This article presents information on the anesthetic management of the carcinoid syndrome patient. The pharmacodynamics and pathophysiology of this rare disease and its hormonal effects on the body are also discussed.

The first report of an association between a carcinoid tumor and a specific syndrome was reported by Biorck and associates in 1952. Since that time, literature on the carcinoid syndrome has appeared more frequently. In 1976, Mason and Steane published two review articles on the subject which have served as reference guides for anesthesia personnel. Fewer than 50 cases of the carcinoid syndrome have been reported to date.

Description

Carcinoid tumors are small and yellow in color, arising in cells in the crypts of Lieberkühn in the gastrointestinal tract. The site of most tumors (50-90%) is the tip of the appendix. These tumors are benign and may in rare instances spread to the regional lymph nodes. They are considered non-secreting tumors.

Tumors found at other sites are usually malignant and pose more of a problem for the anesthetist because of the systemic disturbances produced. The primary lesion is usually located in the ileum, but other tumors may be found in the duodenum, stomach, rectum, and pancreas, and metastasis may be seen in the liver, lungs, or other organs. About 25% of the carcinoid tumors of the gastrointestinal tract produce serotonin and bradykinin, although several other causative substances have been implicated. These include histamine (especially in gastric tumors), prostaglandin, calcitonin, gastrin, glucagon, and such other hormones as ACTH, ADH, and HCG.

The cells of the carcinoid tumors utilize 5-10% of ingested tryptophan for the synthesis of serotonin. If the carcinoid tumor is of the secreting type, as much as 60% of ingested tryptophan may be captured. In the metabolic pathway of serotonin, tryptophan hydroxylase catalyzes the reaction of 5-hydroxytryptophan (5-HTP) from tryptophan. Most tumors also contain the aromatic enzyme L-amino acid decarboxylase which catalyzes the formation of 5-hydroxytryptamine (serotonin). Following its release from the tumor, serotonin is inactivated primarily by the enzyme monamine oxidase by oxidation to 5-hydroxyindoleacetaldehyde which is rapidly converted to 5-hydroxyindoleacetic acid (5-HIAA). This acid is rapidly excreted in the urine and almost all circulating serotonin can be accounted for as urinary 5-HIAA. These steps are shown in Figure 1.

Oates and associates have shown that the tumors also contain a proteolytic enzyme, kallikrein, that is probably released by catecholamines to produce a vasoactive polypeptide, bradykinin.

Serotonin is normally broken down by monoamine oxidase (MAO) in the liver, and the kinins are very rapidly broken down in the plasma (the half-life of a bradykinin is less than 60 seconds). Once released into the bloodstream, these hormones are destroyed after one passage through the liver. It is not until liver metastasis has occurred that the hormones enter the bloodstream in large amounts, unchanged by liver enzymes, and the carcinoid syndrome develops.

Diagnosis and symptoms

The diagnosis of the carcinoid syndrome may be made upon the excretion of 5-HIAA. Normally 2-9 mg/day is present in the urine, but in carcinoid syndrome this may increase to 50-600 mg/day.
Symptoms of the carcinoid syndrome are vasomotor, gastrointestinal, or cardiorespiratory in origin. Characteristic features include flushing, bronchospasm, diarrhea, hypertension or hypotension, and cardiovascular collapse. Valvular lesions of the heart may also be present due to subendothelial fibrosis which may lead to pulmonary stenosis or tricuspid insufficiency. The flush has been described as being pink in color when associated with hypertension and tachycardia (serotoninergic), and blue in color when associated with hypotension and bradycardia (bradykininergic).1,8

Treatment

Patients with carcinoid syndrome have been treated prophylactically with drugs aimed at inhibiting the release of serotonin and/or bradykinin,7 but this is an individual consideration depending on the presenting symptoms of the patient. The treatment of choice is surgical and this is when the contact between the carcinoid patient and the anesthetist is made.

Surgery may involve excision of the primary tumor, removal or inactivation of hepatic metastasis by hepatic artery ligation, or replacement of diseased cardiac valves.6

If the tumor has been secreting large amounts of serotonin, the anesthetist should be aware that the patient will likely be dehydrated and hypovolemic as a result of severe diarrhea and hypertension. Clinically the patient may present with poor tissue turgor, dry skin and mucosa, slow capillary refill, and decreased urine output.8 The preoperative fluid therapy must be vigorous to provide sufficient circulating blood volume prior to surgery.

If the primary tumor is to be excised, the anesthetist must be aware of the symptoms resulting from serotonin and bradykinin release and of the drugs available to counteract these effects.

Literature affirms that bradykininergic dysfunctions result in the most life-threatening problems seen during anesthesia. Bradykinin release is evidenced by changes in the cardiovascular and respiratory systems and symptoms include bronchospasm, flushing, hypotension, and electrolyte disturbances.6

Bradykinins are potent vasodilators peripherally and may also cause increased capillary permeability, allowing plasma and electrolytes to leak from the vascular compartment.6 This increased capillary permeability results in dramatic hypovolemia and edema of the tissues of the extremities which, coupled with the drop in arterial pressure, give rise to a condition called "bradykinin shock." This type of shock has a sequence of events similar to that of anaphylactic shock.9 The bronchospasm too often seen is caused by contraction of the extravascular smooth muscles by bradykinin, precipitating an asthma-like attack.

Of the kallikrein bradykinin inhibitors, aprotinin (Trasylol®) is the most widely used. Déry has postulated that the best dose–response relationship occurred when there were very high levels of circulating kinins at the time when aprotinin was administered.6 The drug, however, is not universally available. If wheezing is present preoperatively, or if prophylactic treatment is to be given preoperatively, aprotinin should be administered one hour prior to surgery in a dose of 200,000 units. Aprotinin may also be given intraoperatively should bronchospasm occur.

Steroids may have been used preoperatively to control severe prolonged flushing by blocking kinin release. Though useful prophylactically, steroids are probably ineffective once the kinins have been liberated. If steroids are to be given during surgery to prevent the generation of kinins, large doses should be administered prior to anesthesia.

The anesthetist must be aware that hypotension may result from surgical manipulation of the tumor. This occurs as a result of bradykinin release. If a vasopressor is needed, the drugs of choice are direct-acting agonists of the adrenergic alpha receptors such as phenylephrine. Sympathomimetic agents that act by norepinephrine release, such as metaraminol, or those that stimulate beta

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**Figure 1**

Carcinoid tumor utilization of tryptophan

<table>
<thead>
<tr>
<th>Tryptophan</th>
<th>Tryptophan 5-hydroxylase</th>
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<tbody>
<tr>
<td>5-HTP</td>
<td>5-HTP decarboxylase</td>
</tr>
<tr>
<td>5-HT</td>
<td>Monoamine oxidase (destruction occurs in liver)</td>
</tr>
<tr>
<td>5-HI</td>
<td>Aldehyde dehydrogenase</td>
</tr>
<tr>
<td>5-HIAA</td>
<td>5-Hydroxyindoleacetic Acid</td>
</tr>
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receptors may make matters worse by causing a paradoxical hypertensive response.

The effect of serotonin release during surgery will be manifested by tachycardia, flushing, and hypertension. Serotonin has a positive inotropic and chronotropic effect on the heart, increasing cardiac output and causing hypertension as a result of vasoconstriction of the circulatory bed. Page states that the cardiovascular effects of serotonin vary according to the state of the peripheral circulation at the time: blood pressure increases when the neurogenic vascular tone is low and, conversely, lowers when the tone is high.

The fact that many anesthetic agents cause peripheral vasodilation helps explain why serotonin causes arterial hypertension and tachycardia in a patient under anesthesia. Should the patient develop a hypertensive crisis during anesthesia, methotrimeprazine, a potent antiserotonin agent, is very effective in lowering blood pressure without changing pulse rate. It also has potent analgesic properties which may potentiate the anesthetic agents already given. Chlorpromazine may also be helpful in lowering blood pressure or ameliorating flushing.

Serotonin does not readily cross the blood-brain barrier, but if large amounts of 5-hydroxytryptophan are released during surgery, a central depressant effect occurs that may explain why these patients are often slow to awaken from anesthesia.

Serotonin release causes hyperperistalsis with resulting nausea, vomiting, abdominal cramps, diarrhea and stimulated glycolysis and glycogenolysis. As a result, these patients will be hyperglycemic and suffer a disturbance in electrolyte balance. If there is long-standing carcinoid disease, hypoproteinemia may ensue as a result of utilization of dietary tryptophan to the metabolic pathway of serotonin, replacement by liver metastasis, and malabsorption due to diarrhea.

If the patient has not been treated proactively with both antiserotonin and antibradykinin drugs to minimize the untoward effects of the release of these two hormones, these drugs should be readily available in the operating room in case a crisis occurs.

If the syndrome has progressed to the point of severe liver metastasis, hepatic artery ligation may be the only alternative to relieve the symptoms. Ligation of the hepatic artery leads to necrosis of the malignant tumor cells of the liver since the main blood supply to the tumor cells comes from the hepatic artery. Survival following hepatic artery ligation is dependent upon three factors: (1) increased extraction of oxygen from portal vein blood, (2) collateral circulation, and (3) presence of aberrant vessels.

Under normal conditions the hepatic artery supplies 25% of the liver's blood and 50% of the liver's oxygen, whereas the portal vein provides 75% of the blood and 50% of the oxygen to the liver. When the arterial supply has been ligated, the liver's oxygen requirements are met by an increased flow through the portal vein. Collateral circulation develops, possibly accounting for the rapidity with which hepatic function recovers.

Symptoms related to serotonin and bradykinin release are also very likely to appear during anesthesia for hepatic artery ligation. The treatment previously described is recommended.

Cardiac involvement is a later development of the syndrome. Right heart failure may supervene in association with pulmonary and tricuspid valve lesions. Lippman and Cleveland in 1973 reported on the care of a patient with metastatic carcinoid who underwent successful replacement of the tricuspid valve.

Anesthetic management

Premedication for the patient with carcinoid syndrome should include a drug with antiserotonin effects. Morphine is to be avoided as it causes both serotonin and histamine release. Droperidol can be given, but its long tranquilizing effect may prolong even further the slow awakening from anesthesia often seen in these patients.

Monitoring during anesthesia should include electrocardiogram, blood pressure—preferably by direct arterial means that can also be used to obtain blood gases—CVP to adequately assess fluid volume, urine output, and measurements of electrolytes and blood sugar. The patient should be carefully and continuously observed to detect the appearance of any type of flush.

Induction should be as smooth as possible to prevent any drastic changes in blood pressure that might trigger both serotonergic and bradykinergic attacks. A bradykininolytic agent should be readily available prior to induction should a vasoressor be needed. This agent might be angiotensin or methoxamine. The use of epinephrine or norepinephrine is discouraged since both increase the release of kallikrein-bradykinin. Topical spray to the larynx should precede intubation.

In the past, the muscle relaxant of choice was pancuronium. The fasciculations from succinylcholine may increase intra-abdominal pressure, causing hormonal release from the tumor and
compressing the tumor, leading to a carcinoid crisis. If liver involvement is extensive, leading to a reduction in cholinesterase production, prolonged apnea may follow the use of succinylcholine. D-tubocurarine, because of its minimal cardiovascular effects, might now be considered the best muscle relaxant to use with carcinoid syndrome patients. Metocurarine gives rise to neither sympathetic ganglion block nor vagolytic action, so the occurrence of hypotension and tachycardia is decreased.

Induction techniques utilizing thiopental and pancuronium have been reported as uneventful. Miller and associates described the anesthetic management of nine patients with carcinoid syndrome, eight of whom developed minor complications during anesthesia. The techniques described in the literature involved induction with thiopental, intubation with succinylcholine, and maintenance with nitrous oxide, oxygen, fentanyl, and pancuronium. If bronchospasm developed, halothane was added, cortisol was administered, and aprotinin was given, if available. If hypertension developed, methotrimeprazine was given.

Theoretically, in considering anesthetic management for patients with carcinoid syndrome, one should avoid agents associated with hypertension, tachycardia, serotonin and histamine release, disturbances of hepatic blood flow, or postoperative hepatic dysfunction. Realistically, however, it is difficult to avoid all such agents. The most commonly agreed upon anesthetic management includes a thiopental, pancuronium, and nitrous oxide sequence with moderate hyperventilation.

Regional anesthesia affords no protection against the carcinoid syndrome, and in most cases is contraindicated. The ganglionic blockade and resulting hypotension may precipitate a carcinoid attack.

Postoperative management

The postoperative period also warrants close observation by the anesthetist. If the patient has had surgery for hepatic artery ligation, severe hepatic dysfunction in the early postoperative period may be seen until collateral circulation takes effect. Any factor that would tend to further increase hepatic oxygen requirements should be avoided, and prophylactic measures should be instituted to avoid pulmonary complications. Hypotension following this type of surgery should be corrected as soon as possible.

Conclusion

A better understanding of the pharmacodynamics and pathophysiology of the carcinoid syndrome will enable the anesthetist to better manage these patients should complications or emergencies arise during anesthesia.

If a patient unexpectedly manifests anaphylactoid reactions such as hypotension, flushing, or bronchospasm under anesthesia that are unexplained by other causes, the possibility of carcinoid syndrome should be considered. Knowledge of the complex pharmacology of carcinoid attacks may prove to be life-saving.

REFERENCES


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