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Review Article

Anesthetic Management of Patients With Carcinoid Syndrome and Carcinoid Heart Disease: The Mount Sinai Algorithm

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THE LAST DECADE has witnessed significant breakthroughs in diagnosis and management of neuroendocrine carcinoid tumors. This field is currently one of the most dynamic areas of gastroenterology[1] with an increasing number of clinical trials, a rapid availability of novel agents, and a wider range of therapeutic procedures with a greater impact on tumor burden and survival.[2] Major advances in the field include the successful combination of multiple imaging techniques to achieve higher identification rates of primary tumor sites,[3] the new pivotal role of telotristat ethyl,[4] everolimus,[5] and ^{177}Lu-Dotatate[6] in present treatment protocols (Fig 1), and a shift toward a more aggressive interventional and surgical approach. Consequently, preoperative detection rates of primary tumor sites have been demonstrated to be as high as 80%, and progression-free survival in patients with already advanced disease is expected to significantly expand. Among patients with neuroendocrine tumors, survival benefit is going to translate into a need for a broader collection of interventional and surgical strategies.[7] In this context, anesthesiologists and surgeons will be challenged by an unusual variety of clinical conditions and scenarios that may trigger substantial morbidity and mortality, particularly in the setting of carcinoid syndrome (CaS) and carcinoid heart disease (CaHD).[8]

Although CaHD might be the first manifestation of CaS in up to 20% of patients,[9] the presence of cardiac involvement has been traditionally considered as a surrogate of disease progression and advanced CaS.[10] The inherent clinical variability of this entity and the perioperative complications associated with it mandate a rapid diagnosis, an accurate decision-making process, and effective intervention strategies.[11] However, the rarity of the disease has led to a relative lack of strong evidence. In fact, recommendations for the use of certain anesthetic drugs are still based on anecdotal but legitimate experiences reported in the literature.[12] In turn, this has carried a significant variability in opinions regarding the optimal management of these patients.[13] The following is a succinct and practical guidance document on anesthetic management of patient with CaS and CaHD based on a systematic review of the literature and complemented by the authors' institutional experience.

Epidemiology

Neuroendocrine tumors represent 0.49% of all malignancies.[14] They occur in between 2.5 to 5 cases per 100,000 of the

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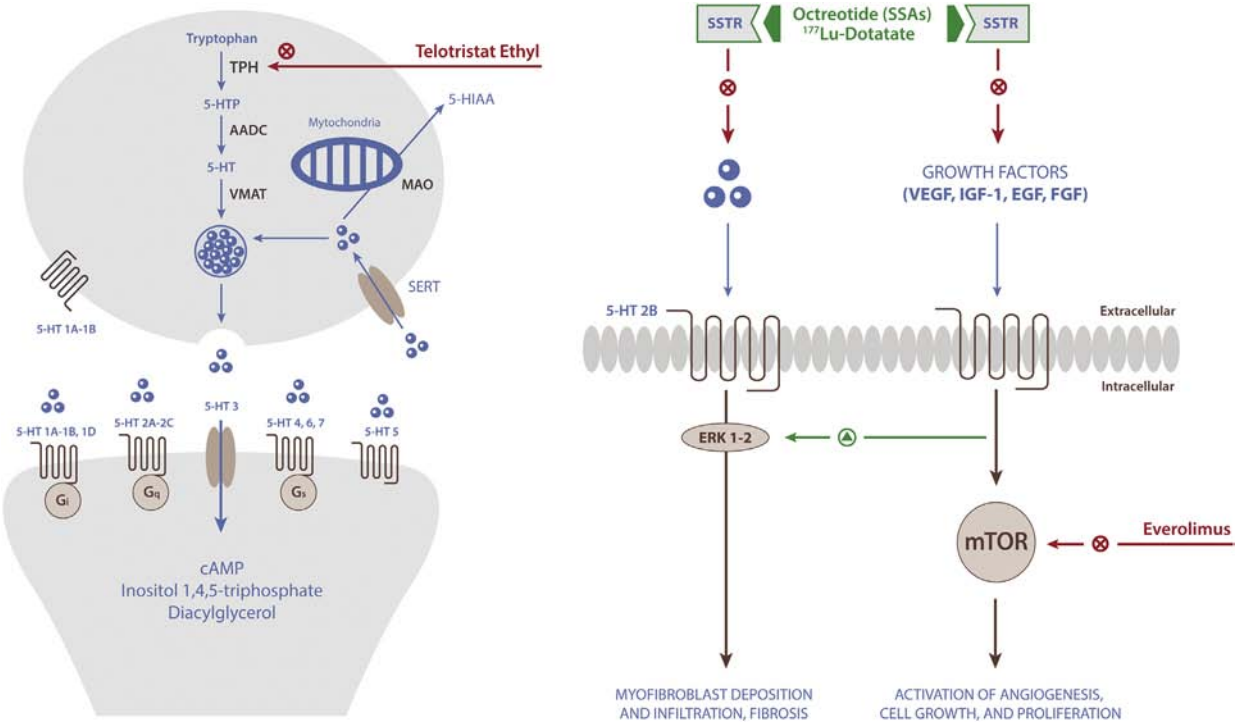

Fig 1. *Left,* Impact of telotristat ethyl on serotonin production, action mechanism, and metabolism. *Right,* Proposed action pathway of octreotide, ^{177}Lu-Dotatate, and everolimus as first line therapies for patients with neuroendocrine tumors, carcinoid syndrome, and carcinoid heart disease (both figures are simplified representations and do not depict the entire enzymatic pathway). AADC, aromatic L-amino acid decarboxylase; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; IGF, insulin growth factor; MAO, monoamine oxidase; mTOR, mammalian target of rapamycin; SERT, serotonin transporter; SSAs, somatostatin analogues; SSTR, somatostatin receptor; TPH, tryptophane hydroxylase; VEGF, vascular endothelial growth factor; VMAT, vesicular monoamine transporter; 5-HIAA, 5-hydroxy-indole-acetic acid; 5-HT, serotonin; 5-HTP, 5-hydroxytryptophan; 5-HTX, serotonin receptor.

population and their incidence is steadily increasing due to imaging sophistication. The most common primary site of neuroendocrine tumors is the gastrointestinal tract (60%), followed by the bronchopulmonary system (27%).[15] Within the gastrointestinal tract, most tumors take origin in the small intestine (34%), followed by the rectum (23%), colon (19%), stomach (8%), and appendix (7%).[16] Although metastatic disease is more frequent in patients with midgut neuroendocrine tumors (up to 75%), around 15% of the patients present with hepatic metastases at diagnosis regardless of the primary site.[17] Metastatic disease allows for the release of vasoactive substances into the systemic circulation and leads to CaS in 30% to 50% of the patients, a constellation of symptoms mainly defined by vasovagal lability and flushing (90%), gastrointestinal hypermotility (70%), abdominal pain (35%), CaHD (30%), and bronchospasm (15%). Although CaHD has been observed in up to 60% of patients with CaS, recent reports have suggested an incidence decline to 20%, potentially due to a more liberal use of somatostatin analogs and the introduction of new antitumoral therapies.[18] Direct myocardial carcinoid metastasis has been seen in 4% of patients[19] (Table 1).

Pathophysiology of Carcinoid Heart Disease

Midgut neuroendocrine tumors are mostly indolent. Symptoms often result from mechanical complications such as gastrointestinal obstruction or bleeding, or from their unique capacity of synthesizing, storing, and releasing large amounts of bioactive substances like serotonin into the systemic bloodstream.[20] In healthy subjects, serotonin is mostly recaptured, inactivated, and metabolized to 5-hydroxyindolacetic acid by the hepatic monoamine oxidase for subsequent renal clearance.[21] In the presence of hepatic metastases, metastatic functional foci secrete copious amounts of serotonin that will

Table 1
Epidemiology of Carcinoid Syndrome and Carcinoid Heart Disease

Hepatic metastases at diagnosis of a neuroendocrine tumor (%)	15
Incidence of carcinoid syndrome (%)	30-50
Incidence of carcinoid syndrome without hepatic metastases (%)	5
Cutaneous flushing in patients with carcinoid syndrome (%)	90
Gastrointestinal hypermotility in patients with carcinoid syndrome (%)	70
Historical incidence of carcinoid heart disease (%)	40-50
Contemporary incidence of carcinoid heart disease (%)	20
Progression to carcinoid heart disease (years)	1.5
Male to female (ratio)	1:2
Mean age at diagnosis (years)	60
First manifestation of carcinoid syndrome (%)	20
Left-sided heart involvement (%)	10
Myocardial metastases (%)	4
Survival of patients at 3 years (%)	30
Current mean survival of patients who have received cardiac surgery (in years)	4

NOTE. Some of the numbers have been appropriately rounded for easier recollection.

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