The Effects of Octreotide in Dilated Cardiomyopathy

An Open-label Trial in 12 Patients

Namlk Kemal ERYOL,¹ MD, Muhammed GÜVEN,² MD,
Ramazan TOPSAKAL,¹ MD, Murat SUNGUR,² MD, Ibrahim ÖZDOGRU,¹ MD,
Tuğrul İNANÇ,¹ MD, and Abdurrahman OĞUZHAN,¹ MD

SUMMARY

Octreotide, a somatostatin analogue, has been found effective in the treatment of acromegalic cardiomyopathy. We investigated whether intermittent octreotide therapy had beneficial effects in patients with ischemic or idiopathic dilated cardiomyopathy, which are refractory to conventional therapy.

Twelve patients with ischemic or idiopathic dilated cardiomyopathy were enrolled in the study. In addition to conventional treatment, octreotide (first 50 μ g and then 25 μ g three times per day for 4 days) was administered and repeated after 1, 2, and 3 months. The patients were evaluated 3 times, before and immediately after the first treatment and after 3 months of treatment, using echocardiography, exercise stress testing, ambulatory ECG, right ventricular catheterization, cardiac enzymes, and the Minnesota living with heart failure questionnaire for quality of life.

There were no significant changes in parameters after the first treatment. However, after 3 months of treatment, there were significant improvements in the left ventricular ejection fraction, left ventricular posterior wall thickness, hemodynamics, exercise capacity, and quality of life. Additionally, ischemic burden and the number of ventricular premature beats also decreased slightly.

Intermittent octreotide therapy led to significant improvements in patients with ischemic and idiopathic dilated cardiomyopathy refractory to conventional treatment. We believe that this therapy should be attempted as an adjunctive therapy in these patients, and that in this respect, randomized, double-blind, clinical, and large-scale studies are required before regular usage is undertaken. (Jpn Heart J 2004; 45: 613-621)

Key words: Dilated cardiomyopathy, Octreotide

THE most common cause of heart failure is a secondary or a primary dilated cardiomyopathy (DCM), defined as a left ventricular chamber exhibiting increased diastolic and systolic volumes and a low ejection fraction.¹⁾ The natural history of the clinical syndrome of heart failure is dependent on the course of myocardial

From the ¹Department of Cardiology, and ²Medical Intensive Care Unit, Erciyes University Medical School, Kayseri, Turkey.

Address for correspondence: Namlk Kemal Eryol, MD, Department of Cardiology, Erciyes University Medical School, Kayseri, Turkey.

Received for publication November 5, 2003.

Revised and accepted February 13, 2004.

failure. Thus, many investigators have attempted to find an appropriate treatment that will improve intrinsic ventricular function. In advanced heart failure, symptoms persist despite therapy with angiotensin-converting enzyme inhibitors and/or other vasodilators, as well as diuretics, and digoxin.²⁾ In these patients, adjunctive therapeutic modalities are clearly needed, and in recent years promising results have been reported with endocrinological therapeutic approaches.³⁻⁵⁾ Octreotide is a somatostatin analogue and many tissues, including heart tissue, have somatostatin receptors, and it mainly inhibits the release of growth hormone (GH).⁶⁾ It was reported that acromegalic cardiomyopathy could be improved not only functionally but also histopathologically by octreotide with direct and indirect effects.⁷⁻⁹⁾ Furthermore, no differences in histological findings were found between acromegalic cardiomyopathy and idiopathic DCM.¹⁰⁾ The histological resemblance in both cardiomyopathies and their partially similar pathophysiologies in late phases suggest that octreotide can be used in nonacromegalic DCM. Thus, we investigated whether octreotide had beneficial effects in patients with either ischemic or idiopathic DCM, which are both refractory to conventional therapy.

METHODS

Patients: Eligibility criteria for entry into the study were ischemic or idiopathic DCM of New York Heart Association class III, an ejection fraction < 40% measured by echocardiography, and refractoriness to conventional therapy. Any past complaint by the patients concerning their conditions, despite having received conventional therapy consisting of isosorbide dinitrate (40 mg/d), ACE inhibitor (5 or 10 mg/d enalapril), diuretics (40 mg/d furosemide and 50 mg/d spironolactone), and digitalis (0.125 mg/d digoxin) for heart failure, was accepted as a criteria for refractoriness. No patients were on β -blockers, nor did we prescribe them. Patients were excluded if they had significant valvular heart disease, atrial fibrillation, ischemic symptoms, active myocarditis, or malignancies. Additional criteria for exclusion were the presence of any significant hepatic, renal, hematologic, or endocrinologic dysfunctions (except diabetes mellitus) through a careful history, physical examination, and laboratory analysis.

Study design: Twelve patients previously diagnosed as DCM were asked to participate in the study. These patients were scheduled to undergo intermittent octreotide (Sandostatin, Novartis) therapy for 3 months in addition to their conventional therapy, and asked to continue taking them after octreotide therapy at home. The initial dose of octreotide was 50 μ g, administered intravenously at 8 AM after breakfast and followed by 25 μ g doses three times a day, with intervals of eight hours, for four days subcutaneously, and repeated after 1, 2, and 3

months. Patients were discharged two days after completion of the intermittent octreotide therapy. Octreotide was administered in reduced doses compared to those used in acromegalic cardiomyopathy⁷⁾ since octreotide has not been used for this indication so far in the literature. Patients were evaluated 3 times, before and immediately after the first treatment and after 3 months of treatment (last treatment) by researchers blind to the study.

This study was approved by the ethics committee and the institutional review board of Erciyes University Medical School, and verbal informed consent was obtained from each patient.

Procedures: Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography,^{11,12)} and the transmitral E/A velocity rate, mitral valve early deceleration time, left ventricular ejection fraction, left ventricular diastolic diameter, and thickness of the interventricular septum and left ventricular posterior wall were assessed. Left ventricular mass was calculated using the Penn convention formula.¹³⁾ Cardiac index, pulmonary artery wedge pressure, pulmonary artery pressure, and central venous pressure were measured by thermodilution after the patients had fasted overnight. Exercise duration was measured by treadmill tests using the Naughton protocol. The Minnesota living with heart failure questionnaire (QLL) was used to measure quality of life. A decrease in the QQL score was accepted as an improvement of quality of life. Cardiac enzymes including CK-MB and troponin-T were quantitatively measured and troponin-T positivity was accepted as above 0.05 mg/dL. A 24-hour ambulatory ECG was performed to detect the mean heart rate, the number of total premature ventricular beats (PVB), and ischemic burden. The sum in minutes of horizontal or down sloping ST depressions of 0.10 mV or more that continued 80 ms after the point J and lasted at least 1 minute was accepted as ischemic burden.

Continuous variables are presented as the mean $\pm$ SD. Categorical variables are presented as frequencies and percentages. General Linear Model (GLM)-repeated measures analysis (using the Sidak test for post hoc comparisons) was used to evaluate the drug effects on continuous variables within treatment periods. Statistical analysis was performed using SPSS (version 10.0). A *P* value of < 0.05 was considered statistically significant.

RESULTS

The characteristics of the study patients are summarized in Table I. The mean age of the patients was 62 ± 10 years and 6 (50%) were female. Eight patients had ischemic DCM and 4 had idiopathic DCM.

Table I. Patient Characteristics ($n = 12$)

Age (years)		62 ± 10
Sex	Male	6 (50%)
	Female	6 (50%)
Hypertension		5 (42%)
Diabetes mellitus		3 (25%)
Causes of DCM	Ischemic	8 (67%)
	Idiopathic	4 (33%)

DCM = dilated cardiomyopathy.

All patients completed the 3-month treatment phase without experiencing any serious adverse side effects. Two patients required a decrease in the diuretic dose during octreotide therapy but not later. In one patient with diabetes mellitus, the fasting glucose level increased somewhat, but a change in the insulin dose was not required.

There were no significant changes in any parameters after the first octreotide treatment. However, left ventricular ejection fraction increased significantly and left ventricular posterior wall thickness decreased significantly after 3 months compared with the baseline measurements ($P < 0.05$). Although there were improvements in diastolic parameters such as an increase in the transmitral E/A velocity rate and a decrease in the mitral valve early deceleration time, they were not statistically significant ($P > 0.05$). Left ventricular diastolic diameter, interventricular septum thickness, and left ventricular mass also tended to diminish, though they too were not statistically significant ($P > 0.05$) (Table II).

Cardiac index and exercise duration increased significantly and the QQL score, mean heart rate, pulmonary capillary wedge pressure, pulmonary artery pressure, and central venous pressure decreased significantly after 3 months compared with the baseline measurements ($P < 0.05$). The number of premature ventricular beats and the value of ischemic burden tended to decrease after octreotide therapy, although they did not reach statistical significance ($P > 0.05$). CK-MB values did not change significantly ($P > 0.05$) (Table III). There was no troponin-T positivity before treatment, nor did it develop after treatment.

Table II. Effects of Octreotide on Echocardiographic Parameters

Parameter	Baseline	After first treatment	After last treatment	P value
EF (%)	33 ± 5	34 ± 4	37 ± 5	0.008
EDT (msec)	203.3 ± 50.3	204.1 ± 23.1	188.3 ± 60.7	NS
E/A	0.96 ± 0.32	1.06 ± 0.43	1.01 ± 0.36	NS
PWDD (mm)	6.97 ± 0.06	6.93 ± 0.06	6.82 ± 0.05	0.04
SDD (mm)	7.78 ± 0.07	7.73 ± 0.08	7.56 ± 0.07	NS*
LVDD (cm)	5.3 ± 0.5	5.2 ± 0.4	5.1 ± 0.4	NS
LVM (gr)	159.4 ± 31.7	151.3 ± 29.6	143.4 ± 32.7	NS*

NS = $P > 0.05$; *In post hoc test, the difference between baseline and after the last treatment is significant.

EF = left ventricular ejection fraction; EDT, = mitral valve early deceleration time; E/A = transmitral E/A velocities rate; PWDD = posterior wall diastolic thickness; SDD = interventricular septum diastolic thickness; LVDD = left ventricular end-diastolic diameter; LVM = left ventricular mass.

Table III. Effects of Octreotide on Hemodynamic, Life Quality, Effort Capacity, Enzyme, and Holter Parameters

Parameter	Baseline	After first treatment	After last treatment	P value
CI (L/min/m ²)	2.1 ± 0.4	2.2 ± 0.2	2.5 ± 0.2	0.002
PCWP (mmHg)	26.0 ± 4.8	23.0 ± 5.3	18.8 ± 7.7	0.001
PAP (mmHg)	52.7 ± 7.7	50.2 ± 5.8	45.8 ± 6.6	0.008
CVP (mmHg)	13.4 ± 2.3	11.2 ± 2.5	7.2 ± 3.3	0.000
QQL	63 ± 8	59 ± 7	55 ± 8	0.003
Effort duration (min)	2.5 ± 1.0	2.9 ± 1.3	3.9 ± 1.8	0.004
CK-MB (IU/L)	21 ± 10	23 ± 6	21 ± 8	NS
TVES	606 ± 502	510 ± 464	499 ± 449	NS
Ischemic burden (minutes)	39.9 ± 30.4	31.7 ± 18.2	34.2 ± 23.1	NS
Mean heart rate	88.7 ± 10.2	75.9 ± 7.9	73.6 ± 7.8	0.038

NS, $P > 0.05$; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; PAP = pulmonary artery pressure; CVP = central venous pressure; QQL = the score of life quality; TVES = number of premature ventricular beats.

DISCUSSION

In congestive heart failure, the primary factor is failure of the ventricle to provide the required volume of ejection. As a result, cardiac output decreases and hemodynamic compensation mechanisms come into play and the sympathetic system is activated. The resultant functional and structural changes, such as hypertrophy and then dilatation, end with myocardial remodeling over time.¹⁴⁻¹⁶⁾ Thus, treatment modalities to prevent this process should be useful in DCM.

Growth hormone is a physiologic regulator of myocardial growth and performance.¹⁷⁾ Several studies have looked at GH secretion in patients with heart failure and reported that subtle alterations in the activity of GH/IGF-I axis were present in DCM.¹⁸⁻²⁰⁾ Thus, since the alterations in GH/IGF-I axis which may occur as a result of octreotide therapy are already present in these patients, and GH excess and deficiency alone were a cause of heart failure,²¹⁾ it is more reasonable to search for indirect, rather than direct, effects in the results achieved through octreotide therapy in patients with ischemic or idiopathic DCM.

In the present study, 3-month octreotide treatment, in addition to conventional therapy, resulted in significant improvements in the patients, with no adverse effects. Octreotide modulates neurotransmission in the central nervous system and produces mainly parasympathomimetic and sympatholytic effects on the heart,^{6,22,23)} and has negative inotropic and chronotropic effects on atria and positive inotropic effects on ventricles.²⁴⁻²⁶⁾ Thus, it increases not only ventricular filling time by decreasing heart rate but also ventricular contractility. In our study, octreotide increased systolic parameters such as cardiac output and left ventricular ejection fraction and decreased heart rate, probably depending on its effects stressed above studies.

Octreotide also lowers oxygen consumption by decreasing the insulin level through sympathetic inhibition as well as through its direct action.²⁷⁾ Additionally, Lombardi, *et al*²⁸⁾ found that octreotide therapy improved the histopathological changes, which are substrate for arrhythmia²⁹⁾ in patients with DCM. Lin, *et al*³⁰⁾ reported that somatostatin could suppress abnormal automatic activity of dog Purkinje fibers through a reduction of transmembrane calcium influx or modulation of intracellular calcium. The slight decrease in ischemic burden and the number of VPB in our study patients, although not significant, could be explained by these beneficial effects.

Octreotide also causes splanchnic vasoconstriction without ischemia.³¹⁾ By shifting blood to peripheral vessels, this may increase systemic blood pressure and perhaps renal blood flow. In addition to its direct sympatholytic effect, this shifting may cause increased activation of the mechanoreceptors and can contribute to inhibition of the increased neurohumoral response and the decrease in catecholamines and renin-angiotensin-aldosterone (RAS) activity in patients with DCM, which prevents renal sodium and water retention. Sieber, *et al*³²⁾ demonstrated that octreotide inhibited RAS activity and decreased aldosterone levels in healthy volunteers. Additionally, Wang, *et al*³³⁾ showed that octreotide increased the elimination of sodium. Similarly, Jonassen, *et al*³⁴⁾ showed that octreotide prevented sodium retention in patients with cirrhosis. Somatostatin analogues also induce diuresis in dogs.³⁵⁾ Decreases both in CVP in our patients after the 3-month treatment and in the need of one patient for diuretic therapy may be a result

of these effects. The resultant decrease in the preload may cause a reduction in the pulmonary congestion. This is one of the possible reasons for the significant improvements in quality of life, exercise capacity, and systolic function. Consistent with our results, it is also reported that inhibition of GH by octreotide increases exercise capacity.³⁶⁾

Octreotide prevents myocyte hypertrophy which develops in heart failure.^{15,37)} This beneficial effect probably resulted from inhibition of GH, renin-angiotensin-aldosterone, and the sympathetic system, cellular proliferation, and other growth factors.^{6,22,28,32)} With these effects, octreotide may also contribute to the prevention of apoptosis and to the regression of myocardial remodeling.^{15,16,37)} Though a period of three months is not enough, we believe that the significant decrease in posterior wall thickness points to these effects of octreotide. Additionally, though not significant, a reduction in left ventricular diastolic diameter and septal thickness, an improvement in diastolic parameters, and the sustained troponin-T negativity also seems to indicate the same effects of octreotide.

A limitation of our study is the lack of a placebo-control group. A placebo effect can not be entirely ruled out. However, given that all patients received conventional therapy before and during octreotide therapy, it is unlikely that the overall clinical improvement was dependent on conventional therapy. Another limitation of the study may be that GH determinations and the GH-IGF-I axis were not evaluated. This is because none of the patients had features of acromegaly. Additionally, it has been shown that the value of GH is rather variable in patients with DCM and even under physiologic conditions.¹⁷⁾

In conclusion, the intermittent administration of octreotide, in addition to conventional therapy, results, to a certain extent, in an improvement in hemodynamics, exercise performance, and quality of life, and perhaps a tendency toward probable attenuation of left ventricular remodeling. Thus, this therapy seems to be effective in the treatment of patients with ischemic or idiopathic DCM and it should be attempted as an adjunctive therapy in these patients, especially those refractory to conventional treatment modalities. Although these results were obtained in a small group of patients without a placebo group, they are encouraging and point to the need for randomized, double-blind trials before regular usage is undertaken.

REFERENCES

1. Bristow MR, Bohlmeier TJ, Gilbert EM. Dilated Cardiomyopathy. In: Alexander RW, Schlant RC, Fuster V, ed. *Hurst's The Heart*. New York: McGraw-Hill, 1998; 2039-55.
2. Wyne J, Braunwald E. The cardiomyopathies and myocarditides. In: Braunwald E, ed. *Braunwald Heart Disease*. Philadelphia: W.B. Saunders Company, 1997; 1404-34.

3. Houck WV, Pan LC, Kribbs SB, *et al.* Effects of growth hormone supplementation on left ventricular morphology and myocyte function with the development of congestive heart failure. *Circulation* 1999; 100: 2003-9.
4. Giustina A, Volterrani M, Manelli F, *et al.* Endocrine predictors of acute hemodynamic effects of growth hormone in congestive heart failure. *Am Heart J* 1999; 137: 1035-43.
5. Genth-Zotz S, Zotz R, Geil S, Voigtlander T, Meyer J, Darius H. Recombinant growth hormone therapy in patients with ischemic cardiomyopathy. Effects on hemodynamics, left ventricular function, and cardiopulmonary exercise capacity. *Circulation* 1999; 99: 18-21.
6. Lamberts AWJ, van der Lely AJ, De Herder WW, Hofland LJ. Octreotide. *N Engl J Med* 1996; 334: 246-54.
7. Chanson P, Timsit J, Masquet C, *et al.* Cardiovascular effects of the somatostatin analog octreotide in acromegaly. *Ann Intern Med* 1990; 113: 921-5.
8. Nishiki M, Murakami Y, Sohmiya M, *et al.* Histopathological improvement of acromegalic cardiomyopathy by intermittent subcutaneous infusion of octreotide. *Endocr J* 1997; 44: 655-60.
9. Shimakura A, Miyakoshi H, Ohkuwa H, *et al.* Improvement of cardiac function after treatment with octreotide followed by trans-sphenoidal surgery in an acromegalic patient who presented with congestive heart failure. *Jpn Heart J* 2002; 43: 69-77.
10. von den Heuvel PACMB, Elbers HRJ, Plokker HWM, Bruschke AVG. Myocardial involvement in acromegaly. *Int J Cardiol* 1984; 6: 550-3.
11. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072-83.
12. Taylor R, Waggoner AD. Doppler assessment of left ventricular diastolic function: a review. *J Am Soc Echocardiogr* 1992; 5: 603-12.
13. Devereux RB, Alonso DR, Lutas EM, *et al.* Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450-8.
14. Epstein FH, Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; 341: 577-85.
15. Hunter JJ, Chien KR. Signaling pathways for cardiac hypertrophy and failure. *N Engl J Med* 1999; 341: 1276-83.
16. Del Carlo CH, O'Connor CM. Cardiac troponins in congestive heart failure. *Am Heart J* 1999; 138: 646-53.
17. Fazio S, Palmieri EA, Biondi B, Cittadini A, Sacca L. The role of the GH-IGF-I axis in the regulation of myocardial growth: from experimental models to human evidence. *Eur J Endocrinol* 2000; 142: 211-6.
18. Jenkins RC, Ross RJM. The growth hormone IGF-I axis in dilated cardiomyopathy. *Clin Endocrinol* 1999; 50: 415-6.
19. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris P. Edema of cardiac origin: Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation* 1989; 80: 299-305.
20. Broglio F, Fubini A, Morello M, *et al.* Activity of GH/IGF-I axis in patients with dilated cardiomyopathy. *Clin Endocrinol* 1999; 50: 417-30.
21. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. *Endocr Rev* 1994; 15: 555-73.
22. Rettig R, Geist R, Sauer U, Rohmeiss P, Unger T. Central effects of somatostatin: pressor response, AVP release, and sympathoinhibition. *Am J Physiol* 1989; 257: R588-94.
23. Campbell G, Gibbins IL, Morris JL, *et al.* Somatostatin is contained in and released from cholinergic nerves in the heart of the toad *Bufo marinus*. *Neuroscience* 1982; 7: 2013-23.
24. Day SM, Gu J, Polak JM, Bloom SR. Somatostatin in the human heart and comparison with guinea pig and rat heart. *Br Heart J* 1985; 53: 153-7.
25. Hirai S, Hasegawa J, Mashiba H. Positive inotropic effect of somatostatin in guinea-pig ventricular muscles. *J Mol Cell Cardiol* 1989; 21: 607-16.
26. Du XY, Schoemaker RG, Bos E, Saxena PR. Different pharmacological responses of atrium and ventricle: studies with human cardiac tissue. *Eur J Pharmacol* 1994; 259: 173-80.
27. Xu Y, Lu L, Zhu P, Schwartz GG. Beta-adrenergic stimulation induces transient imbalance between myocardial substrate uptake and metabolism *in vivo*. *Am J Physiol* 1998; 275: H2181-90.
28. Lombardi G, Colao A, Ferone D, *et al.* Cardiovascular aspects in acromegaly: Effects of treatment. *Metabolism* 1996; 45 (suppl 1): 57-60.

29. Pogwizd SM, McKenzie JP, Cain ME. Mechanisms underlying spontaneous and induced ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy. *Circulation* 1998; 98: 2404-14.
30. Lin CI, Su MT, Luk HN, Wu HL. Suppressive effects of somatostatin in dog Purkinje fibres. *Br J Pharmacol* 1988; 93: 192-8.
31. Tyden G, Samnegard H, Thulin L, *et al.* Circulatory effects of somatostatin in anaesthetized man. *Acta Chir Scand* 1979; 145: 443-6.
32. Sieber C, Gnadinger M, del Pozo E, Shaw S, Weidmann P. Effect of a new somatostatin analogue SMS 201-995 (sandostatin) on the renin-aldosterone axis. *Clin Endocrinol* 1988; 28: 25-32.
33. Wang SS, Lee FY, Wu SL, *et al.* Effects of long-term administration of octreotide on sodium retention and atrial natriuretic peptide in carbon tetrachloride-induced cirrhotic rats. *J Hepatol* 1997; 26: 1128-34.
34. Jonassen TE, Christensen S, Sorensen AM, *et al.* Effects of chronic octreotide treatment on renal changes during cirrhosis in rats. *Hepatology* 1999; 29: 1387-95.
35. Mountokalakis T, Levy M. Effect of a selective octapeptide analogue of somatostatin on renal water excretion in the dog. *Metabolism* 1985; 34: 408-9.
36. Padayatty S, Perrins EJ, Belchetz PE. Octreotide treatment increases exercise capacity in patients with acromegaly. *Eur J Endocrinol* 1996; 134: 554-9.
37. Sakamoto H. Cardiovascular effects of octreotide, a long-acting somatostatin analog. *Cardiovasc Drug Rev* 1999; 17: 358-73.