Short Term Effects of Octreotide in Hypertrophic Cardiomyopathy

OCTREOTİD'İN HİPERTROFİK KARDİYOMİYOPATİDE KISA DÖNEM ETKİLERİ

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Summary

Octreotide, a long-acting somatostatin analog, has been shown to have direct antiproliferative effects in a wide range of cell types in vitro and in vivo. The purpose of the present study was to evaluate the effect of octreotide treatment for 5 months in hypertrophic cardiomyopathy (HCM). Four patients with primary HCM were treated subcutaneously with octreotide at a dose of 0.1 mg b.'t.d. during the first month and then for the following four months the patients were administered 0.1 mg s.c. once weekly in order to maintain the supression achieved during the first month. The mass reduction observed in HCM after octreotide treatment seems to support the hypothesis that hypertrophy seen in these patients may be related to the activation of insulin like growth factor-! (IGF-I) receptors. Mass regression resulted from a decrease in wall thickness after octreotide treatment can be considered as a promising approach in HCM treatment.

Key Words: Hypertrophic cardiomyopathy, Octreotide

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Özet

Uzun etkili bir somatostatin analoğu olan octreotid'in çeşitli hücre tipleri üzerinde direkt antiproliferatif etkileri olduğu in vitro ve in vivo ortamlarda gösterilmiştir. Bu çalışmanın amacı hipertrojik kardiyomiyopati'de (HCM) 5 aylık octreotid tedavisini değerlendirmektir. Primer HCM'li 4 hastaya birinci ay günde 2 kere 0.1 mg ve daha sonraki 4 ay ise ilk ay elde edilecek etkinin sürdürülmesi için haftada bir kere 0.1 mg olmak üzere subkutan yolla octreotid uygulandı. Octreotid tedavisinden sonra HCM'de görülen kitle azalması bu hastalarda bulunan hipertrojinin insulin like growth factor-l'in aktivasyonu ile ilişkili olduğu hipotezini desteklemektedir. Octreotid tedavisi sonrası duvar kalınlıklarındaki azalma sonucu elde edilen kitle azalması, HCM'de ümit veren bir tedavi yaklaşımı olarak ileri sürülebilir.

Anahtar Kelimeler: Hipertrofik kardiyomiyopati, Octreotid

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Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease characterized by an unexplained increase in left ventricular wall thickness (1). Since growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (b-FGF), and insulin-like growth factor (IGF-I) have potent mitogenic effects on in vitro smooth muscle cells (SMC) and induce SMC chemotaxis, they have been suggested to play a role in the regulation of SMC proliferation (2). IGF-I, b-FGF and PDGF receptors belong to a broad family of growth factor receptors, each sharing the common feature of a tyrosine kinase domain in the cytoplasmic portion of the molecule. Binding of growth factors induces autophosphorylation of the beta-subunit of the receptor and activation of tyrosine kinase. Deactivation of these growth factor receptors involves specific protein tyrosine phosphatases. Somatostatin, a growth-inhibitory peptide found throughout the body, can inhibit the stimulatory effects of certain growth factors by activating protein tyrosine phosphatases (3). Octreotide, a long-acting somatostatin analog has been shown to have direct antiproliferative effects in a wide range of cell

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types in vitro and in vivo, and this agent has been used therapeutically in the treatment of gastrointestinal neoplasms and pituitary tumors (4). Other potential applications include management of pain, headache, rheumatoid arthritis, and diabetic microangiopathy, as well as prevention of postoperative pancreatic complications (fistulae, pancreatitis, abscess) (5). The objective of the present study was to investigate the effects of octreotide therapy on cardiac structural abnormalities in H C M by means of echocardiography.

Patients and Methods

Four patients (1 male and 3 females) with H C M whose mean age was 51.4 years were treated with daily octreotid injections. Written informed consent was obtained from each patient. The baseline characteristics of the patients are listed in Table 1. The patients who had been followed with the diagnosis of H C M for 2 to 5 years were treated with s.c. octreotide injections at a dose of 0.1 mg b.i.d. during the first month and then for the following four months the patients were administered 0.1 mg s.c. once weekly in order to maintain the suppression achieved during the first month. A complete 2-dimensional echocardiographic examination was performed in all patients with a Toshiba Sonolayer SSH 65A ultrasound system with a 2.5 MHz transducer. The diagnosis of H C M was based on the echocardiographic demonstration of unexplained left ventricular hypertrophy. The pattern of left ventricular hypertrophy was asymmetric septal type in one patient (25%) and concentric type in three (75%) patients. Two patients had systolic anterior motion (SAM) of the mitral valve with septal contact while one patient had mild initral stenosis because of calcific deposits in the mitral annular region. Doppler examination of the two patients with S A M revealed late systolic dagger-shaped peak velocities reaching 3m/s, which corresponds to a peak instantaneous pressure gradient 27 mmHg in the left ventricular outflow tract as well as moderate eccentric mitral regurgitation. A ll patients had undergone cardiac catheterization. Concomitant medication was not discontinued throughout the study. The functional capacity of all patients were class III of New York Heart Association. Before the onset of treatment, at the end of month 1 and month 4, a detailed history of all patients was taken, their physical examination, electrocardiogram and 2-dimensional echocardiography were performed. Dimensions of left ventricular cavity, diameters of left ventricular outflow tract and the thickness of septum and posterior wall were measured from the parasternal long axis by means of a 2.5 M Hz transducer. Measurements were performed using a leading edge-to-leading edge convention by an echocardiographcr blinded to the clinical data. The sum of QRS voltage in all 12 leads was also used to assess the possible regression of left ventricular hypertrophy at the end of the therapy.

Results

No patients had coronary artery disease. Subjectively, three of the four patients reported a general sense of well-being with treatment and better functional class N Y H A than it was previously found. One patient complained of diarrhea which subsequently disappeared spontaneously. The resting pressure gradients of two patients with mitral-septal contact decreased from 27 to 21 mmHg. Left ventricular mass decreased minimally (mean 10%) in all patients at the end of the first month. There was no significant decrease in growth hormone levels with octreotide treatment during the first month. S A M that had contacted interventricular septum

Table 1. Patient characteristics at baseline

	1.Patient (YKo)	2.Patient (SG)	3.Patient (YKa)	4.Patient (HK)
Age (yr)	24	54	57	56
Sex (M/F)	F	F	M	F
Pseudo Ml pattern	+	0	+	
Coronary Angiography	Normal	Normal	Normal	Normal
HCM	Asymétrie septal type	Concentric type	Concentric type	Concentric type
Concomitant therapy	Antiarrhythmics Ca antagonists	ACE inhibitors Ca antagonists	Ca antagonists	Antiarryhthmics

Table **2.** Comparison of results at the end of the four weeks

	Patient			Patient 2			Patient 3			Patient 4		
Variable	Basal	4"' week	Reduction percent	Basal	week	Reduction percent	Basal	4"' week	Reduction percent	Basal	4.1. week	Reduction percent
1VS (mm)	33.9	30.2	% 1 1	24.4	22.1	%9	24.6	21.6	%I2	27.1	24.3	
PW (mm)	10.2	9.1	% 1 1	14.2	12.7	%11	15.6	13.6	%I3	15.2	13.1	%I4
LV mass index (gr/BSA)	310	280	%I0	227	204	%I0	247	219	% 1 1	211	188	%1 1
SAM	0	0		+	+		+	+		0	0	
Milral-septal contact	0	0		+	0		+	0		0	0	
LVOT (mm)	21.6	22.1		18.6	19.4		18.2	19.1		I6..3	17.6	
EE %	%66	%7()		%84	%8I		%80	%77		%83	%80	
12-Lead sum of voltage (uV)	162	156		152	136		113	114		122	88	
Pericardial fibrosis	+	+		+	+		+	+		+	+	
NYHA Class	III	II		III	I		III	I		111	II	
GH (mlU/ml)	8.4	8.2			7.6		5.2	5.8			6.7	

(hione, i:present, EF:ejection fraction, IVS:interventricular septum, LV:left ventricle, LVEDdrlcft ventricle end diastolic diameter, LVESd:left ventricular end systolic diametcr,LVOT:left ventricular outflow tract,PVV.posterior wall,SAM:systolic anterior motion, GH: growth hormone level

(IVS) changed to S A M not contacting TVS at the end of four weeks of therapy. Left ventricular outflow tract (LVOT) diameter increased minimally. The sum of QRS voltage in all 12 leads slightly decreased only in two with concentric hypertrophy. Comparison of results at the end of study is presented in Table 2. We believed that 0.1 mg/wcek dose of the drug was sufficient for the supression of IGF-I receptors and therefore, we followed the patients by administering the 0.1 mg/week dose of the drug in the 4-month period. As a result, the values at the end of four months remained the same as the values of the first month.

Discussion

Propranolol and calcium channel blockers are used in H C M to reduce the risk of sudden death and to manage arrhythmia. A few surgical procedures are used in symptomatic patients who have not responded well to medical treatment.

Growth factors such as PDGF, b-FGF, and IGF-I have been implicated in the regulation of SMC proliferation and migration because all are potent SMC mitogens in vitro and induce SMC chemotaxis (2,3). Myocardial tissue possesses both IGF-I and insulin receptors (6,7). Grant suggests that by reducing SMC proliferation, somatostatin analogues may have clinical relevance in reducing the high incidence of restenosis observed after percutaneous transluminal coronary artery interventions (4). Although there are several recent studies showing regression of left ventricular hypertrophy with octreotide treatment in acromegaly (8-11), this agent is still not commonly used in H C M.

In the present study, octreotide treatment resulted in a mild regression in left ventricular hypertrophy at the end of first month without changing hemodynamic parameters and ejection fraction . In association with the regression of LV hypertrophy, minimal increase in LVOT diameter and disappearance of mitral-septal contact was observed. In addition, the minimal reduction in the sum of QRS voltage of 12 leads in E C G should also be taken into consideration (12). Decreased interstitial edema or myocyte regression via inhibition of IGF-I appeared to be the mechanism of LV hypertrophy regression in these patients. This is the second sUidy conducted in a group of H C M patients to demonstrate regression of left ventricular mass by octreotide without causing any adverse effects . In our patients, mass regression was due to a decrease in wall thickness. Giinal et al. found reduction of 24% in left ventricular mass within four weeks (13,14). They administered the drug s.c. at a dose 0.05 mg t.i.d. three tunes for the first week and 0.1 mg b.i.d. following three weeks and they used angiotensin

converting enzyme inhibitors for maintenance therapy. They obtained a dramatic reduction in LV mass at the end of first month.

Some limitations in our study should be addressed. The functional capacity could not be assessed by exercise tolerance test. NYHA classification might not reflect actual functional capacity in HCM. In addition, endomyocardial biopsies and determination of myocardial levels of insulin-like growth factor-I could not be performed. Since the sample size was too small and the statistical assessment of echocardiographic measurements could not be performed. Therefore, we believe that further studies with greater sample size are needed to assess the efficacy of octreotide treatment in primary HCM.

In conclusion, the findings of mass decrease and improvement of other parameters after octreotide treatment in HCM supports the hypothesis that hypertrophy may be directly related to the deactivation of IGF-I receptors. Although the size of our study group would not allow us to talk about the efficacy of octreotide therapy in HCM, we do believe that long term administration of octreotide treatment at a dose rate of 0.1 mg b.i.d. can be a promising therapeutic approach in decreasing LV mass in HCM.

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