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EFFECT OF OCTREOTIDE ON GROWTH HORMONE SECRETION IN PATIENTS WITH ACROMEGALY

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SUMMARY – A majority of growth hormone secreting pituitary adenomas respond well to somatostatin and somatostatin analogues. The acute action of octreotide, a synthetic somatostatin analogue, on growth hormone secretion was assessed in 42 patients with clinically and laboratory verified acromegaly. Octreotide was administered subcutaneously in a dose of 50 μg. Blood sampling was performed at 1-hour intervals during 6 hours of testing. The mean basal values of growth hormone (χ±SE) was 26.3±4.5 ng/ml (range 6.1-66.6 ng/ml), and of IGF-I 2940±171.7 IU/l (range 2350-4856 IU/l). Reduction in growth hormone values below 5 ng/ml was recorded in 31 (73.8%), suppression by more than 50% in 5 (11.9%) and by more than 45% in 3 (7.1%) patients. Maximal suppression was noticed in the first two hours of testing. In 3 (7.1%) patients, resistance to octreotide with no change in growth hormone values was observed. In conclusion, octreotide reduces growth hormone values in most acromegalic patients. A small proportion of acromegalic patients do not respond well to octreotide, probably due to the lack of somatostatin receptors on tumor cells. We consider the acute octreotide test as a very useful tool in triage of acromegalic patients eligible for medicamentous treatment.

Key words: *Acromegaly, drug therapy; Octreotide, therapeutic use; Octreotide, pharmacology*

Introduction

Growth hormone (GH) secreting pituitary tumors are associated with elevated levels of GH and its target factor, insulin-like growth factor I (IGF-I). Most of them are macroadenomas at the time of diagnosis, and patients with these large tumors have a high rate of surgical failure and require adjunctive therapy to suppress GH secretion[1]. External irradiation as a therapeutic modality is associated with significant side effects, including hypopituitarism, which impair the long term benefit[2].

In the mid-1980s, somatostatin and the somatostatin analogue octreotide were first used to treat GH-cell adenomas[3]. The response to octreotide is dependent on the presence of somatostatin receptors in the tumor. Although most tumors contain somatostatin receptors in densities that are comparable to those in normal somatotrophs and respond normally to somatostatin, 10% to 30% of GH-secreting tumors have reduced numbers of somatostatin receptors or express different subtypes of receptors (five classes are known at present), and therefore exhibit diminished responses to pharmacotherapy[4].

In order to predict long term responsiveness to octreotide in patients with acromegaly, we used acute suppressive effect of a single 50 μg injection of octreotide[5].

Patients and Methods

The acute action of octreotide on GH secretion was assessed in 42 patients (22 female and 20 male, mean age 48.1±2.4 years) with verified pituitary somatotrophinoma and full-blown clinical picture of acromegaly. Serum IGF-I, basal GH concentration (calculated from mean values

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during the 6-hour basal secretion test), and GH values on oral glucose tolerance test (oGTT) with 100 g glucose were determined[6]. GH values of less than 1 ng/ml after glucose load were considered as appropriate suppression. Computed tomography (CT) of the pituitary region was performed on a Siemens Somatom with 2-mm cuts of the sella. IGF-I and GH values were determined using IRMA and classic RIA, respectively. The minimum detection limit for IGF-I was 152 IU/l, and IRMA intra-assay precision on IGF-I determination was 4.5%. Theoretical sensitivity of RIA, used to determine GH values, was 0.25 ng/ml, and intra-assay precision was 5.9%. Reference values of IGF-I ranged between 600 and 2200 IU/l, and GH upper limit was 5 ng/ml.

The acute octreotide test was performed with 50 μg s.c. injection of octreotide. Blood samples were obtained immediately before, and then at 1-hour intervals during the 6-hour test duration. The results were expressed as mean and standard error ($\chi \pm SE$). All patients volunteered in the study and were informed in detail on the purpose of the test.

Results

The presence of a tumor mass of less than 10 mm in diameter was confirmed by CT in 11 female patients, and macroadenoma was diagnosed in 31 patients. The mean

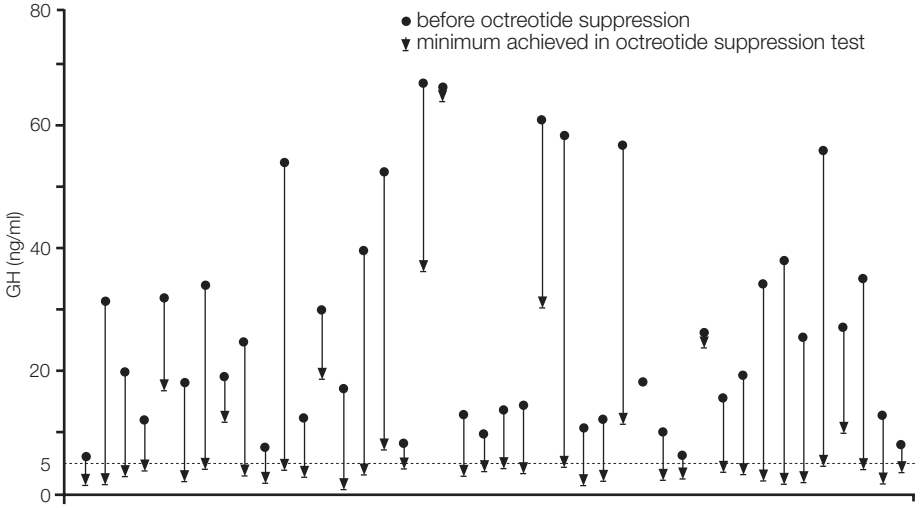

Fig. 1. Growth hormone values in 42 acromegalic patients during octreotide suppression test

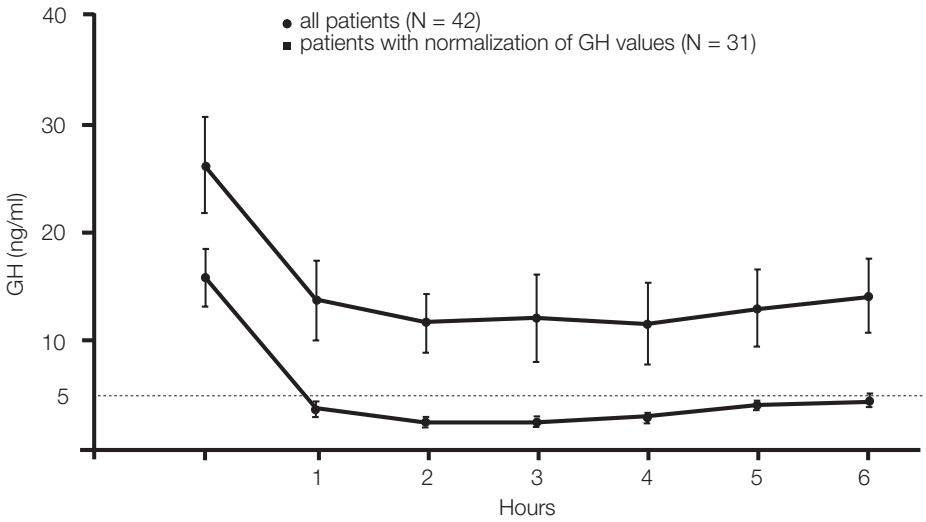

Fig. 2. Growth hormone values in 42 acromegalic patients during octreotide suppression test

basal GH value χ±SE) was 26.3±4.5 ng/ml (range 6.1-66.6 ng/ml). The mean IGF-I value was 2940.2±171.7 IU/l (range 2350-4856 IU/l). None of our patients responded to oGTT with reduction in GH values.

Octreotide was used in the form of 50 μg s.c. injection. Blood samples were drawn at 1-hour intervals over 6-hour test duration. GH value reduction of ≤5 ng/ml was observed in 31 (73.8%), suppression by more than 50% in five (11.9%), and by >45% in three (7.1%) patients (Table 1, Fig. 1). Resistance to octreotide with no change in GH values was recorded in three (7.1%) patients. Maximal suppression was observed during the first two hours of the octreotide test (Fig. 2).

Table 1. Results of acute octreotide test in 42 acromegalic patients

Test result	No. of patients	% of patients
GH normalization	31	73.8
Suppression >50%	5	11.9
Suppression >45%	3	7.1
Octreotide resistance	3	7.1

GH=growth hormone

Discussion

Somatostatin analogues are amongst the most important advances in endocrinology over the past 20 years. They are indicated in patients with acromegaly in whom there is a large macroadenoma not likely to be cured by surgery, or in whom surgery was unsuccessful, contraindicated, or refused. Somatostatin analogues can be used either as primary pharmacotherapy for acromegaly or as an adjunctive treatment in patients receiving irradiation, or in those awaiting surgery who have severe symptoms such as headache or episodes of sleep apnea[7,8]. Lombardi *et al.* in a study including 557 acromegalic patients showed that octreotide administration normalized IGF-I levels in 48.5% and shrank tumor size in 40.3% of patients. The latter effect seems to favor the complete removal of the somatotrophinoma at the surgery. Furthermore, preoperative treatment with octreotide was shown to improve the clinical status of the patients (especially headache, hyperhidrosis, and joint pain) and to reduce postoperative complications[9]. Lamberts investigated octreotide therapy success in 46 acromegalics and predicted biochemical 'cure' (defined by mean 24-hour GH normalization and serum IGF-I normalization) in about half of the patients during therapy with 300 μg octreotide daily. He also observed tumor shrinkage in about 50% of patients, probably because of the drug-induced individual cell decrease rather than cytotoxic or vascular effect of the drug[10]. Almost identical results were obtained by Melmed, who reports on GH normalization in 47% and IGF-I reduction to reference values in up to 70% of acromegalic patients[1].

The discovery and use of octreotide really heralded a new era for the pharmacological treatment of somatotrophinomas, and new investigations are aimed at discovering different somatostatin receptor subtypes, since it is known that it exerts its action through receptor binding. To date, 5 receptor classes have been identified, and octreotide probably binds to subtypes 2 and 5. Most tumors contain receptors in amounts that resemble those of normal somatotrophs[11]. However, 10% to 30% of tumors have reduced numbers of receptors or express different receptor subtypes and therefore exhibit a correspondingly decreased response[5]. Keeping in mind the cost of octreotide and similar agents, efforts have been made to find a tool to predict the patient's response before embarking upon this approach. We tested the effects of an acute s.c. octreotide injection as a tool of long term responsiveness to somatostatin analogues. We achieved normalization in 73.8% and suppression by >50% in 11.9% of patients, which was consistent with the results reported by Frohman[5]. Maximal suppression was achieved during the first two hours of the test, then GH raised slightly almost reaching the upper limit (5 ng/ml) and remained stable throughout the test duration. This GH dynamics differed from that observed by Frohman. In his study, maximal suppression of GH levels occurred at 2-4 hours, whereafter it began to rise reaching the preinjection value.

The mean hourly GH level at 2-6 hours from octreotide injection exhibited a high degree of correlation with the 24-hour integrated GH level. It also correlated with the plasma level of IGF-I, which is a useful marker of the overall response.

Conclusion

Octreotide normalizes GH values in most acromegalic patients (73.8%). Maximal suppression is achieved during the first two hours of acute octreotide suppression test. However, some patients fail to respond to the action of octreotide, probably because of the low number of somatostatin receptors expressed on tumor cells or of different

receptor subtypes present on cell membranes. We believe that acute octreotide test is very useful for triage of acromegalic patients eligible for medicamentous treatment with somatostatin analogues.

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Sažetak

UTJECAJ OKTREOTIDA NA LUČENJE HORMONA RASTA U BOLESNIKA S AKROMEGALIJOM

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Većina adenoma hipofize koji luče hormon rasta zadrže osjetljivost na somatostatin i njegove analoge. Ispitivano je akutno djelovanje oktreotida, sintetskog oktapeptidnog analoga somatostatina, na razinu hormona rasta u 42 bolesnika s klinički i laboratorijski potvrđenom akromegalijom. Oktreotid je primijenjen supkutano u dozi od 50 μg. Uzorci krvi za određivanje hormona rasta uzimani su svakog sata u razdoblju od šest sati. Prosječna bazalna vrijednost hormona rasta bila je 26,3±4,5 χ±SE) ng/ml (raspon 6,1-66,6 ng/ml), a IGF-I 2940,2±171,7 IJ/l (raspon 2350-4856 IJ/l). Nakon primjene oktreotida razina hormona rasta u serumu snizila se na normalne vrijednosti (<5 ng/ml) u 31 (73,8%) bolesnika, u 5 (11,9%) bolesnika nastupilo je sniženje za više od 50%, a u 3 (7,1%) za više od 45%. Maksimalno je sniženje u ovih bolesnika uslijedilo jedan do dva sata nakon početka testa. Troje (7,1%) bolesnika pokazalo je rezistenciju na oktreotid. Njihove vrijednosti hormona rasta ostale su gotovo jednake onima u bazalnim uvjetima. Zaključeno je da oktreotid normalizira razinu hormona rasta u većine akromegaličnih bolesnika, međutim, u nekih se ne postiže zadovoljavajući odgovor, vjerojatno zbog malog broja somatostatinskih receptora na membrani tumorskih stanica. Smatramo da je akutni test s oktreotidom koristan u odabiru akromegaličnih bolesnika za konzervativno liječenje analozima somatostatina.

Ključne riječi: *Akromegalija, medikamentno liječenje; Oktreotid, terapijska primjena; Oktreotid, farmakologija*