The carcinoid syndrome is a result of the release of multiple carcinoid tumor factors, particularly serotonin, kinins, and histamine. These factors cause flushing, hemodynamic instability, right-sided heart disease, bronchospasm, and gastrointestinal symptoms. A thorough preoperative assessment concentrating on these areas is necessary. The use of invasive monitors perioperatively, with the avoidance of drugs and techniques that can exacerbate the syndrome, is beneficial. Octreotide, both prophylactically and acutely, provides the best medical therapy available.

Key words: Carcinoid syndrome, carcinoid tumor, octreotide, serotonin.

Background
Carcinoid tumors are rare, slow-growing neoplasms capable of metastasizing, predominantly to the liver. These tumors originate from enterochromaffin cells (neuroendocrine) and as such are capable of secreting bioactive substances. If the bioactive substances reach the systemic circulation without first being metabolized in the liver, they are capable of producing the carcinoid syndrome. This lack of metabolism results from hepatic metastases and/or primary tumors that do not drain into the portal system. Carcinoid tumors are associated with multiple endocrine neoplasms.

The majority of the carcinoid tumors are located in the submucosa of the bronchial tree and gastrointestinal (GI) tract. While the most common sites for carcinoid tumors are the appendix, rectum, and ileum, they can also be located in the genitourinary tract, thyroid, and breast. These cancers have an incidence of approximately 1 to 10 per 100,000 persons, with approximately the same incidence among men and women and proportionally similar rates between blacks and whites.¹

The neoplasms tend to be found in a bimodal distribution, occurring in patients between 25 and 45 years old and in patients older than 60 years of age. The overall 5-year survival rate is 80%, ranging from 99% for patients with appendiceal tumors to 33% for those with tumors of the sigmoid colon. With the presence of distance metastases, the 5-year survival drops to 18%.²

Patients with carcinoid tumors can undergo surgery for a variety of indications. Curative procedures are most often performed on tumors located within the bronchus, ovary, or testis, because these tumors tend to spread locally, without distant metastases. Also, carcinoid tumors that release bioactive substances directly into the systemic circulation tend to produce early symptoms, resulting in early detection.

The majority of patients with carcinoid tumors undergo palliative procedures with some requiring debulking of the tumor, or relief of GI obstruction, or both. Patients with hepatic metastases may undergo hepatic artery embolization, the rationale being that the carcinoid metastases require the arterial blood supply while the liver can survive on portal venous blood alone. Surgery to remove isolated hepatic metastases may be performed, since it
is these hepatic metastases that produce the majority of the symptoms.

Many patients with carcinoid syndrome have involvement of the right side of the heart, requiring repair or replacement of the tricuspid or pulmonary valve. Incidental surgeries, typically associated with the two age brackets, also occur. For instance, in the 25 to 45-year-old group, trauma, cesarean sections, and appendectomies (carcinoid tumors of the appendix can mimic appendicitis) are common. In the older population, transurethral resection of the prostate and vascular surgery are common.

Carcinoid syndrome

The carcinoid syndrome occurs when the secreted bioactive substances produced by the carcinoid tumor are not metabolized by the liver. This occurs when the tumor has produced hepatic metastases, releasing factors into the circulation distal to the liver. It also occurs with certain tumors that do not drain into the portal circulation, e.g., those of bronchial, ovarian, or testicular origin. As a result, only 5% of all carcinoid tumors will actually produce the symptoms associated with the syndrome. Attacks can be brought on by stress, physical activity, or eating foods high in serotonin, such as bananas. A point to note is that during surgical manipulation of the tumor, large amounts of bioactive substances can be released, exceeding the ability of the liver to clear, thus producing symptoms. The pulmonary circulation is also apparently able to clear these bioactive substances explaining why the left heart is usually free of involvement (except for bronchial tumors).\(^3\)

Pathophysiology

Clinical manifestations of carcinoid syndrome are listed in Table I. The most common signs and symptoms involve the vascular and gastrointestinal systems. The majority of patients experience an episodic cutaneous flushing of the head and neck. They usually have very labile blood pressure, but the variation in pressure may not coincide with the flushing. The most common GI symptom is diarrhea. The cardiac manifestations result from fibrous tissue growth within the endocardium, stimulated by the bioactive secretions. Since the pulmonary system can effectively remove the bioactive substances, typically only the right side of the heart is affected. The most common valvular lesions are tricuspid regurgitation and pulmonary stenosis. The fibrotic tissue can also interrupt the electrical conduction pathways, contributing to the development of arrhythmias.\(^4\) When a bronchial tumor is present, left-sided heart lesions, pulmonary hypertension, and bronchospasm can result. Serotonin synthesis, which normally uses 1% of the body's supply of tryptophan, can use up to 60% of the available tryptophan. This may result in proteinemia and pellagra-like symptoms, since niacin production, which requires tryptophan, is especially curtailed.

These manifestations occur as a result of approximately 20 bioactive substances, most of which are listed in Table II. The three major bioactive factors appear to be kinins; 5-hydroxytryptamine (5-HT), better known as serotonin; and histamine.

<table>
<thead>
<tr>
<th>Table I</th>
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<tr>
<td>Clinical manifestations</td>
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<tr>
<td>Vasomotor—incidence 80%</td>
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<td>Cutaneous flushing, hypertension, and hypotension</td>
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<tr>
<td>Gastrointestinal hypermotility—incidence 80%</td>
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<tr>
<td>Diarrhea, cramps, nausea, vomiting</td>
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<tr>
<td>Cardiac involvement (right-sided lesion)—incidence 40%</td>
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<tr>
<td>Pulmonic and tricuspid fibrosis</td>
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<tr>
<td>Tachyarrhythmias</td>
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<tr>
<td>Pulmonary—incidence 20%</td>
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<tr>
<td>Bronchospasm, hypertension</td>
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<tr>
<td>Altered tryptophan metabolism</td>
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<tr>
<td>Pellagra, especially dermatosis</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Hepatomegaly</td>
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<tr>
<td>Proximal myopathy</td>
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<td>Glucose intolerance</td>
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Serotonin appears to be the most important. It is synthesized from tryptophan and metabolized to 5-hydroxyindoleacetic acid (5-HIAA) and excreted in the urine (Figure 1). Elevated levels of urinary 5-HIAA provide a marker of excessive serotonin production and hence the presence of a carcinoid tumor.

There are at least three types of serotonin receptor sites within the body.\(^3\) The 5-HT\(_1\) receptor is located on the following:

1. Vascular endothelium, producing vasodilation through release of prostaglandins and endothelial-derived relaxing factor.
The plasma kinins are the most potent endogenous vasodilators known (10 times the potency of histamine). They increase capillary permeability, produce edema, flushing, diarrhea (tachykinin), and bronchospasm.

In addition to the kinins and histamines, catecholamines and gastrin are important because of their ability to stimulate release of other major factors involved in the carcinoid syndrome, and their presence needs to be considered in the diagnosis and treatment of carcinoid syndrome. The syndrome can present with a variable clinical picture for a combination of reasons. The tumors are capable of secreting differing proportions of the 20 bioactive factors and can alter these proportions over time. The metastases can secrete different factors than the primary tumor. During surgery, the release of bioactive factors can be altered. Anesthetic agents can mask the clinical manifestations of some factors, while exacerbating others.

**Diagnosis**

The metabolite of serotonin is excreted in the urine. Urinary 5-HIAA levels greater than 25 mg per 24 hours are considered diagnostic (normal levels are less than 10 mg per 24 hours). More recently, the pentagastrin challenge test has taken advantage of the ability of gastrin to stimulate the release of the other bioactive substances. After drawing a basal level of 5-HT in peripheral blood, pentagastrin (0.6 μg/kg) is given intravenously. Blood samples are drawn at 1, 2, and 5 minutes, and serotonin levels are estimated by using liquid chromatography and electrochemical analysis. A positive challenge test produces increases in plasma 5-HT and substance P levels and should not precipitate additional symptoms other than flushing. Both tests can be used also to monitor the response of the syndrome to medical management.

**Treatment**

The first line of therapy for carcinoid syndrome is focused on the ability of somatostatin (an inhibitory peptide) to antagonize and suppress the release of the tumor products. Somatostatin binds to specific surface receptors of the tumor cells, which eventually decreases cyclic adenosine monophosphate, resulting in decreased secretion. Because somatostatin has a short half-life (2 to 3 minutes), a synthetic analog, octreotide acetate (Sandostatin®, 1 mcg/kg/hour subcutaneously [SQ] and 50 minutes intravenously [IV]) is used clinically. Octreotide is a treatment for acromegaly, insulinoma, and acquired immune deficiency syndrome-related diarrhea. Octreotide is a convenient drug to use, as it can be stored refrigerated for 3 years and costs...
approximately $5.00 (United States) for 100 μg. Major side effects are pain on injection, biliary stasis, hepatic dysfunction, altered glucose regulation, and GI upset. As a maintenance drug, octreotide (50 to 100 μg SQ, 1 to 3 times daily, maximum dose of 600 μg/day) improves flushing, diarrhea, bronchospasm, and hemodynamic stability. During carcinoid crises (profound hypotension and associated flushing that are unresponsive to fluid, calcium, phenylephrine, and epinephrine), octreotide (100-200 μg IV) can be effective.

Octreotide provides a nonelective approach for the treatment of the carcinoid syndrome by inhibiting the release of the bioactive substances. Other treatment modalities consist of blocking the receptor sites of the various factors, and for this older nonspecific serotonin antagonists have been used. Of these, cyproheptadine hydrochloride (Periactin®) appears beneficial in relieving diarrhea. Ondansetron hydrochloride (Zofran®), a new antiemetic agent, is a 5-HT₃ specific antagonist that has been reported effective in treating the flushing, diarrhea, and nausea in patients with carcinoid syndrome and has also been reported to alleviate pruritus. Ketanserin, an investigational drug, is a peripheral 5-HT₂ receptor antagonist, with affinity also at H₁, alpha₁, and dopamine receptors. It has been used to treat the hypertension and bronchospasm associated with the carcinoid syndrome. Other 5-HT antagonists (e.g., methysergide and droperidol) have been used to decrease the effects of serotonin.

H₁ and H₂ antagonists have been used prophylactically to minimize the effects of histamine release, but the H₂ blocker may provide little additional benefit over using just an H₁ blocker. However, for patients receiving an H₂ blocker, coverage with the H₁ antagonist is recommended to avoid the potentially unopposed H₁ stimulation.

Corticosteroids have been used because of their ability to inhibit the kinin (kallikrein) system and to stabilize lysosomal membranes. Similarly, aprotonin (Trasylol®), a serine protease inhibitor, also inhibits kinin synthesis by preventing conversion of kallikrein. Since aprotonin is a relatively expensive drug, the cost-benefit ratio limits its prophylactic use.

**Preoperative assessment and workup**

Preoperative evaluations should focus on the control of the associated signs and symptoms and assessment of which organ systems are involved. A patient, newly diagnosed with carcinoid syndrome, should be medically treated with octreotide in the intensive care unit for 4 to 6 days prior to surgery. A patient already being treated can be hospitalized prior to surgery, but does not need to be admitted to the intensive care unit. These latter patients may require an increase in their baseline medications because of the increased stress levels associated with impending surgery. The new patients should have an endocrinology consultation to assess electrolytes and hormonal status and to ensure adequate medical control of the syndrome prior to surgery. The patient should be asymptomatic after adequate treatment with octreotide, and the pentagastrin challenge test may be used to assess the effectiveness of therapy.

A cardiology consultation is recommended to determine the extent of right-sided heart involvement (the left side of the heart also, if a bronchial tumor is present), and this can best be done using echocardiography. The echocardiographic evaluation can also assess hemodynamic stability and volume status.

A pulmonary system should be evaluated for potential bronchospasm and its response to therapeutic intervention. In addition, the presence of a bronchial carcinoid tumor suggests the potential for hemoptysis and pulmonary hypertension. Hepatic function is important to assess since the presence of the carcinoid syndrome usually implies that metastases to the liver have occurred. Renal function may be impaired because of ischemia secondary to renal vasoconstriction.

**Anesthetic implications**

The patient with carcinoid syndrome should receive octreotide (100 μg, subcutaneously) 1 hour prior to surgery. Current practice suggests that octreotide with a small amount of benzodiazepine for sedation may provide adequate preoperative coverage. However, hydrocortisone, H₁ and H₂ blockers, droperidol, and aprotonin have also been used as premedicants. An arterial line and a central line should be used to help monitor electrolytes (and glucose), hemodynamic response, and volume status. A pulmonary catheter may be of benefit but is difficult and dangerous to place with the right-sided heart anomalies.

The carcinoid syndrome appears to be primarily mediated via humoral, not neuronal pathways (i.e., the bioactive factors are carried through the systemic circulation). Therefore regional anesthesia may not be protective. In fact, the sympathetic block and resulting hypotension can trigger the release of endogenous catecholamines, which in turn can trigger the release of the bioactive tumor substances, precipitating a crisis. Still, epidural anesthesia has been successfully used to perform transurethral resection of the prostate.

The depth of anesthesia is very important, es-
especially during stressful times (i.e., during induction, incision, and surgical manipulation), because part of the surgical stress response involves the release of endogenous catecholamines. Using the same argument as above, this release could trigger a carcinoid crisis. However, too deep an anesthetic level can result in hypotension that can also produce a reflexive release of endogenous catecholamines. Therefore, a slow, careful induction is important, with concern for possible aspiration risk in the nauseated patient.

Drugs that may have deleterious effects include those associated with histamine release (e.g., curare, morphine, atracurium, etc.) and those associated with catecholamines (beta agonists, such as epinephrine, ephedrine, etc.). The latter group should be avoided because of their potential to release serotonin and other tumor factors. Succinylcholine, via an increase in intra-abdominal pressure with fasciculations, may precipitate a crisis by releasing bioactive substances. Also ketamine, because of its sympathetic stimulation and release of endogenous catecholamines, should be avoided.

Drugs that have been used safely for induction are etomidate, providing hemodynamic stability, and propofol, which if used cautiously to avoid hypotension, will help prevent tachycardia. Fentanyl has been the narcotic most commonly used with cases involving carcinoid syndrome. Benzodiazepines, particularly midazolam, have been used as anxiolytic and amnestic agents. Nondepolarizing agents such as pancuronium and vecuronium have been used for muscle relaxation. Inhalational agents, isoflurane and nitrous oxide, may be used safely if hypotension is avoided. The direct-acting alpha agents, phenylephrine and methoxamine, have been used to treat hypotension. Hypertension has been treated with beta-selective blockers, especially short-acting esmolol. Labetalol has also been used effectively, but because of the potential risk of inducing bronchospasm (nonspecific beta blockade), it should be used cautiously. Similarly, nitroprusside has been successfully used to treat hypertension, but caution is necessary to avoid producing hypotension that could precipitate a crisis.

**Intraoperative crises**

Three types of carcinoid crises may occur: hypotension, hypertension, and bronchospasm. The most difficult to deal with is hypotension. The first line of therapy is to use volume, followed by an alpha agonist (i.e., phenylephrine) and calcium. If this is not effective, octreotide 100 µg IV, has been successful at restoring blood pressure within 5 minutes. Although epinephrine has also been used successfully, theoretically it could trigger the release of more bioactive substances, exacerbating the problem. An angiotensin infusion has been also used, but the drug is difficult to obtain, requiring the contact of CibaGeneva Pharmaceuticals (Summit, New Jersey). Thus, angiotensin would probably best be used for a patient who has had prior perioperative episodes of uncontrolled hypotension and who is returning to surgery.

Usually, hypertension is relatively easy to treat by just deepening the level of anesthesia or giving more narcotics. Beta blockers and nitroprusside can be added judiciously. Ketanserin (5-HT2 blocker) has also been successfully used to treat persistent hypertension.

A case report described successful treatment of refractory bronchospasm with IV octreotide. The use of beta agonists should be avoided since they may trigger the release of additional offending factors. Increasing inhalational agents and administering H1 blockers or ketanserin may also be of short-term benefit. Corticosteroids and H2 blockers are of benefit prophylactically and help limit the severity of the spasm. Phosphodiesterase inhibitors, such as aminophylline, may aggravate the crisis by reflex release of catecholamines.

**Postoperative concerns**

If curative surgery has been performed, the loss of bioactive secretions will alter the patient's volume and hemodynamic status. Serotonin is capable of reducing anesthetic requirements. Therefore, since the secretion of serotonin may be decreased after the removal of the tumor, the anesthetic requirements may increase. If the surgical procedure removes metastases or debulks some of the primary tumor, the concentration of various bioactive substances may change, altering the patient's baseline state and response to drugs.

It is important that postoperative patients who still have carcinoid tumor, remain free from stress. Thus, adequate pain control is essential. However, too much analgesia may lead to hypotension, triggering a crisis. Therefore, these patients are likely candidates for patient-controlled analgesia devices using analgesics that do not release histamine.

**Unanticipated cases**

Because of the fairly low incidence of carcinoid syndrome, it is difficult to have a high index of suspicion. The best clues available are the location of the surgical procedure (e.g., GI tumor resections) and the signs and symptoms (e.g., hypotension and flushing, unresponsive to volume and pressors). Part of the differential diagnosis is anaphylactic shock. The history of the inciting event may provide a clue (e.g., hypotension immediately
after tumor manipulation versus hypotension following infusion of an antibiotic). The recommended therapy for anaphylaxis is epinephrine, which may actually exacerbate the problem if it results from a carcinoid crisis. If concerned about the possibility of a carcinoid crisis, one should start with a small dose of epinephrine (10 μg) and see how the patient responds. Alternatively, octreotide 100 μg IV may be given.

In a reported case, a patient who had a previous resection of a bronchial carcinoid tumor, but currently was believed to be free from carcinoid syndrome was to undergo bronchoscopy.\(^6\) After induction with propofol and succinylcholine, the patient became flushed, tachycardic, and hypotensive within 2 minutes following insertion of the rigid bronchoscope. Anaphylactic shock was considered and a fluid bolus, calcium and 1 mg of epinephrine were given. Bradycardia developed and was treated with an isoproterenol infusion. Hydrocortisone was administered concurrently. The possibility of a carcinoid crisis was considered, and 50 μg octreotide and 10 mg ketanserin were given with rapid improvement. The postoperative workup, however, revealed antibodies to succinylcholine, leaving an unclear etiology for the episode. Regardless of the cause, it is noteworthy that the patient's condition still responded to the octreotide.

Since octreotide is inexpensive, with a long refrigerator shelf-life, it would be prudent to keep it readily available for unanticipated cases.

Summary

The carcinoid syndrome is a rarely occurring complex associated with carcinoid tumors. These slow-growing neoplasms originate from neuroendocrine cells and, thus, are capable of secreting a variety of bioactive substances, which are usually cleared by the hepatic and pulmonary circulation. However, hepatic metastases and tumors that do not drain into the portal circulation allow these bioactive amines to produce systemic manifestations. The major symptoms are cutaneous flushing, labile blood pressure, diarrhea, abdominal cramping, and bronchospasm. This syndrome can also involve the right-sided heart valves and altered tryptophan utilization.

Preoperative workup and assessment in consultation with an endocrinologist are recommended to ensure that the manifestations are under adequate medical management. The patient should be asymptomatic prior to surgery. A cardiologic workup should evaluate the right-sided heart function, possibly using echocardiography to investigate involvement of the pulmonic valves, or tricuspid valves, or both.

Currently the best medical therapy available is octreotide, a synthetic, long-acting somatostatin that prevents the release of these bioactive substances. It is used prophylactically and acutely when a crisis occurs.

REFERENCES


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