaging. Our unpublished data are in accordance with previously published data. Our preliminary study included 10 consecutive patients (2 men, 8 women) with residual tumors after endoscopic transsphenoidal adenomectomy. Patients were prescribed with Sandostatin LAR 3 months after surgery. We compared the values of GH and IGF-1 in preoperative and postoperative acute tests performed 3 months after initiation of Sandostatin LAR. For the TD, 0.5 mg of sc octreotide was used and GH values were measured each hour for the next 3 hours, while IGF-1 values were measured at 5 pm and 24 h after application. Previous research showed that

Table 1. Predictive value of an acute octreotide suppression test

Study	Test dose	Number of patients	Test dose criteria	Treatment goal	Predictive value of test dose	Conclusion
Response defined as nadir of GH						
Karavitaki et al. 2005	100 µg s.c.	30	Nadir GH < 5.25mU/l	GH < 5mU/l	PPV 94% NPV 100	useful
Biermasz et al. 2005	50 µg iv	18	Nadir GH < 5mU/l	GH < 5mU/l Norm. IGF1	sens. 100% spec. 100% PPV 73% NPV 57%	useful
Gilbert et al. 2005	50 µg s.c.	33	Nadir GH < 5mU/l	GH < 5mU/l	sens. 80% spec. 83%	useful
Response defined as percent of change						
Colao et al. 1996.	100 µg s.c.	68	Mean GH 50% fall	GH < 5 µg	PPV 43 NPV 78%	not useful
De Herder et al. 2005	50 µg s.c.	28	Mean GH >50% fall >75% fall	Norm. IGF1	PPV 58% NPV 100% PPV 73% NPV 77%	not useful
Pokrajac et al. 2005	50/100 µg s.c.	47	GH nadir <5 mU/l GH > 75% fall	GH < 5mU/l Norm. IGF1	PPV 82% NPV 50% PPV 72% NPV 40%	not useful

PPV - positive predictive value; NPV - negative predictive value; GH - growth hormone

even partial resection has a role in treatment of somatotropinomas since it may enhance the response to SAT [29]. Our results showed that patients had significantly lower levels of initial GH postoperatively and thus better response during the test. GH values during the preoperative test and IGF-1 values three months after administration of SAT showed a strong positive correlation. Therefore, the results of the preoperative octreotide test are more important in predicting response to long- term SAT but further studies are required.

4. Conclusion

SA are considered as the first-line medical treatment of acromegaly [30]. In many centres OST has been performed before commencing SAT in order to predict long-term response to this treatment. To date, there have been several studies that analysed relationship between the results of OST and response to long-term SAT treatment [19-27] (Table 1). Published data indicates that it is crucial how we define good response during the OST. Nadir of GH to 5mU/l or less during the OST has an excellent predictive value for evaluation of long-term response to SAT. On the other hand, if we define response as percentage of change of GH from it's baseline values, than the OST is not a useful diagnostic test [21-23].

Author contributions

MS gave the idea for the article, wrote the article and gave the final approval. JMR performed literature review, participated in drafting the article and gave the final approval. GM, HIP, VČ, LP and MV critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

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