Two case reports:
The use of methotrimeprazine as an antiserotonin agent in anesthesia for patients with carcinoid tumors.

PATRICK A. PINDER, CRNA
Garland, Texas

The author considers the effects of serotonin on anesthesia for patients with carcinoid tumors, and addresses ways to keep those effects from causing any life-threatening complications. Two case reports are presented in which methotrimeprazine (Levoprome®) proved to be a valuable agent for such patients.

Anesthesia for carcinoid syndrome can potentially cause a multitude of problems for the anesthetist. As the entire syndrome was extensively detailed by Margaret Kent, CRNA, in the April, 1983 issue of the AANA Journal,1 this author will merely outline the syndrome as an introduction to the case studies.

The impact of the carcinoid syndrome on anesthesia arises from the many different substances that can be secreted by the carcinoid tumors. The systemic disturbances encountered in this complex syndrome are usually caused by the body’s altered response to a normal humoral factor. The two factors that usually cause the most disturbances are bradykinin and serotonin.

Bradykinins are split away from an alpha2-globulin in the plasma or tissue fluids. The important enzyme causing this split is kallikrein, which is present in the blood in an inactive form. Kallikrein can be activated by several chemical and physical effects on the blood. As kallikrein becomes activated, it acts to release kallidin, which is a mixture of bradykinin and another similar kinin. These kinins only persist for a few minutes before being digested by enzyme carboxypeptidase.2

The kinins as a group cause a very powerful vasodilation. For instance, injection of 1 μg of bradykinin into the brachial artery of a man increases the blood flow through the arm as much as six times.2

Bradykinin in circulation can cause life-threatening problems, but fortunately the patient usually presents symptoms preoperatively and these can be treated.

In the two case studies presented here, neither patient had ever presented bradykinic symptoms, but that did not preclude their occurring intraoperatively. To lessen the chances of the symptoms occurring, steroids were given preoperatively to block kinin release or minimize the response. Vaspressors were readily available.

Serotonin, a chemical 5-hydroxytryptamine, is present in large concentrations in the chromaftin tissues of the gastrointestinal tract, mast cells and other abdominal structures. It is also present in high concentrations in the platelets. Serotonin can have either a vasodilator or vasoconstrictor effect depending on the condition or the area of circulation. Even though their effects can sometimes be very powerful, the function of serotonin on circulation is not entirely known.2

Occasionally, tumors comprised of chromaffin tissue develop called carcinoid tumors. These
tumors secrete tremendous quantities of serotonin and can cause vomiting, diarrhea, flushing of the skin, tachycardia and hypertension.

The diagnosis of carcinoid syndrome is usually made by a 24-hour measurement of 5-HIAA (5-hydroxyindoleacetic acid) in the urine. Normal levels usually run between 2.9 mg/day, but in both of the cases presented here, levels were well above the established normals. Serotonin is normally broken down by MAO (monoamine oxidase) in the liver. When carcinoid tumors metastasize to the liver, even in micrometastasis, the breakdown is slowed and high 5-HIAA levels develop.

One unusual characteristic about serotonin is that even though it is circulating in large amounts in this disease, it is not constantly giving its full epinephrine-like effects. This is one reason that the anesthetist, when giving anesthesia to these patients, must constantly be aware of the fact that these effects can surface at any time, or not at all. Additionally, consideration must be given not to over compensate for the possible effects of serotonin on circulation.

Another reason care must be taken in treating for serotonin before symptoms become evident is the possible presence of bradykinin. When serotonin release does present itself, it can present with a pink flush or mottled areas of vasodilatation in the skin, hypertension, and/or tachycardia.

In the two cases presented here, the problems encountered were seemingly related to serotonin release. In each case, the effects of serotonin were seen at different stages of surgery.

**Case study 1**

A 75-year-old, 57 kg female with a documented case of carcinoid syndrome presented for surgery. Pertinent readings included: 5-HIAA 143 mg/day, Hct 43.9, and Hgb 12.3. The patient had no known allergies and was not taking any regular medication at home. She had no past history of problems with her heart, lungs, or kidneys. The last anesthetic she had had was two years ago for a bowel resection for carcinoid tumor, but at that time she did not have symptoms of carcinoid syndrome. She currently, however, exhibited a history of carcinoid syndrome type symptoms including gastrointestinal disturbances of vomiting, diarrhea and skin flushing. She was presently scheduled for a laparotomy, possible liver resection and possible bowel resection.

*Preoperative medication.* Medication included hydrocortisone sodium 250 mg IM, 2 hours preoperatively; meperidine 50 mg, diphenhydramine 50 mg, and atropine sulfate 0.4 mg IM, 45 minutes preoperatively. After arrival in the operating room, the patient was given another 250 mg hydrocortisone IV. Her blood pressure was 150/90, pulse 90; the patient appeared calm and relaxed.

*Induction.* Induction was slow and deliberate so as to avoid any abrupt changes in the patient's vital signs. Fentanyl 5 cc was given slowly IV and when it reached its effectiveness in approximately one minute, induction was completed with etomidate 16 mg. Pancuronium 8 mg was given for relaxation. After the patient was intubated and placed on the ventilator, an arterial line was inserted for continual blood pressure monitoring. Before surgical incision, an additional 5 cc of fentanyl was administered IV.

*Intraoperative medication.* To avoid wide fluctuations in vital signs, enflurane 0.5-2.0% was administered as needed, in addition to oxygen 2 L and nitrous oxide 4 L. The case proceeded uneventfully, although increasing concentrations of enflurane were required to maintain blood pressure at 150/80. Due to the size and location of the tumor, the procedure consisted of lysis of adhesions and ileocolostomy.

During closure, it became apparent that after the anesthetic was discontinued, blood pressure was going to rise appreciably. After reversal with neostigmine 4 mg and glycopyrrolate 0.4 mg, spontaneous respirations were established. Over the next 5-minute period, a pronounced facial flush appeared and blood pressure rose from 150/76 to 210/100. Methotrimeprazine (Levoprome®) 20 mg was administered IM. Within 3 minutes, the facial flush faded and blood pressure returned to the 150/80 range.

*Recovery.* The patient was transferred to the recovery room and then to the intensive care unit for observation. Recovery was uneventful, however, and no additional methotrimeprazine was required for hypotension.

**Case study 2**

A 61-year-old 100 kg male with a documented carcinoid lesion of the colon (by biopsy) presented for cholecystectomy, cholangiogram and right hemicolectomy. Pertinent readings included: Hct 52.6, and Hgb 17.8. Although the patient had not previously exhibited any of the physical symptoms of carcinoid syndrome, his 5-HIAA was 62.4 mg/day.

The patient was allergic to codeine, but otherwise his history was negative.

*Preoperative medication.* Medication included hydrocortisone 100 mg IM, 7 hours preoperatively; this was repeated 1 hour preoperatively. Meperidine 75 mg, diphenhydramine 50 mg and atropine...
sulfate 0.4 mg were given IM 1 hour preoperatively. Hydrocortisone 250 mg was given IV after the patient’s arrival in the operating room. Preoperative vital signs were BP 130/80 and pulse 110.

Induction. Induction was carried out with etomidate 22 mg. Pancuronium 10 mg was given for relaxation for an anticipated lengthy procedure.

Intraoperative medication. Anesthesia was maintained with oxygen 2 L, nitrous oxide 4 L and enflurane 0.5-4.0% as needed. An automatic non-invasive monitor was used to monitor blood pressure.

Following induction, vital signs stabilized at 120/70 and pulse 80. After approximately 40 minutes, the colon lesion was reached and surgical manipulation began. During the next 10 minutes, blood pressure began to rise, reaching 190/110. A profound flush appeared upon the patient’s face and his pulse rose to 120. Methotrimeprazine 10 mg was administered IM and within 5 minutes, the facial flush disappeared. Vital signs stabilized with blood pressure 126/80 and pulse 100. They remained stable throughout the remaining four hours of anesthesia.

Recovery. Recovery was uneventful with no further fluctuations in blood pressure or pulse.

Discussion
Carcinoid tumors can be found anywhere, from the gastric cardia to the anus, and have been found in the bronchus. In addition, oat cell carcinoma, which also secretes large amounts of serotonin, is clinically indistinguishable from carcinoids. Fortunately, only about 25% of these tumors cause the symptoms of carcinoid syndrome.

The difficulties that may be encountered when giving anesthesia for patients with carcinoid syndrome are well documented. Mason and Steane had perhaps the most comprehensive report, when they reviewed 40 cases and found complications involving 27. When complications do develop, treatment must be directed at the metabolic or peripheral effects with a specific mediator.

The cause of the facial flush that can accompany other symptoms in this syndrome is unclear. Some reports imply that bradykinin release may be responsible while others suggest serotonin. The most extensive study reported describes two different types of flush depending on the causative substance: a bluish flush and hypotension when caused by bradykinin and a pinkish flush when associated with serotonin.

Phenothiazines have many uses in treating a variety of diseases, and their use for the carcinoid syndrome has been documented in treating symptoms of excessive serotonin. In these cases, it was believed that the symptoms indicated excessive serotonin and methotrimeprazine was the drug used to successfully treat the complications.

Conclusion
Methotrimeprazine is a phenothiazine derivative and a powerful antiserotonin agent. The fact that it is a potent central nervous system depressant must be considered when used during general anesthesia. Although it is classified as an analgesic, it exhibits a powerful sedative effect. Methotrimeprazine is for intramuscular use only. Although its analgesic effect takes from 20-40 minutes to work, its antiserotonin effect seems to work within 5 minutes.

It should be noted that although methotrimeprazine could be used preoperatively, its sedative effects and central nervous system depressant effects, combined with general anesthesia, could mask other complications of the carcinoid syndrome. These are namely the possible hypotensive signs of bradykinin release.

The source of facial flush and hypertension has not been conclusively defined. However, in the two cases reported here, they were treated as though caused by a serotonin release and the results were excellent.

For use against the unusual effects of serotonin associated with carcinoid tumors, methotrimeprazine has shown itself to be a powerful antiserotonin agent in the cases described. Although there may be incongruities with its use, the anesthetist may want to consider it as part of the armamentarium for these complex cases.

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**AUTHOR**

Patrick A. Pinder, CRNA, is a graduate of Western Kentucky University Department of Nursing and a 1975 graduate of Hamot Medical Center, School of Nurse Anesthesia in Erie, Pennsylvania. He is currently in the free lance practice of anesthesia, primarily practicing at Richardson Medical Center in Richardson, Texas.

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