Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 58; Numer/Number 4/2007
ISSN 0423–104X

The importance of presurgical somatostatin analogue therapy in acromegaly

Znaczenie przedoperacyjnego zastosowania analogów somatostatyny w akromegalii

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Abstract
Different types of treatment, including surgery, medical therapy and radiotherapy, are possible in achieving control of acromegaly. Of the medical therapies available, somatostatin analogues are effective in the majority of patients and can induce pituitary tumour shrinkage. The rationale and outcome of somatostatin analogue treatment before surgery in patients with acromegaly is briefly presented. In summary, the benefits of somatostatin analogues given preoperatively should be considered carefully as optimisation of cardiovascular, respiratory and metabolic functions is clinically relevant for perioperative morbidity. Somatostatin analogues also induce significant shrinkage of GH-secreting pituitary tumours, although this does not seem to be helpful in terms of improved surgical outcome.

(Pol J Endocrinol 2007; 58 (4): 356–360)

Key words: *acromegaly, somatostatin analogues, tumour shrinkage, pituitary tumour surgery*

Streszczenie
W leczeniu akromegalii możliwe jest zastosowanie różnych form terapii (leczenie operacyjne, farmakoterapia, radioterapia). Analogi somatostatyny wykazują skuteczność u większości pacjentów i mogą powodować zmniejszenie wielkości gruczolaka przysadki. Krótki przegląd przedstawia uzasadnienie i wyniki stosowania analogów somatostatyny przed leczeniem chirurgicznym. W podsumowaniu, korzyści przedoperacyjnego zastosowania analogów somatostatyny powinny być starannie rozważone celem optymalizacji zaburzeń kardiologicznych, oddechowych i metabolicznych ważnych dla chorobowości okołooperacyjnej. Analogi somatostatyny powodują również istotne zmniejszenie guzów przysadki wydzielających GH, chociaż nie udowodniono jego wpływu na poprawę wyników leczenia neurochirurgicznego.

(Endokrynol Pol 2007; 58 (4): 356–360)

Słowa kluczowe: *akromegalia, analogi somatostatyny, zmniejszenie guza, leczenie operacyjne guzów przysadki*

Introduction

Acromegaly is a rare disease associated with premature mortality, mainly because of cardiovascular disease[1]. The control of levels of growth hormone (GH) to below 2.5 μg/L) and of IGF-I (normalised for age and gender) is reported to bring mortality within the norm [2]. Surgery, medical therapy and radiotherapy can all be used to achieve disease control. First-line surgery is generally effective in patients with small tumours [3]. In more recent years first-line therapy with somatostatin analogues has been shown to be efficacious in approximately 50% of patients and to induce tumour shrinkage by > 30% on average in approximately 80% of patients [4]. First-line medical treatment with dopamine agonist is not efficacious but can be of help in combination with somatostatin analogues [3]. Treatment with the recently available GH-receptor antagonist [5] is effective in normalising IGF-I levels in 75–90% of patients resistant to previous therapies [6] but cannot currently be used as first-line treatment in Europe.

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Table I
Presurgical somatostatin treatment

Tabela I
Przedoperacyjne leczenie somatostatyną

Author (ref. no)	Year	Number of patients	Treatment			Outcome		
			Type	Dose	Duration (months)	Remission Rate (%)	Patients with shrinkage (%)	Degree of Shrinkage (%)
Barkan [28]	1988	10	OCT	0.15–1 mg/d	0.75–7.5	80	100	20–54
Plöckinger [29]	1994	10	OCT	0.3–1.5 mg/d	3–6	80	50	26–85
Lucas-Morante [30]	1994	10	OCT	0.3 mg/d	1.4	60	60	9–78
Stevenaert [31]	1996	64	OCT	0.3–1.5 mg/d	0.75–39	71	23	>25
Colao [15]	1997	21	OCT	0.15–0.6 mg/d	3–6	55	23	≥ 30
Newman [32]	1998	26	OCT	0.3–1.75 mg/d	3–60	40	46	≥ 10
Tamura [33]	1998	9	OCT infusion	0.12–0.24 mg/d	0.5–1	89	67	≥ 20
Tachibana [34]	1999	3	OCT	0.2 mg/d	0.5	67	67	~50
Kristof [35]	1999	11	OCT	0.15–0.9 mg/d	1.7–6.7	55	36	29–48
Baldelli [36]	2000	23	LAN	30 mg/q10–14d	6–24	78	22	≥ 20
Colao [37]	2001	15	LAR	20–40 mg/q28d	15–24	73	80	25–100
Abe [38]	2001	90	OCT	0.1–1.5 mg/d	3–21	69	31	11–35
Amato [39]	2002	11	LAR	10–30 mg/q28d	24	37.5	36	10–25
Amato [39]	2002	12	LAN	30 mg/q10–14d	24	41	50	10–25
Bevan [40]	2002	27	OCT → LAR	0.3–0.6 mg/d → → 20–30 mg/q28d	12	79	73	> 30
Colao [41]	2006	34	LAR	20–30 mg/q28d	6	69.7	74	> 30
Colao [4]	2006	99	LAN or LAR	20–30 mg/q28d 30–120 mg/q28d	12	42.4	72.7	> 25

OCT — s.c. octreotide, LAN — lanreotide, LAR — octreotide-LAR

Cardio- and cerebrovascular disease and respiratory and metabolic dysfunction, the major complications of acromegaly [2] are well known to be major risk factors before surgery, especially in the elderly [8]. Therefore the control of hypertension, diabetes, arrhythmias, diastolic dysfunction, pulmonary dysfunction and sleep apnoea is important in patients undergoing anaesthesia and surgery.

This brief review reports on the rationale and outcome of somatostatin analogue treatment before surgery in patients with acromegaly.

Treatment with somatostatin analogues before surgery and surgical outcome

Surgery is efficacious in controlling GH and IGF-I excess in 70–90% of patients with microadenomas and approximately 50% of those with macroadenomas when the surgery is performed by dedicated neurosurgeons with experience in pituitary adenomas [9]. In a recent study in which 506 patients were operated on for GH-secreting adenomas [10], cure of acromegaly was obtained in 75.3% of 142 microadenomas, 74.2% of 105 intrasellar macroadenomas and in less than 50% up to 10% of patients bearing larger tumours. This cure rate appears to be similar to that observed with somatostatin analogues, even if the numbers related to the latter treatment were smaller [4]. Several studies have reported the efficacy of treatment with somatostatin analogues before surgery (Table I). The majority of the patients achieved disease control with somatostatin analogues before surgery, and tumour shrinkage (by more than 20%) was reported in a variable percentage of patients. It is worth noting that most of the studies were performed using a subcutaneous formulation of octreotide, which is less effective than the depot formulations such as octreotide LAR (long-acting release) or lanreotide-autogel (slow release). The statistical estimation of disease control rose from a 68% success rate for patients with macroadenomas treated with

primary pharmacotherapy to 81% (and even 87% for non-invasive macroadenomas) for patients undergoing surgery followed by postoperative somatostatin analogues [5]. The question of whether shrinkage of tumours before surgery may facilitate their complete resection has not been examined in a controlled randomised blinded manner and therefore cannot be answered rigorously. However, when the modern depot formulations are used more than 80% of patients treated for 12 months have a tumour shrinkage greater than 20% and more than 50% have a tumour shrinkage greater than 50% [4]. These results should be considered of major relevance in patients with large macroadenomas, where it is known that there is little likelihood of cure with first-line surgery.

Peri-operative morbidity in patients treated with somatostatin analogues before surgery

In the hands of experienced neurosurgeons morbidity and mortality during and immediately after trans-sphenoidal excision of a GH-secreting tumour is low [11, 12]. In any case, the extent and magnitude of perioperative complications should be assessed since most patients can present with several severe systemic complications [2]. The life expectancy of patients with acromegaly is currently longer than in previous decades because of improved medical care. It is, however, well known that the longer the duration of the disease, the more likely the occurrence of complications such as diabetes, cardio- and cerebrovascular disease and respiratory problems [2]. Thus the role of first-line pharmacotherapy before surgery in preventing or ameliorating perioperative complications is an important clinical question.

Overall, patients with acromegaly experience anaesthetic morbidity [13]. In 28 patients with acromegaly examined retrospectively and compared with 28 sex- and age-matched controls undergoing general anaesthesia, 42.8% of the patients had anaesthetic-associated haemodynamic changes, compared with 17.8% in the control group; during anaesthesia blood glucose levels were higher and urine output was lower in the patients compared with controls [13]. Importantly, a significantly higher number of patients had a difficult intubation (42.8% *vs.* 3.6%), and fiberoptic intubation was required in 25% of patients with acromegaly compared with none of the controls [13]. It is, therefore, likely that reducing soft tissue swelling before surgery can reduce the rate of complications during anaesthesia.

In addition to these direct effects on the anaesthetic procedure, cardiovascular disease, the most important determinant of morbidity and mortality in acromegaly, is of concern for preoperative assessment. Before surgery both overt and underlying cardiovascular disease should be evaluated [2]. The most common manifestations include left ventricular hypertrophy with increased wall thickness and cavity dimension, ultimately developing concentric biventricular cardiomyopathy with diastolic and eventually systolic dysfunction, reduced left ventricular ejection fraction on effort and at rest and finally cardiac failure [2]. Other complications, including dyslipidaemia, insulin resistance or overt diabetes mellitus, may also contribute to ischaemic heart disease, further compromise cardiovascular function [2], and lead to deleterious effects during and after surgery.

Improved cardiac function has been reported with octreotide, octreotide LAR, and lanreotide [2]. Surprisingly, even 1 d of octreotide infusion improved systolic and diastolic functional indices at rest, anaerobic threshold and workload and oxygen consumption at maximal exercise, as assessed by echocardiography and bicycle ergometry [14]. An increased prevalence of simple to life-threatening arrhythmias may complicate perioperative outcomes. The frequency of late potentials, a predictor of ventricular dysrhythmias (including severe ventricular dysrhythmias with sudden death), is significantly higher in patients with active acromegaly compared with healthy control subjects [2]. Three to six months of either octreotide [15] or lanreotide [16] treatment normalised electrocardiogram recordings in most patients, and sinus arrhythmia, supra-ventricular and ventricular tachycardia improved.

Hypertension occurs in 20–51% of patients with active acromegaly [17] and aggravates acromegalic cardiomyopathy, atherosclerosis, and cardio- and cerebrovascular disease [2]. Blood pressure control may not correlate with GH or IGF-I levels and the effects of somatostatin analogues on blood pressure in patients with acromegaly are unclear.

The integrity of the respiratory system is a critical preoperative clinical concern because a twofold increase in mortality due to respiratory disorders has been reported in acromegaly [2]. Respiratory disorders commonly occur in acromegaly and are mainly attributed to changes in the thoracic cage, tissue swelling and thickening of the upper respiratory tract and enlargement and distortion of the glottic structures with additional folds. Lowering GH levels using somatostatin analogues before surgery may facilitate anaesthetic intubation, as reported for improved sleep apneoa [18], and a decrease in tongue volume [19].

Preoperative control of blood sugar levels may be efficiently achieved by standard therapy. However, GH is a potent insulin antagonist, and carbohydrate intolerance and diabetes mellitus are encountered in up to 30% of patients with acromegaly (2). Elevated glucose and insulin levels may complicate the peri-operative period and a reduction in GH and IGF-I levels is expected to improve carbohydrate intolerance. However, the effects of somatostatin analogues on carbohydrate to-

lerance are variable, as either improvement or impairment may be observed during treatment [20]. Although the final long-term effect of somatostatin analogues on glucose tolerance is still poorly understood, the possibility of controlling diabetes before surgery is appealing, as diabetic patients are known to be at higher risk of developing adverse surgical outcomes related to complications of the disease (atherosclerosis, nephropathy, and neuropathy), poor wound healing and increased susceptibility to infection [21]. A recently available treatment for acromegaly is the GH-receptor antagonist, pegvisomant. This has been shown to improve glucose tolerance in patients with acromegaly [7, 22, 23]. The use of pegvisomant before surgery in diabetic patients with acromegaly has never been reported, although it is likely to improve glucose and insulin levels.

In summary, the benefits of somatostatin analogues given preoperatively should be considered carefully, as optimisation of the cardiovascular, respiratory and metabolic functions is clinically relevant for perioperative morbidity [24]. Indeed, first-line surgery should be limited to patients with small enclosed tumours and those who do not present systemic complications [24]. Somatostatin analogues also induce significant shrinkage of GH-secreting pituitary tumours, although this does not seem to be helpful in terms of improved surgical outcome [25–27].

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