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The Role of Pharmacotherapy in Perioperative Management of Patients with Acromegaly

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The major complications of acromegaly, including cardiovascular and cerebrovascular disease and respiratory and metabolic dysfunction, are associated with a significant increase in morbidity and mortality (1–3). These complications are well known to be major risk factors in perioperative patients, especially the elderly (4–8). Therefore, controlling cardiovascular and cerebrovascular disease, pulmonary dysfunction, and hyperglycemia is important in patients undergoing anesthesia and surgery. This review evaluates the rationale for administering somatostatin analog treatment before either transsphenoidal resection of a GH-secreting pituitary adenoma or any other surgical procedure requiring general anesthesia in the patient with uncontrolled acromegaly.

Preoperative pharmacotherapy and remission rates

Does treatment with somatostatin analogs before surgery improve surgical outcome? In the hands of an experienced surgeon and if rigorous criteria are used to interpret surgical results [GH \leq 1 ng/ml after oral glucose tolerance test (OGTT) and normalized IGF-I levels], approximately 90% of patients with microadenomas and 50% of those with macroadenomas are controlled by surgery in the most experienced centers (9). In a recent study, 70% of 57 surgically treated patients (67% of whom harbored macroadenomas) exhibited normalized IGF-I, and 61% exhibited nadir GH less than 1 μ g/liter 12 months after surgery (10). Summarizing 14 studies (Table 1), 55–89% of patients harboring mostly macroadenomas experience disease control if short-term treatment with somatostatin analogs is administered before surgery, and 23–100% exhibit more than 20% tumor shrinkage. If tight control is achieved with sc octreotide (GH \leq 1 ng/ml after OGTT and normal IGF-I levels; Ref. 1), 55–75% of patients have controlled hormone levels, and 36–50% exhibit tumor shrinkage. Insufficient studies have been conducted using octreotide LAR (long-acting release) or lanreotide SR (slow release), but remission rates may well be higher because patient compliance is improved and control of serum hormone levels by slow-release drugs is readily attainable. The statistical estimation of disease control rose from 68% success rate for patients with macroadenomas treated with primary phar-

macotherapy to 81% (and even 87% for noninvasive macroadenomas) for patients undergoing surgery followed by postoperative somatostatin analogs (11). The question of whether shrinkage of tumors before surgery may facilitate their complete resection has not been examined in a controlled, randomized, blinded manner and therefore cannot be rigorously answered.

Is the response to primary treatment with somatostatin analog more favorable than when these drugs are administered after surgery or irradiation? Baldelli *et al.* (12) addressed this question by comparing serum GH responses to lanreotide in 3 groups of patients (71 who underwent surgery, 24 who were irradiated, and 23 newly diagnosed and not yet treated; Fig. 1). After 6 months, the response to lanreotide in naive patients was more favorable than that observed in previously irradiated patients, and after 12 months it was also improved over previously operated patients. No such observed difference was reported for IGF-I levels. The authors concluded that prior radiotherapy probably caused partial somatostatin resistance. In contrast, another study found no differences in GH or IGF-I levels in 15 naive patients and in operated patients receiving long-term octreotide LAR for up to 24 months (13). Seventy-three percent of newly diagnosed patients had GH levels of 2.5 ng/ml or less, and 53% had normal IGF-I levels after octreotide LAR treatment. In patients who underwent surgery before medical treatment, 76% had GH of 2.5 ng/ml or less, and 71% had normal IGF-I levels (13).

Therefore, currently available results indicate that primary therapy does not seem beneficial for the already excellent outcomes achieved with microadenoma resections. As for macroadenomas, preoperative biochemical control may improve cure rates.

Perioperative morbidity

Does pharmacotherapy alter the frequency of perioperative morbidity in patients undergoing surgery? Although morbidity and mortality during and immediately after transsphenoidal excision of a GH-secreting tumor is low (11, 14, 15), in the hands of experienced neurosurgeons the extent and magnitude of perioperative complications should be assessed. Large variability in surgical expertise influences cure rates after surgery (whether reported or not). With improved medical care, life expectancy of patients with acromegaly is now longer, com-

Abbreviations: LAR, Long-acting release; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; OGTT, oral glucose tolerance test; SR, slow release.

TABLE 1. Outcomes of somatostatin analog perioperative treatment

Author (ref. no.) Year	Number of patients	Tumor type	Treatment	Treatment duration	Treatment outcomes	
					Remission rate (%) (definition of cure)	Shrinkage No./total (%) ^a Degree of shrinkage ^b
Barkan (58) 1988	10	M	Octreotide, 150–1000 μg/d	3–30 wk	8/10 (80%) ^{AS} GH ≤ 4.6 ng/ml, post OGTT ≤ 2 ng/ml, normal IGF-I)	10/10 (100%) 20–54%
Plöckinger (59) 1994	10	M	Octreotide, 300–1500 μg/d	3–6 months	8/10 (80%) ^{AS} (IGF-I normal) 6/8 (75%) ^{AS} (GH ≤ 1 ng/ml post OGTT)	5/10 (50%) 26–85%
Lucas-Morante (60) 1994	10	M	Octreotide, 300 μg/d	42 d	6/10 (60%) ^{AS} (GH < 2 ng/ml post OGTT, IGF-I < 1.5 U/ml)	6/10 (60%) 9–78% (mean 30%)
Stevenaert (61) 1996	64	Mostly M	Octreotide, 300–1500 μg/d	3 wk–39 months	46/64 (71%) ^{AS} (GH ≤ 2 ng/ml, GH post OGTT ≤ 1 ng/ml, normal IGF-I)	15/64 (23%) >25%
Colao (26) 1997	22	21 M, 1 m	Octreotide, 150–600 μg/d	3–6 months	12/22 (55%) ^{AS} (GH ≤ 5 ng/ml, normal IGF-I)	5/22 (23%) ≥30%
Newman (62) 1998	26 ^c	NA	Octreotide, 300–1750 μg/d	3–60 months	10/26 (40%) (GH ≤ 2 ng/ml) 17/25 (68%) (normal IGF-I)	6/13 ^d (46%) ≥10% 3/13 ^d (23%) >25%
Tamura (63) 1998	9	6 M, 3 m	Octreotide infusion, 120– 240 μg/d	2–4 wk	8/9 (89%) ^{AS} (GH ≤ 1 ng/ml post OGTT)	6/9 (67%) ≥20%
Tachibana (64) 1999	3	M	Octreotide, 200 μg/d	2 wk	2/3 (67%) ^{AS} (GH ≤ 5 ng/ml)	2/3 (67%) ~50%
Kristof (65) 1999	11	10 M, 1 m	Octreotide, 150–900 μg/d	7–27 wk	6/11 (55%) ^{AS} (GH ≤ 1 ng/ml post OGTT, normal IGF-I)	4/11 (36%) 29–48%
Baldelli (12) 2000	23 ^c	15 M, 8 m	Lanreotide, 30 mg q10–14 d	6–24 months	18/23 (78%) (GH ≤ 7.5 mU/liter; GH ≤ 3 mU/ liter post OGTT) 16/23 (70%) (normal IGF-I)	5/23 (22%) ≥20%
Colao (13) 2001	15 ^c	12 M, 3 m	Octreotide LAR 20–40 mg q28d	15–24 months	11/15 (73%) (GH ≤ 2.5 ng/ml) 8/15 (53%) (normal IGF-I)	12/15 (80%) 25–100%
Abe (66) 2001	90 ^c	83 M, 7 m	Octreotide 100–1500	3–21 months	62/90 (69%) ^{AS} (GH ≤ 2.5 ng/ml, normal IGF-I)	28/90 (31%) 11–35%
Amato (67) 2002	11 ^c	10 M, 10 m	Octreotide LAR 10–30 mg q28d	24	4/11 (37.5%) ^{BS} (GH ≤ 5 mU/liter, normal IGF-I)	4/11 (36%) 10–25% 3/11 (27%) 20–50% 1/11 (9%) >50%
	12 ^c		Lanreotide 30 mg q10–14 d	24	5/12 (41%) ^{BS} (GH ≤ 5 mU/liter, normal IGF-I)	6/12 (50%) 10–25% 4/12 (33%) 20–50% 1/12 (8%) >50%

No., Number of newly diagnosed patients not undergoing surgery or radiotherapy before treatment with somatostatin analogs; ^{AS}, after surgery; ^{BS}, before surgery; M, macroadenoma; m, microadenoma; NA, not ascertainable.

^a Number of patients exhibiting tumor shrinkage of the total (percentage in *parentheses*).

^b Degree of reduction in tumor size in percentage.

^c Patients previously untreated with surgery and/or irradiation.

^d Thirteen patients had pituitary magnetic resonance imaging before and after 6 months of therapy.

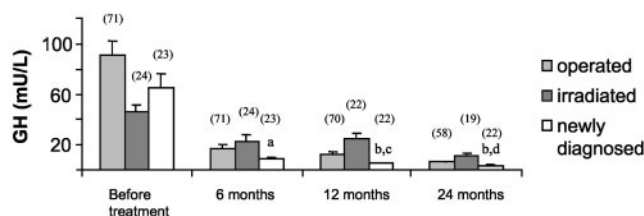


FIG. 1. GH levels during long-term lanreotide treatment in operated, irradiated, and newly diagnosed patients. Number of patients is shown in parentheses. a, $P < 0.05$ vs. irradiated; b, $P < 0.05$ vs. operated; c, $P < 0.0005$ vs. irradiated; d, $P < 0.005$ vs. irradiated. Figure was compiled from data derived from Ref. 12.

pared with previous decades, and the longer the duration of the disease, the more likely the occurrence of complications such as diabetes, cardio- and cerebrovascular disease, and respiratory problems. The frailty of older age renders these patients more prone to complications of acromegaly compared with younger patients, and their ability to undergo surgery safely is compromised. Thus, it is important to determine whether primary pharmacotherapy before surgery prevents or ameliorates perioperative complications.

Overall, patients with acromegaly experience anesthetic morbidity (16). Cardiovascular, pulmonary, and metabolic parameters were examined retrospectively in 28 patients with acromegaly compared with 28 sex- and age-matched controls undergoing general anesthesia. Although no significant major hemodynamic changes or differences in response to vasoactive drugs during anesthesia were noted, 12 of 28 patients (>20%) had anesthetic-associated hemodynamic changes, compared with only 5 in the control group. Gas exchange abnormalities in some patients did not significantly impact anesthesia. Blood glucose levels were higher, and urine output was lower in patients with acromegaly during anesthesia compared with controls. Twelve of 28 patients with acromegaly had a difficult intubation (*vs.* 1 of 28 controls), and 3 required fiberoptic intubation (*vs.* none of the controls). Therefore, lessening soft tissue swelling and improving hemodynamic function before surgery may ameliorate some of these complications.

In addition to these direct effects on the anesthetic procedure, several unique clinical factors of acromegaly also contribute to perioperative morbidity. These complications are largely caused by the deleterious impact of high GH or IGF-I levels; all require careful clinical evaluation and management.

Cardiovascular disease is the most important determinant of morbidity and mortality in acromegaly, responsible for approximately 60% of deaths (3, 17, 18), and is therefore of concern for preoperative assessment. Even patients with shorter disease duration and younger patients exhibit impaired cardiac structure and function (19).

Before surgery, both overt and underlying cardiovascular disease should be evaluated. Early manifestations include left ventricular hypertrophy (LVH) with increased wall thickness and cavity dimension, increased stroke volume and cardiac index (19–21), and ultimately development of concentric biventricular cardiomyopathy with diastolic (21–23) and eventually systolic dysfunction, reduced left ventricular ejection fraction (LVEF) on effort and rest, and finally

cardiac failure (17). A recent study found that 10 of 102 newly diagnosed patients (90% males) with acromegaly had overt high output heart failure (20). Moreover, other acromegaly complications including dyslipidemia, insulin resistance, or overt diabetes mellitus may also contribute to ischemic heart disease, further compromise cardiovascular function, and lead to deleterious effects during and after surgery.

To date, there is insufficient data regarding cardiovascular morbidity and mortality during and after surgery in acromegaly. It is reasonable to assume that the longer the duration of the active disease (24) and the older the patient (25), the more severe and prevalent the cardiac disease, and more cardiovascular complications during and after surgery are expected. Hence, improving cardiac performance before surgery should be beneficial. Improved cardiac function has been reported with octreotide, octreotide LAR, and lanreotide (24–29). In patients who achieved disease control, there was a reduction in left ventricular mass and septal and posterior wall mass after 1 wk to 10 yr of therapy (24, 25, 27–29). Although improved LVEF at rest, during, and after exercise was observed in controlled patients after 6 months to 5 yr of octreotide LAR (27), and 1 yr and 5 yr of sc octreotide (25, 30), other reports did not show improved LVEF even after 18 months treatment with lanreotide (29). Diastolic dysfunction did not improve after therapy (25). Surprisingly, even 1 d of octreotide infusion to 10 patients with LVH improved systolic and diastolic functional indexes at rest, anaerobic threshold, and workload and oxygen consumption at maximal exercise, as assessed by echocardiography and bicycle ergometry (31). Similar results were reported after a single lanreotide injection (32). Insufficient data exist regarding the relationship between suppression of GH/IGF-I levels with pharmacotherapy and subsequent cardiac effects in patients with established severe cardiomyopathy. This would suggest a beneficial impact of preoperative octreotide administration on cardiac indices.

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 (prevalence of 23% *vs.* 0%, respectively). Only 2 of 36 controlled patients (GH ≤ 1 ng/ml after OGTT and normal IGF-I) had late potentials (33). Ninety-two percent of daily ventricular premature complexes disappeared after 4 wk of treatment with octreotide before transsphenoidal surgery (34). Heart rate decreased in patients with LVH who were treated with somatostatin analogs (28, 32) and only if GH/IGF-I levels were controlled (25, 30). Three to 6 months of octreotide treatment normalized electrocardiogram recordings in 7 of 11 patients, and sinus arrhythmia, supraventricular, and ventricular tachycardia improved in 6 of 11 patients (26).

Hypertension occurs in 20–51% of patients with active acromegaly (17, 35) and aggravates acromegalic cardiomyopathy, atherosclerosis, and cardio- and cerebrovascular disease (36). Preoperative blood pressure control may not correlate with GH or IGF-I levels. Effects of somatostatin analogs on blood pressure in patients with acromegaly are unclear. A decrease in systolic blood pressure occurred in 10

patients with LVH treated with octreotide (28), and decreased systolic and diastolic pressure were reported in 5 of 8 patients treated with octreotide for 6 months (26). In contrast, no differences in blood pressure were demonstrated in more prolonged studies with octreotide (25, 30), octreotide LAR (27), or lanreotide (29). However, systolic blood pressure was reduced in 10 patients after a single lanreotide injection (32). It is therefore unclear whether or not treatment with somatostatin analogs is beneficial for short- or long-term blood pressure control in these patients.

Integrity of the respiratory system is a critical preoperative clinical concern because a 2-fold increase in mortality due to respiratory disorders was reported in patients with acromegaly. Importantly, duration of disease did not correlate with respiratory mortality (3). Respiratory disorders occur commonly in acromegaly and are mainly attributed to tissue swelling and thickening of the upper respiratory tract, including macroglossia, hypertrophied nasal structures, and enlargement and distortion of glottic structures with additional folds. Laryngeal and pharyngeal soft tissue hypertrophy and vocal cord swelling may result in vocal cord fixation with laryngeal stenosis, which makes intubation difficult and necessitates preoperative fiberoptic intubation or tracheostomy (37, 38). Between 10 and 30% of anesthetic intubations for surgery in acromegaly are reported as difficult (38). Vocal cord edema, mass, length, elasticity, and voice changes improve within 10–14 d of lowering GH levels by surgical tumor excision (39) or octreotide treatment (40) and imply that lowering GH levels using somatostatin analog before surgery may enable easier anesthetic intubation.

Increased lung volumes and lung distensibility with normal diffusion capacity were demonstrated in patients with acromegaly, presumably due to an increase in alveolar size (41). The impact of these changes on lung function during anesthesia and surgery has not been evaluated. Normalization of lung distensibility and volume was partly achieved as GH levels were suppressed by surgery or somatostatin analogs to under 2 ng/ml after OGTT (41).

Sleep apnea was reported in 20–81% of patients with acromegaly (42–46) especially in men over 50 yr old (46). Intermittent upper airway obstruction with collapse of both the tongue base and soft palate edges as a result of macroglossia and soft-tissue swelling with pharyngeal hypertrophy (42, 44, 47, 48) and/or the existence of central sleep apnea (46) may hamper both pre- and postoperative status of the patient with acromegaly. Sleep apnea is also associated with increased risk for and mortality from coronary heart disease (49, 50), myocardial infarction (51), cerebral infarction (52), and hypertension (50). Although the correlation between GH/IGF-I serum levels and severity of sleep apnea is controversial (42, 46), controlled serum GH levels by sc octreotide were shown to revert the condition within a few days (43, 53, 54), and complete resolution of the disorder is apparent after 6 months of octreotide treatment (54). The number of apneic events per hour, total apnea time, and oxygen saturation improved by approximately 50% in 19 patients with acromegaly treated with octreotide for 6 months (45). Serum GH levels and total sleep apnea time did not correlate (45). Sleep apnea may complicate postoperative extubation in an already swollen hypertrophied larynx (55). Therefore, correction of sleep apnea before anesthesia and sur-

gery may be beneficial for patients with acromegaly, mainly by preventing hypertension and cardio- and cerebrovascular complications.

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 (26). Hyperglycemia and hyperinsulinemia may complicate the perioperative period, especially during surgical recovery. Reducing GH and IGF-I levels is expected to improve carbohydrate intolerance. However, the effect of somatostatin analogs on glucose tolerance varies, because octreotide reduces GH levels but also may inhibit insulin secretion. Twenty-two of 90 (23%) patients treated with octreotide developed impaired glucose tolerance or became overtly diabetic, but 3 of 11 diabetic patients became euglycemic during treatment (56). Six months of octreotide treatment resulted in normalized blood glucose levels in three of four patients treated with oral glucose-lowering drugs. Two of four diabetic patients who required insulin were switched to oral glucose-lowering drugs during octreotide treatment (26). Although the net long-term effect of somatostatin analogs on glucose tolerance is yet unclear, the ability to control diabetes before surgery is appealing because diabetic patients are at increased risk for adverse surgical outcomes related to complications of the disease (atherosclerosis, nephropathy, and neuropathy), poor wound healing, and increased susceptibility to infection (57).

In summary, the benefits of using somatostatin analogs before surgery should be carefully considered because optimization of cardiovascular, respiratory, and metabolic functions is important for perioperative morbidity. Somatostatin analogs do not significantly shrink GH-secreting pituitary tumors, compared with the shrinkage of prolactinomas under treatment with dopamine receptor agonists, although there seems to be an improvement in remission rates in patients treated pharmacologically before surgery. The need for preoperative pharmacotherapy should be evaluated in patients with active acromegaly facing surgery. A prospective, controlled study is required to assess the beneficial impact of preoperative somatostatin treatment on perioperative morbidity.

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