Anesthesia and the malignant carcinoid syndrome

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The authors examine the history and pathophysiology of malignant carcinoid syndrome, and review the anesthetic management for patients with this complex disorder. The need for cooperation between physician, surgeon and anesthetist in the care of these patients is emphasized.

Carcinoid tumors have been recognized since 1882, but it was not until 70 years later, in 1952, that bizarre clinical symptoms were attributed to these particular tumors. The term carcinoid was first used by Oberndorfer in 1907 because these tumors were rarely malignant, although it was known that liver metastasis occurred. In 1930, Masson showed that granules in the cells of these tumors reduced silver salts. He called the tumors argentaffinomas.

Up to 90% of the tumors occur in the appendix and are generally thought of as being non-secreting tumors. These are usually surgically removed as they give rise to appendicular obstruction; the preoperative diagnosis in such cases is acute appendicitis. The extra-appendicular carcinoids are those of concern to the anesthetist because of the systemic disturbances that occur secondary to the tumor.

The primary lesion is usually located in the ileum, but it may also be found in various organs such as the duodenum, stomach, rectum, and pancreas. The extra-appendicular carcinoid tumors arise from the argentaffin Kultschitzky cells of the gastrointestinal tract, and are usually malignant growths which spread to adjacent lymphoid tissue in the abdomen. Metastases commonly occur in the liver and the lungs. About 25% of these malignant carcinoid tumors produce vasoactive hormones, especially 5-hydroxytryptamine (serotonin) and bradykinin. Ureles has stated that only 4% of carcinoid tumors produce vasoactive substances in a quantity large enough to produce the debilitating symptoms that characterize the disease.

Many times, these tumors are dormant until liver metastasis occurs. With the occurrence of liver metastases, vasoactive hormones enter the suprahepatic venous blood without having been exposed to the destructive action of liver enzymes. They are then able to exert their pharmacological effects. The presence of liver metastases seems to be essential for the development of the typical carcinoid syndrome.

The carcinoid cell

It is important to review the carcinoid cell when attempting to understand the biochemistry and pharmacology of the malignant carcinoid syndrome. The cell has two components, the enterochromaffin granule and the lysosome.

The enterochromaffin granule is the site of biosynthesis, storage, and release of serotonin. The uptake of tryptophan by the serotoninergic granules of the argentaffin cells normally accounts for 5-10% of the whole ingested tryptophan.
amounts of tryptophan are consumed by eating foods such as bananas, tomatoes, avocados, red plums, walnuts and eggplant. In the presence of a tumor, approximately 60% of this ingested tryptophan is consumed by the carcinoid cell; as a result, malnutrition and hypoproteinemia may develop. Tryptophan's uptake into the tumor cells can be substantially decreased by maintaining a diet low in tryptophan.

Modifications of the normal pattern of plasma proteins can be induced three ways: (1) by extensive uptake from the carcinoid tumors, (2) by loss of hepatic tissue through metastatic involvement, and (3) by dietary tryptophan deprivation. Preoperatively, the anesthetist should assess this problem because an adjustment in the anesthetic management of the patient may be necessary.

The other infrastructure of the carcinoid cell is the lysosome. Lysosomes are small vesicles, covered with a very thin membrane which is filled with an array of enzymes. The enzymes are of two types, hydrolases and proteinases.

Of the hydrolases, acid phosphatase, glucuronidase, acid ribonuclease, and acid deoxyribonuclease have been isolated. Among the proteinases, pepsinases, trypsinases, and kallikrein have been identified. Once liberated, each can react with cell or plasma proteins to break the peptide bonds of large molecules, or to withdraw some amino acids from the long protein chains.

Though the pharmacodynamics of these proteinases have not been completely elucidated, it is known that damage to the lysosomal membrane, and subsequent leakage of its kallikrein stores may be caused by mechanical trauma, pH variations, anoxia, alcohol intoxication, and catecholamines. Under normal circumstances, bradykinin and associated kinins are rapidly destroyed by kinases and plasma aminopeptidases. It is assumed that as long as a stimulus for their production continues, the protective kinase mechanisms can be overrun. This allows the highly active kinins to produce their pharmacological effects.

Effects of 5-hydroxytryptamine
Cardiovascular effects. Serotonin, a potent smooth muscle stimulant, has both positive chronotropic and inotropic effects upon the myocardium. The clinical implications seem to vary according to the state of the peripheral circulation at the time the serotonin is released. With increased blood pressure, serotonin usually causes peripheral vasodilation and hypotension. Conversely, when the neurogenic tone is low, vasoconstriction and hypertension is observed. Because many anesthetic agents produce peripheral vasodilation, serotonin release under anesthesia usually causes arterial hypertension and tachycardia.

It should be noted that serotonin is a potent constrictor of the pulmonary vasculature. Serotonin is one of the few drugs with a greater effect on the pulmonary vasculature than on the systemic circulation. Though small increases in pulmonary pressure may enhance cardiac output and thus increase blood pressure, larger increases in pulmonary pressure may actually decrease cardiac output and lead to poor peripheral circulation and hypoxia.

Right-sided heart lesions may be associated with the release of serotonin in patients with carcinoid tumors. Contraction of the fibrous tissue produces distortion of valves, usually leading to predominant stenosis of the pulmonary valve and insufficiency of the tricuspid valve. Left-sided heart lesions are less common because approximately $\frac{3}{5}$ of the serotonin is metabolized as venous blood flows through the lungs.

Central nervous system effects. Serotonin is present in large amounts in the cells of the lower brain stem and the hypothalamus. Although only small amounts of serotonin cross the blood brain barrier, it has been established that serotonin is a transmitter substance in the brain. A central nervous depressant effect has been associated with drugs that increase brain levels of serotonin. Some researchers feel that anesthesia increases brain levels of serotonin. The slow emergence from anesthesia is thought to be due to this increase.

Gastro-intestinal effects. An increase in gut motility is observed in patients with malignant carcinoid syndrome, and is responsible for the diarrhea which occurs in these patients.

Metabolism effects. It has been shown that serotonin plays a role in carbohydrate metabolism, stimulating glycolysis and glycogenolysis. This may explain the mild hyperglycemia observed in patients with the carcinoid syndrome. As previously stated, protein metabolism may be grossly upset due to the 50% increase in uptake of dietary tryptophan.

Other effects. Serotonin is an antidiuretic of unknown etiology, therefore, care must be taken with regards to fluid management of these patients. It has also been demonstrated that serotonin increases the stimuli to the carotid chemoreceptors and in so doing, stimulates respiration. This increase in activity may trigger nearby adrenergic nerve centers which may in turn contribute to the pressor response found with serotonin secretion.
Effects of bradykinin

Flushing. It was initially thought that serotonin caused the characteristic flush observed with the carcinoid syndrome. Various descriptions of the flush include: violaceous, pink, purple, fiery red, spotted or patchy, or diffusely homogeneous. More recently, the flushing has been attributed to the release of large amounts of bradykinin and other vasodilating peptides from the carcinoid cell. Bradykinins are potent vasodilators and cause hypotension.

Shock. The release of kinins modifies the permeability of the capillary walls. This leads to a creation of new fenestrations in the capillary endothelium. Considering the severe peripheral vasodilation that occurs secondary to kinin release, it is easy to understand the dramatic hypovolemia that occurs with the increase in capillary pore size. Leakage of both plasma proteins and electrolytes is high. The steps of bradykinin shock are sudden erythroderma, collapse of arterial blood pressure, and tissue edema. This is similar to anaphylactic shock.

Bronchospastic attacks. These attacks were previously attributed to the release of serotonin. Extravascular smooth muscle contracts in response to the release of kinins. This effect is not abolished with the administration of atropine or ganglionic blocking agents. This may give rise to bronchospasm, especially in asthmatic patients.

The carcinoid syndrome

Clinical symptoms. The principal manifestation of the malignant carcinoid syndrome is recurrent episodes of paroxysmal flushing that predominantly covers the upper trunk, neck and face. These attacks are induced by eating, the straining associated with defecation, alcohol ingestion, fear, anxiety, anger, consumption of hot beverages, hypotension, and palpation of the intra-abdominal mass. Eventually, telangiectatic changes occur, especially in the face, secondary to leakage of blood from the capillaries. Dermatitis has been noted to occur in the extremities with associated pruritus. These symptoms have been attributed to kinin release.

Diarrhea, cramps and non-bloody mucoid watery stools occur even when low blood levels of serotonin exist. Quite often, these patients become diaphoretic and febrile with an attack. Irregular bronchospastic respirations may coincide with the onset of diarrhea. Some patients develop a dry cough which is non-productive.

With advanced disease, a patient may develop a hyperdynamic circulation in high output failure with low peripheral vascular resistance because of the development of tricuspid insufficiency and pulmonic stenosis. Chronically engorged external jugular veins and increased central venous pressure are often seen. Edema eventually develops as a result of the heart failure, peripheral vasodilation and leakage of plasma proteins.

Laboratory Tests. Urinary levels of 5-hydroxyindoleacetic acid (5-HIAA), a by-product of serotonin, can be measured and can be useful for screening patients. The normal amount of 5-HIAA excreted every day is about 1.5-10 mg. Patients with the carcinoid syndrome usually excrete more than 25 mg in a 24-hour period. Urinary levels of histamine have also been noted to increase in these patients. The plasma serotonin levels can also be measured. The upper limit in the normal range is 200 ng/ml.

Provocative testing has been attempted to confirm the diagnosis of the carcinoid syndrome. The kinin peptides (formed by the proteolytic enzyme kallikrein) have been found to be increased in the hepatic venous blood when the patient is given intravenous epinephrine. This test involved administering 5 mg of intravenous epinephrine which produced symptoms of a carcinoid attack. With subsequent reports of vascular collapse and hypertension, it is now suggested that pressor amines be avoided when attempting to evaluate carcinoid syndrome.

Medical treatment

Five groups of drugs have been used to treat the symptoms of carcinoid syndrome. The results have not been promising.

Antiserotonin drugs. These have been used for relief of diarrhea. Other symptoms have not been improved with the use of these drugs. Methysergide (Sansert®), alpha methyldopa (Aldomet®), chlorpromazine (Thorazine®), p-chlorophenylalanine, and cyproheptadine hydrochloride (Periactin®) have been tried with varying success. There is little correlation between urinary levels of 5-HIAA and treatment with these drugs. One must weigh the helpful effects of these drugs against their detrimental side effects. For example, long term methysergide use may cause retroperitoneal fibrosis. Drowsiness is often seen with phenothiazines and antihistamines. Aldomet® may cause orthostatic hypotension and hemolytic anemia.

Kallikrein-bradykinin inhibitors. Treatment with these drugs has also been discouraging, however aprotinin (Trasylol®), a kallikrein-trypsin inhibitor, has been used successfully. Unfortun-
ately, these effects are not consistent. Kellermeyer attributed the inconsistency to the higher affinity of kallikrein for its substrate as compared with that of kallikrein for aprotinin.\textsuperscript{13}

Some researchers have advocated the use of epsilon-aminocaproic acid (EACA).\textsuperscript{8} EACA is a synthetic proteinase and fibrinolytic inhibitor which antagonizes the kallikrein-bradykinin system. Unfortunately, it is a non-specific enzyme inhibitor and inactivates the peptidases responsible for the breakdown of bradykinin in plasma. It has been reported as enhancing the activity of kinins in vitro.\textsuperscript{18} Because of widespread clotting, some authors feel that other drug regimens should be tried before using EACA.

Salicylates have been reported to inhibit kallikrein activation, but the results are variable.\textsuperscript{14}

Corticosteroids. These are known to stabilize lysosomal membranes which decrease the release of proteolytic and hydrolytic enzymes. Cline reported that cortisol appeared to inhibit the formation of plasma kinins, possibly by preventing kallikrein activation and also by inhibiting the interaction of activated kallikrein and kininogen.\textsuperscript{15} The use of steroids to prevent kinin formation is preferable to using them for patient treatment once the kinins have been released. Large doses of corticosteroids should be given to patients prior to the administration of anesthesia.

Adrenergic blockers. These have been used to treat flushing because intravenous administration of catecholamines may result in flushing. Adrenergic blockers also help prevent damage to lysosomal membranes caused by catecholamines.\textsuperscript{8}

Cytotoxic agents. These include 5-fluorouracil, vinblastine sulfate, cyclophosphamide and streptozotocin. However, their use is limited by the occurrence of serious side effects.

Anesthetic management

Surgical excision of the primary tumor is recommended since the results of medical treatment are variable. With surgery, however, survival has been reported to increase by as much as 20 years.\textsuperscript{8} The primary tumor may be of varying size, so small that it can be difficult to find, or so large that obstructive symptoms are noted. Hepatic surgery may involve hepatic lobectomy, removal of hepatic metastases, or hepatic dearterialization. Valve replacement in cardiac carcinoid patients is still in the pioneer stage.

Preoperative treatment with antiserotonin and antibradykinin drugs may be indicated. Chlorpromazine, which has an antiserotonin effect, is a useful sedative for these patients. Morphine sulfate is contraindicated because it causes a release of serotonin from the small intestine. Also, histamine release may precipitate bronchospasm.

Bradykininolytic agents should be available prior to the induction of anesthesia. It has been recommended that 200,000 units of aprotinin be available one hour before surgery so that an immediate infusion can be started during the induction of anesthesia should a crisis occur. Another suggested therapy is that 25,000 units of aprotinin be infused every hour during surgery.\textsuperscript{11}

The induction of anesthesia should be smooth; the patient should not hold his breath or cough. Also, positioning the patient must be done gently, as this may precipitate a carcinoid attack.

Intubation should be as non-stimulating as possible. One author recommended using a superior laryngeal nerve block to aid in blocking the increase in blood pressure associated with intubation.\textsuperscript{16} D-tubocurarine is not recommended because it may cause bronchoconstriction secondary to histamine release and its ganglionic blocking properties may precipitate a serotoninergic attack.

Succinylcholine is also not recommended because the increase in intra-abdominal pressure which occasionally occurs may cause hormone release. Plasma pseudo-cholinesterase levels may also be reduced because of tissue wasting and tryptophan uptake into tumor cells. This could lead to prolonged respiratory distress and/or apnea postoperatively.

Gallamine is also a poor choice of muscle relaxant because of vagal inhibition resulting in tachycardia. Pancuronium bromide is the muscle relaxant of choice for patients with carcinoid tumors. Information concerning beneficial effects with the use of metocurine is not available.

The anesthetic technique should promote cardiovascular stability. A neurolept technique may be most suitable, especially as droperidol has been shown to have an antiserotonin effect.\textsuperscript{11} The alpha blocking effects of droperidol may also be helpful to treat flushing and other bradykininergic symptoms by helping to stabilize lysosomal membranes through blockage of catecholamine release. One drawback with droperidol is its long action which may act synergistically with other anesthetic agents and prolong emergence from anesthesia upon completion of the surgical procedure.

Vasopressors of the catecholamine type should not be used as they may precipitate a bradykininergic attack. Using a sympathomimetic amine with direct action, such as Neo-synephrine\textsuperscript{®} (phenylephrine), would be a good choice for treating

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hypotension because the hormones released during a carcinoid attack act directly upon the receptors.

One must be cautious when using a vasoressor so that a serotoninergic attack is not precipitated. Norepinephrine is contraindicated. Regional anesthesia may be contraindicated because the resulting hypotension may precipitate a carcinoid attack.

It is important to monitor patients closely during surgery by utilizing invasive as well as non-invasive techniques. The pulse and electrocardiogram should be monitored closely for the possibility of arrhythmias, which should be treated promptly. If not converted, then one should re-evaluate the serotonin-bradykinin physiopathology and treat accordingly.

An intra-arterial cannula is advisable for the continuous monitoring of systemic arterial pressure. Central venous pressure, as well as pulmonary artery and pulmonary capillary wedge pressure monitoring may also be indicated, especially in the presence of known heart involvement. Electrolytes, blood glucose levels, arterial blood gases and urinary output are recommended intraoperative parameters that can be utilized to assess the patient's status. Close monitoring of the patient postoperatively is essential as some deaths have been reported during this period.

REFERENCES

AUTHORS
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