ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors

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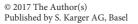
Abstract

Neuroendocrine tumors of the small intestine are the most common causes of the carcinoid syndrome. Carcinoid heart disease occurs in more than half of the patients with the carcinoid syndrome. Patients with carcinoid heart disease who need to undergo surgery should also undergo preoperative evaluation by an expert cardiologist. Treatment with long-acting somatostatin analogs aims at controlling the excessive hormonal output and symptoms related to the carcinoid syndrome and at preventing a carcinoid crisis during interventions. Patients with a gastrinoma require pre- and postoperative treatment with high doses of proton pump inhibitors. Patients with a glucagonoma require somatostatin analog treatment and nutritional supplementation. Patients with a VIPoma also require somatostatin analog treat-

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ment and intravenous fluid and electrolyte therapy. Insulinoma patients generally require intravenous glucose infusion prior to operation. In patients with localized operable insulinoma, somatostatin analog infusion should only be considered after the effect of this therapy has been electively studied.

Introduction

Preoperative Diagnostic Procedures

Prior to surgery or other interventional treatment in patients with neuroendocrine tumors (NET), the tumor type and hormone production must be assessed in order to provide appropriate treatments as well as to avoid life-threatening crises that may occur due to the presence of hormonal syndromes associated with some of these tumors [1]. In addition, the presence of any triggering factors should be determined.

A low threshold for further cardiac workup should be utilized in patients with the carcinoid syndrome, employing NT-proBNP measurements and echocardiography, or cardiac magnetic resonance imaging, since the reported incidence of different grades of cardiac involvement could be as high as 50% [2]. However, more recent studies suggest that the prevalence of carcinoid heart disease (CHD) has decreased during the last decades to about 20%, probably due to the use of somatostatin analogs [3].

Carcinoid Syndrome: Pre- and Perioperative Therapy

Carcinoid Syndrome

NET of the small intestine are the most common causes of the carcinoid syndrome that occurs in 20–30% of patients with liver metastases from these NET. The classical (typical) carcinoid syndrome is usually characterized by cutaneous flushing, gut hypermobility with diarrhea and bronchospasm with wheezing and shortness of breath [4]. The syndrome is occasionally also encountered in patients with large lymph nodes, peritoneal, ovarian lesions (primary or metastases) or bronchial carcinoids, where secretory products exceed the capacity of inactivation by the liver, or bypass the liver being released directly into the systemic circulation [5, 6]. Preoperatively, patients with small intestinal NET need to be carefully evaluated and treated for manifestations of the carcinoid tumor, paying particular attention to reveal previously unnoticed diarrhea or flushing, and incipient CHD, and in such cases protective actions should be taken to prevent a carcinoid crisis during surgery [7, 8]. Patients with or without carcinoid syndrome may present with large desmoplastic fibrotic reactions of the peritoneum usually around the involved lymph nodes, which may cause obstructive associated symptoms.

Preoperative Fluid Electrolyte, Vitamin, and Protein Abnormalities

Diarrhea in patients with carcinoid syndrome may cause dehydration, electrolyte abnormalities, and hypoproteinemia [7, 8]. In the presence of carcinoid syndrome, the essential amino acid tryptophan is converted to serotonin, leaving inadequate amounts of tryptophan for conversion to niacin and proteins, which contributes to hypoproteinemia [8]. Niacin deficiency may cause pellagra, with dermatitis, diarrhea, and dementia [9]. In addition, deficiencies of other fat-soluble vitamins, following prior treatment with somatostatin analogs, should be looked for and adequately substituted [10]. Patients with severe diarrhea, weight loss and hypoproteinemia require parenteral nutrition with adequate supplementation before surgery is undertaken.

Carcinoid Heart Disease

CHD occurs in more than half of the patients with carcinoid syndrome, with serotonin being an important mediator [11–13]. However, it can remain undiagnosed as shown in a recent study of 150 patients with carcinoid syndrome, of whom 37% with CHD exhibited no physical signs [14].

Fibrotic plaques affect the valves and cavities of the right ventricle, with thickening of valvular leaflets and shortening of the chordae tendineae, resulting in tricuspid regurgitation and pulmonary stenosis. Tricuspid valves have been affected in 95% of patients, while pulmonary valves have been less frequently involved. Left-sided valvular lesions are rare because mediators are cleared or inactivated in the lungs before reaching the left side of the heart, but can occur due to patent foramen ovale, lung tumors or overwhelming disease. Concomitant mitral and aortic regurgitation has occasionally been demonstrated [12, 13]. A 5-hydroxyindoleacetic acid (5-HIAA) level of ≥300 μmol/24 h and ≥3 episodes of flushing per day are considered to be independent predictors of the development or progression of CHD [3]. It has recently been suggested that plasma 5-HIAA measurements could also serve as an additional tumor marker that could potentially ameliorate the need of urinary 5-HIAA measurements [15].

Diagnosis of CHD is difficult, and cardiac symptoms do not appear until late stages of the disease. Diagnosis of CHD requires 2-dimensional echocardiography and Doppler examination to assess the severity of valvular stenosis and regurgitation (CHD guidelines) [13]. Moreover, NT-proBNP has been shown to exert a high sensitivity and specificity (87 and 80%, respectively) in predicting CHD and it has also been shown to correlate with patient survival [16]. Severe tricuspid regurgitation also strongly correlates with poor survival in patients with carcinoid syndrome.

In patients with carcinoid valvular heart disease, morbidity from abdominal operation is markedly increased. CHD poses 2 distinct challenges for the anesthesiologist: carcinoid crisis and low cardiac output syndrome secondary to right ventricular failure [17]. Patients may have incipient cardiac failure and be poor candidates for surgery, or they may fail to recover after operation. Moreover, right-sided heart failure increases central venous pressure and may markedly increase the risk of bleeding, from hepatic veins, especially during liver surgery [13]. Echocardiography should be done in all patients with the carcinoid syndrome, and patients with moderate CHD should always be discussed with cardiologists before surgery. In case of significant heart disease, a cardiothoracic surgical evaluation and possible surgical valvular replacement may be required before major abdominal operation [13, 17, 18].

Reconstructive valve replacement surgery has been reported to be of obvious value for patients with advanced heart disease and right ventricular failure, with low mortality in young patients but high risk in patients older than 60 years of age [11, 19, 20]. However, in a recent meta-analysis, age was not found to be a contributing factor of higher mortality [21]. During cardiac surgery, risks for carcinoid crisis may be high because patients often require vasoactive medication to support the circulatory system, which may trigger carcinoid crisis [2]. In a series of 22 patients who underwent valve replacement, 4 died within 30 days postoperatively and in 1 of them carcinoid crisis was the main cause of death [3]. There is still controversy regarding the use of vasoconstrictor amines in case of hypotension as there are several reports in favor of and against their use [7, 8, 19]. However, approximately 90% of 11 patients who underwent valvular replacement and received inotropic agents to wean them off, cardiopulmonary bypass did not experience any symptomatic exacerbation while being on concomitant octreotide cover [17]. In addition, patients pretreated with long-acting somatostatin analogs required higher doses of octreotide infusions (median 320 vs. 750 µg) [17].

Carcinoid Crisis

Patients with carcinoid syndrome are at risk for developing a carcinoid crisis during either minor or major surgery or other types of intervention, such as arterial embolization, radiofrequency ablation, endoscopic procedures, diagnostic procedures or treatment with peptide receptor radionuclide therapy [7, 8, 22–25]. The presence of CHD and high 5-HIAA levels have been shown to represent predictors of an emerging carcinoid crisis [26]. Patients undergoing such procedures or minor operations should be carefully assessed for the presence of such risks and relevant therapeutic interventions should be utilized if required. The crisis may also be provoked by severe emotional stress, induction of anesthesia during ravage of the abdomen, or as a result of tumor manipulation or tumor necrosis during surgery or intervention [27].

Patients with carcinoid crisis may have sudden changes in blood pressure, most often hypotension, sometimes combined with prolonged and excessive flushing, hyperthermia, and occasional bronchospasm. Some may have attacks of hypertension and occasional hypertensive crisis due to tumor release of catecholamines [28–30]. Patients with large tumor load, high chromogranin A levels, or high urinary 5-HIAA values are more likely to experience a carcinoid crisis during surgery; however, not all of these risk factors have consistently been confirmed [2]. Catecholamines released from the adrenals or sympathetic neurons are thought to contribute to the release of tumor products, and thus appropriate pain relief can reduce the stress response [7, 8, 27]. This is particularly important as intraoperative hypotension may occur in both functioning and apparently nonfunctioning tumors with the most important predictor being the presence of hepatic metastases [27].

Sometimes the crisis complication presents with vague symptoms, and patients continue to be unstable postoperatively, or fail to recover after surgery, which emphasizes the importance of being aware of an undiagnosed carcinoid crisis, possibly reversible with appropriate treatment [31]. Previous treatment with long-acting somatostatin analogs aims at controlling the excessive hormonal output and symptoms related to the carcinoid syndrome and prevent a carcinoid crisis. In some cases, addition of ondansetron may help control the diarrhea [32].

The ideal scheme and dosing of octreotide to prevent the development of a carcinoid crisis have not been clearly established [27, 31]. Acute intravenous administration of octreotide has been reported to provide rapid reversal of a carcinoid crisis, and the current focus of carcinoid

therapy is to prevent mediator release with octreotide prophylaxis [2, 7, 8, 18, 22, 26, 31]. This has largely replaced the use of other drugs for acute treatment. If patients already receive long-acting somatostatin analogs, these medications should continue. However, as intraoperative carcinoid events are not easily predicted, there is no standard octreotide administration regimen and various schemes have been proposed [2]. It has been suggested that for minor procedures or lower-risk patients, a reasonable scheme is the subcutaneous administration of octreotide 100–200 μg 2–3 times/day during surgery [2]. However, as a carcinoid crisis can also be induced even with minor surgical procedures, intravenous octreotide infusions should also be readily available to be used when necessary. For elective intra-abdominal or other major operations, the administration of octreotide 100 μg 3 times/day subcutaneously for 2 weeks has been suggested prior to surgery [2, 33]. However, intravenous octreotide is currently considered the most preferable mode of administration [31]. With acute operations, octreotide is beneficial even if given for only 24 h before surgery, since this may achieve adequate suppression of basal amine and peptide levels [34]. However, a single dose of 500 μg of octreotide was shown not to be sufficient to inhibit perioperative complications as well as previous treatment with somatostatin analogs [27]. Perioperative prophylactic treatment with intravenous octreotide, at a starting dose of 50–100 μg/h (mean dose 100–200 μg/h) is currently used by most centers as an appropriate regimen and shown to successfully prevent crisis during major surgery with little side effects in some studies [7, 8]. Although this has not been substantiated by any prospective study, most experts initiate treatment with intravenous octreotide 12 h before escalating the dose as necessary until symptom control and continued at least 48 h after the operation with dose titration as required. Some patients may still have symptoms and require additional intravenous octreotide and doses up to 500 μg/h have been administered [2, 31]. A study that formally assessed the efficacy of octreotide in preventing carcinoid crisis has found that intraoperative complications (e.g., flushing, sustained hypotension, bronchospasm, acidosis [pH <7.2], and ventricular tachycardia) developed in 11% of patients who did not receive the medication compared to none of those who received intraoperative octreotide ($p = 0.023$). In addition, a recent meta-analysis has suggested that patients pretreated with somatostatin analogs (mainly octreotide) may require even higher doses [31]. However, although octreotide is of proven value in preventing and treating carcinoid crisis, the current literature relies on small sample size studies and relatively low quality of data. In addition, the inconsistent use of the term carcinoid crisis and the paucity of reported articles preclude the adaption of a universally accepted octreotide dosing scheme [2, 31].

Atypical Carcinoid Syndrome

A less common atypical carcinoid syndrome may be encountered in patients with tumors originating from the foregut including mostly the lung, but also the stomach and duodenum [6, 35]. The syndrome consists of patchy, intensely red flush, sweating, itching, sometimes also cutaneous edema, bronchoconstriction, salivary gland swelling, lacrimation, and cardiovascular instability mainly manifested as hypotension [6, 35]. It is usually encountered in patients with liver metastases and is due to the release of both histamine and serotonin. Patients with the atypical carcinoid syndrome have a decarboxylation deficit and therefore only seldom have excess urinary excretion of the serotonin metabolite 5-HIAA [6, 36]. Urinary estimates of the histamine metabolite methylimidazole acetic acid may serve as a tumor marker [22, 36]. Cytoreductive surgery or hepatic artery embolization may occasionally be contraindicated due to the risk of uncontrolled release reactions.

In the presence of an atypical carcinoid syndrome, the patients should be treated with octreotide before and during surgery or intervention [6, 35] (see Atypical Carcinoid Syndrome). Patients with the severest reactions (e.g., mainly patients with lung carcinoids) may require higher doses of octreotide (100–200 μg/h) and sometimes also saline infusion [6, 35]. Histamine-liberating substances like morphine or tubocurarine and adrenergic drugs should be avoided during anesthesia as they may cause further histamine release and lead to the development of hypotension [2]. Combination with H_1 receptor blockers (loratadine) and H_2 blockers (ranitidine) is recommended in the presence of severe symptoms, and sometimes also cortisone (dexamethasone), since histamine release and its peripheral actions may not be blocked by somatostatin analogs [6, 36].

Specific Recommendations Concerning Anesthesia
Premedication

Premedication is focused on relieving existing symptoms and preparing for a potential carcinoid crisis [37]. All patients' maintenance medications should be continued and benzodiazepines and antihistamines could be used to decrease anxiety and stress [7]. Monitoring the central venous pressure may aid in fluid management,

but interpretation may be difficult in the presence of CHD with tricuspid regurgitation or pulmonary stenosis [7, 8]. As rapid blood pressure changes are commonly encountered in such patients, invasive monitoring is typically required; it is started before the induction of anesthesia and maintained throughout the procedure [2]. Arterial catheter monitoring is considered for major surgery since the hypotension seen with induction agents may trigger a carcinoid crisis [38]. Accurate airway pressure monitoring is necessary to rapidly detect the onset of bronchospasm whereas continuous temperature monitoring and warming devices are needed as hypothermia could trigger a carcinoid crisis [2].

Drugs that stimulate the sympathetic nervous symptoms or cause histamine release such as morphine and *d*-tubocurarine should be avoided [33]. Propofol, thiopental sodium, and etomidate have been used to induce anesthesia. Propofol has a more profound effect in suppressing catecholamine release and may be the best agent in patients with carcinoid syndrome as long as hypotension is avoided [39]. Furthermore, only nondepolarizing neuromuscular blockers that do not cause histamine release should be used [7]. Due to its cardiovascular stability, vecuronium and rocuronium can be safely used [2]. Safe use of succinylcholine has also been documented. During maintenance of anesthesia, special attention should be paid to avoid right ventricular overload and strain to prevent right ventricular failure and the development of cardiovascular alterations that mostly present as blood pressure and heart rate instability rather than rhythm abnormalities [2, 7].

Hypotension is the most common problem during anesthesia, but in this situation sympathomimetic drugs should be avoided, since they may worsen hypotension by triggering further release of peptides. However, this view is not widely accepted as several reports have shown that the use of inotropic agents along with octreotide can restore the cardiovascular instability [2, 27]. Hypotension tends to occur when large bulky metastases are manipulated and in such instances stopping the procedure until hemodynamic control is restored is a simple maneuver [7, 8]. Intravenous octreotide can correct hypotension within 10 min and thereafter, and is used in combination with volume expanders.

Hypertension is also treated by prevention of peptide release with octreotide, and by increasing the depth of anesthesia. Bronchospasm can occasionally be severe, and since β-receptor agonists and theophylline may precipitate mediator release and worsen bronchospasm, they should be used with extreme care [7, 8]. Octreotide may

be used for the release of bronchospasm, and steroids (dexamethasone) may still have a role in such patients. Flushing may occur and may in itself not be problematic but it is a warning of potential cardiovascular instability, and indicates increased requirement of octreotide. Recovery from anesthesia may also be substantially delayed [27, 40].

Postoperative Period

Preoperative treatment with octreotide should continue and should cease slowly over the first postoperative week rather than stop abruptly. Hypovolemia and pain causing sympathetic stimulation should be avoided in the postoperative period. Non-histamine-releasing opioids such as fentanyl have been used with no adverse effects for postoperative analgesia. Endocarditis prophylaxis may be required if significant carcinoid-induced valvular heart disease is present, although this approach is still a matter of debate [41]. Epidural and spinal anesthesia have been successfully used in patients with carcinoid tumors mainly undergoing noncarcinoid surgery [42]. Care should be taken to evaluate and premedicate these patients adequately, as hypotension may commonly occur with these techniques [2].

Pancreaticoduodenal NET: Pre- and Perioperative Therapy

Among patients with pancreaticoduodenal NET, preoperative and prolonged postoperative treatment with adequately high dosed proton pump inhibitors (PPIs) is needed for patients with gastrinoma mainly to prevent gastrojejunal bleeding, and perioperative glucose monitoring is used to avoid hypoglycemia in patients with insulinoma. Patients with glucagonoma require somatostatin analog treatment and nutritional supplementation to heal the skin lesion prior to surgery, and perioperative anticoagulation to prevent thrombosis. Patients with VIPoma need to be resuscitated with preoperative somatostatin analog treatment and intravenous fluid and electrolyte therapy before being subjected to surgery [1, 6].

In some studies, perioperative somatostatin or somatostatin analog treatment has been demonstrated to result in a significant reduction in the pancreatic fistula rate after elective pancreatic surgery, without having an influence on postoperative mortality [43]. Octreotide 100–200 μg subcutaneously 3–4 times/day for 6–8 days may reduce the risk for fistulation and minimize leakage after a difficult resection or enucleation of endocrine pancreatic

tumors, but may not be routinely required. However, recent prospective trials showed that such an approach had no effect [44, 45]. If somatostatin has been used, it should be weaned slowly rather than discontinued abruptly. Patients subjected to splenectomy in association with removal of an endocrine pancreatic tumor are given vaccinations against meningococcus and *Haemophilus influenza* and Pneumovax the day prior to hospital discharge to prevent postsplenectomy sepsis.

Gastrinoma

Gastrinomas are predisposed to gastrointestinal perforation and hemorrhage, which may cause death after pancreaticoduodenectomy. During and 3 months after surgery, patients need adequately high doses of PPIs to efficiently control the acid hypersecretion that persists even after removal of the primary tumor mainly by residual hypertrophy of gastric mucosa [46]. The dose of antisecretory drug is titrated to reduce the acid hypersecretion to ≤10 mEq/h, or to lower values in patients with previous acid-reducing surgery or severe reflux disease. High initial doses of PPIs (such as 60–80 mg/day of omeprazole) are frequently prescribed, with dose adjustment as necessary based on symptom response. In the acute setting where oral medications may be contraindicated, intravenous formulations are effective. A starting dose of 80 mg of pantoprazole given by a 15-min infusion every 8 h was recommended because it controlled gastric acid hypersecretion in all Zollinger-Ellison syndrome patients studied both acutely and up to 7 days [47]. However, many specialized pancreatic centers preconize to treat patients with high doses of PPIs following 1–3 months after pancreaticoduodenectomy. Octreotide can be used to treat Zollinger-Ellison syndrome but it does not add significantly to the acid-reducing effect of PPIs, which is the preferred medication [48]. Patients should maintain their medication with PPIs for some weeks after surgery since many continue to hypersecrete acid for some time [49].

Insulinoma

Preoperative diazoxide treatment is sometimes used to control hypoglycemia prior to operation, but may cause severe fluid retention and edema in some patients. It is generally not recommended prior to surgery for benign insulinoma. Patients with insulinoma and significant hypoglycemia should preferably be submitted to surgery without delay, and without diazoxide. At times of hypoglycemia, dextrose administration, intramuscular glucagon, and potassium replacement may be required as a res-

cue procedure. Patients with severe hypoglycemia may require intravenous glucose infusion on the night prior to operation to avoid risk of unrecognized hypoglycemia [50]. In the operating room, glucose is removed from the intravenous solution to allow glucose monitoring with a rise in glucose anticipated within minutes to an hour after insulinoma resection [50]. Small doses of insulin may be required during the first postoperative days. After surgery for large insulinomas, patients may need glucose infusion as insulin effects may still prevail for some time, and blood glucose levels should be monitored. Preoperative octreotide infusion should only be considered after the effect of this therapy is electively studied. In some insulinoma patients, octreotide infusion might lead to more severe hypoglycemias by suppression of the contraregulatory hormones. It is claimed that only in half of the non-metastatic or benign insulinomas might octreotide have a positive effect [51].

Glucagonoma

Glucagonoma patients may have troublesome skin disease and some patients may be cachectic. Somatostatin analog treatment, amino acid infusion, and antibiotics may improve the condition and heal the skin lesion before surgery [52]. Patients have substantial risk for deep vein thrombosis and pulmonary embolism, and should perioperatively receive prophylactic high-dose molecular heparin as anticoagulation treatment [53].

VIPoma

In VIPoma patients, secretory diarrhea is generally extensive, with severe loss of potassium and bicarbonate leading to metabolic acidosis, dehydration, and hypokalemia [52]. Patients need to be resuscitated from life-threatening fluid losses and electrolyte abnormalities with somatostatin analog treatment, as well as intravenous and electrolyte therapy, before being subjected to surgery.

Syndromes Related to Ectopic Hormonal Secretion

Occasionally the substances secreted by gastrointestinal NET are not directly related to the tissue of origin and the corresponding clinical syndromes are related to these ectopically secreted compounds [54]. Appreciation of the presence of such syndromes is highly relevant, because if the clinical presentation is not identified, it may delay the diagnosis of the underlying neoplasia and lead to increased morbidity and mortality. Some of these syn-

dromes, such as Cushing syndrome due to ectopic adrenocorticotrophic hormone and hypercalcemia due to ectopic parathyroid hormone-related peptide secretion, may markedly increase the operative risk and need to be adequately treated prior to any intervention [54]. In patients with uncontrolled hormonal syndrome due to ectopic hormone secretion, hepatic artery embolization or chemoembolization and/or debulking surgery can be discussed.

Adrenocorticotrophic hormone secretion leading to Cushing syndrome has mostly been encountered with lung NET, but can occasionally be seen with gastrointestinal tumors [54, 55]. Drugs aiming at controlling the hormonal secretion, either at the tumor level (somatostatin analogs, cabergoline), the adrenals (metyrapone, ketoconazole, O,p′-DDD) or rarely the glucocorticoid receptor, markedly reduce the operative risk, which may be considerably high if the hypercortisolism remains untreated [56]. In refractory cases, intravenous etomidate has successfully been used but requires intensive monitoring [57]. Hypersecretion of parathyroid hormone-related peptide by metastatic NET seems to be exclusively associated with metastatic pancreatic NET and has a major clinical impact because poorly controllable hypercalcemia is associated with increased morbidity and mortality [58]. In such cases and other more rare syndromes, early diagnosis and management are essential [54].

Minimal Consensus Statement on Preoperative Evaluation and Therapy

Preoperatively, patients with NET and carcinoid syndrome need to be carefully evaluated. Patients with severe diarrhea, weight loss, vitamin deficiencies, and hypoproteinemia require parenteral nutrition and adequate supplementation for reversal of fluid, electrolyte, vitamin and protein abnormalities, before major surgery is undertaken. Patients with carcinoid syndrome should be examined with echocardiography and NT-proBNP measurement to diagnose the possible presence of incipient CHD prior to abdominal surgery. Even patients with moderate CHD should be discussed with cardiologists before surgery as symptoms may be absent in a significant number of patients. In case of significant heart disease, a thoracic surgical evaluation and possible surgical revision of valvular heart disease should be considered before major abdominal operation, especially liver resection, is undertaken.

Minimal Consensus Statement on Perioperative Prophylaxis and Treatment to Prevent Carcinoid Crisis

Patients with carcinoid syndrome should receive octreotide prophylaxis to prevent the development of carcinoid crisis during surgery. Patients with CHD and/or high 5-HIAA levels are at higher risk. If patients already receive octreotide or other somatostatin analogs, this medication should be continued while awaiting surgery. Patients who have not received octreotide can be given 100–200 µg 3 times/day subcutaneously for 2 weeks prior to surgery. If more acute operation is needed, octreotide is given as an intravenous infusion for 1–2 days before surgery. Perioperative treatment is recommended with intravenous octreotide; infusion is started 12 h before anesthesia at a dose of 50–100 µg/h using dose titration until resolution of the symptoms (mean dose 100–200 µg/h). Remaining symptoms of carcinoid syndrome indicate the need for additional intravenous octreotide. In case of a carcinoid crisis reaction with hypotension during anesthesia, adrenergic drugs should be used cautiously and further octreotide infusion should be given even at doses as high as 500 µg/h. Patients previously treated with somatostatin analogs may require even higher doses.

Minimal Consensus Statement on Recommendation Concerning Anesthesia

Monitoring of central venous pressure is of value during surgery for NET with carcinoid syndrome, but may be difficult to interpret in the presence of CHD with right-sided failure. Preoperative medication and anesthesia should exclude drugs that may stimulate the sympathetic system or cause histamine release. If hypotension occurs, sympathomimetic drugs should be used cautiously, and increased intravenous octreotide should be given. Hypotension is treated by the prevention of peptide release with octreotide, and by increasing the depth of anesthesia. In the presence of bronchospasm, β-receptor agonists should be used with great care or, instead, octreotide is recommended, possibly together with steroids (dexamethasone). Flushing during anesthesia should constitute a warning of cardiovascular instability and indicates increased requirement of octreotide. Preoperative treatment with octreotide should continue and be weaned slowly over the first postoperative week rather than abruptly stopped. Hypovolemia and pain-causing sympathetic stimulation should be avoided in the postopera-

tive period. Non-histamine-releasing opioids such as fentanyl have been used with no adverse effects for postoperative analgesia.

Minimal Consensus Statement on Pre- and Perioperative Management of Pancreaticoduodenal NET

Patients with gastrinoma require treatment with a titrated dose of PPIs before, during and few weeks after the operation to be protected from hypersecretion. Insulinoma patients should be subjected to careful glucose monitoring during and after surgery. Patients with glucagonoma require somatostatin analog treatment and nutritional supplementation to heal the skin lesion prior to surgery, and perioperative anticoagulation to prevent thrombosis. Patients with VIPoma need to be resuscitated with preoperative somatostatin analog treatment and intravenous fluid and electrolyte therapy before being subjected to surgery. A high index of suspicion is required to identify syndromes related to ectopic hormonal secretion prior to surgery and initiate appropriate treatment.

Appendix

Other Antibes Consensus Conference Participants
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