Pre-treatment with somatostatin in the anaesthetic management of a patient with carcinoid syndrome

Winston C.V. Parris MD, John A. Oates MD,
Jay Kambam MD, Richard Shmerling MD,
John F. Sawyers MD

Carcinoid syndrome produces flushing, bronchoconstriction and gastrointestinal hypermotility secondary to serotonin, histamine, bradykinin and prostaglandin release. A variety of drugs, foods and anaesthetic agents may provoke this syndrome. Under anaesthesia, the flushing produced may be associated with acute hypotension and cardiovascular collapse; this phenomenon is called a carcinoid crisis. Recently, somatostatin analogue has been used successfully to treat intraoperative carcinoid crisis. In this report, we present a 66-year-old lady with carcinoid syndrome who was pre-treated with 50 µg somatostatin analogue IV and IM prior to surgical manipulation. The anaesthetic course was relatively uneventful and the patient did well postoperatively.

Carcinoid syndrome¹ is characterized by intermittent flushing of the upper body and face, bronchoconstriction, gastrointestinal hypermotility with diarrhoea, telangiectasia and right-sided heart disease. This syndrome results from the secretion of a number of vasoactive substances in patients with carcinoid tumours.² These patients have consistently high levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), suggesting that the humoral manifestations of carcinoid syndrome may be attributed to the overproduction of serotonin by these tumours. However, other vasoactive substances³ may play

varying roles in the pathogenesis of this disease, including bradykinin, prostaglandins, histamine, substance P and others of lesser importance.

A variety of drugs, foods, emotions, environmental factors and anaesthetic agents may provoke an acute episode of flushing in patients with carcinoid syndrome. Under anaesthesia, this flushing may be associated with acute hypotension and cardiovascular collapse.⁴ This phenomenon is called carcinoid crisis. Recently, somatostatin⁵ and its synthetic analogue have been used successfully to treat carcinoid crisis intraoperatively. The mechanism of action appears to be the inhibition of mediator release from the tumour. In all previously described cases, somatostatin analogue was used after the development of carcinoid crisis.⁴ We present a patient with carcinoid syndrome who was pre-treated with somatostatin analogue prior to the operative manipulation of the tumour. Apart from transient mild hypotension, the anaesthetic course was relatively uneventful and the patient did well postoperatively.

Case report

A 66-year-old woman was admitted for elective resection of hepatic metastases of carcinoid tumour. She was diagnosed as having carcinoid syndrome 14 years previously and was treated with 5-fluorouracil intravenously and orally. Her symptoms were well controlled by 5-fluorouracil but this was discontinued eight years later when she developed abnormal liver function tests and thrombocytopenia. Notwithstanding, she remained reasonably healthy and functioned as a productive schoolteacher and housewife. Her 5-HIAA urinary levels throughout the 14 years of treatment were moderately elevated and ranged from 19 to 45 mg/24 hours (normal < 10 mg/24 hours). During the summer before her current admission, she developed severe flushing of the face and upper body, severe diarrhoea and occasional hypertension while her 5-HIAA urinary levels were significantly elevated (120 mg/24 hours) from previous levels.

Further investigation at the time of admission showed

Key words

SYNDROMES: carcinoid syndrome; PHARMACOLOGY: somatostatin.

From the Departments of Anesthesiology, Medicine (J.A.O.) and Surgery (J.F.S.), Vanderbilt University Medical Center, Nashville, Tennessee.

Address correspondence to: Dr. W.C.V. Parris, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee 37232.

three discreet nodular metastases of the liver on CT Scan and this was confirmed by magnetic resonance imaging (MRI). Echocardiogram showed tricuspid valve stenosis and tricuspid regurgitation. There was no evidence of right- or left-sided heart failure. Because of her worsening clinical signs and symptoms and the sudden elevation of her urinary 5-HIAA levels, exploratory laparotomy with hepatic resection of metastases was planned.

The patient was classified as ASA physical status III and was premedicated with diazepam 5 mg PO 90 minutes prior to surgery. Following the application of the routine monitors (Dinamap BP apparatus, ECG monitor, peripheral nerve stimulator, pulse oximeter, pre-cordial stethoscope and system for analysis of respiratory and anaesthetic gases), an arterial line and an internal jugular venous line were established. The preoperative blood pressure was 136/70 mmHg; pulse $74 \cdot \text{min}^{-1}$; mean central venous pressure 15 mmHg; electrocardiogram showed normal sinus rhythm; oxygen saturation 98 per cent (pulse oximetry). Immediate preoperative laboratory data were: haematocrit, 33.7 per cent, haemoglobin, 11.7 g, platelet count $210,000/\text{cm}^3$, prothrombin time, 12 seconds (control, 12 seconds); partial thromboplastin time, 28 seconds (control, 28 seconds); urinary 5-HIAA, 136 mg/24 hours; sodium, $145 \text{ mEq} \cdot \text{L}^{-1}$; potassium, $4.2 \text{ mEq} \cdot \text{L}^{-1}$; chloride, $108 \text{ mEq} \cdot \text{L}^{-1}$; CO_2 , $26 \text{ mmol} \cdot \text{L}^{-1}$; glucose, $90 \text{ mg} \cdot \text{dl}^{-1}$; blood urea nitrogen, $20 \text{ mg} \cdot \text{dl}^{-1}$.

After pre-oxygenation, anaesthesia was induced with fentanyl 450 μg and diazepam 5 mg IV. Tracheal intubation was facilitated by the administration of 8 mg vecuronium IV and a peripheral nerve stimulator was used to determine the optimal intubating conditions. Anaesthesia was maintained with fentanyl (total 1250 μg) nitrous oxide (2.0 L) and oxygen (1.0 L) with intermittent isoflurane (0.25 to 0.5 per cent).

The patient tolerated induction of anaesthesia without any haemodynamic changes. Skin preparation and draping (performed without significant mechanical stimulation) were uneventful and immediately after incision of the peritoneum but before surgical manipulation commenced, the patient was given somatostatin analogue 50 μg IV and 50 μg SC. The somatostatin analogue, considered an experimental drug, was provided by Sandoz Laboratories and Institutional Review Board permission was sought and obtained prior to using the drug. Informed consent was obtained from the patient preoperatively. During the manipulation of the liver the patient developed mild flushing of the head and neck with tachycardia (from a baseline of 60 to $110 \cdot \text{min}^{-1}$) and mild hypotension (from baseline $140/80$ to $93/52$ mmHg). While preparations to administer more somatostatin were being made, the blood pressure slowly began to rise again and remained in the normal range for the remainder of

the operation. Thus, no additional somatostatin was administered.

Laparotomy revealed that the liver was very fibrotic, nodular and cirrhotic and that no resectable masses were seen nor palpated. A large carcinoid tumour of the proximal ileum was resected and end-to-end ileal anastomosis was performed. Left oophorectomy was also performed because the left ovary was enlarged and cystic on gross examination. Subsequent histological examination of both the ileum and the ovary confirmed the diagnosis of carcinoid tumour.

Intraoperative arterial blood gases were within normal limits; central venous pressure did not change significantly during the case and the anaesthetic course was uneventful apart from the previously mentioned brief and mild hypotension. The fentanyl was reversed with naloxone 0.4 mg IV and naloxone 0.4 mg IM while the vecuronium was reversed with glycopyrrolate 0.8 mg and edrophonium 70 mg IV. The patient was extubated in the operating room and taken to the recovery room in satisfactory condition. She was observed overnight in the Surgical Intensive Care Unit and was transferred to her room the following day. Her postoperative course was uneventful and she was discharged home on the 12th postoperative day without any anaesthetic or surgical complications.

Discussion

The term carcinoid was first used by Oberndorfer⁶ in 1907 to describe the tumours which produce the symptom complex of flushing, bronchoconstriction, diarrhoea and cardiac disease. The term was applied to these tumours because they resembled carcinoma histologically but followed a more benign course than other malignant tumours. Although serotonin^{7,8} appears to be the most important mediator of this syndrome, other mediators do play a major role and they include bradykinin,⁹ histamine,¹⁰ prostaglandins,¹¹ substance P¹² and several others.¹³

There are several agents that may evoke flushing in patients with carcinoid syndrome. These include epinephrine, norepinephrine, isoproterenol and dopamine.¹⁴ It is interesting to note that while the α -antagonist phentolamine may prevent flushing induced by epinephrine, norepinephrine and dopamine, propranolol does not block flushing induced by epinephrine. The ingestion of foods may precipitate flushing probably by the consequent release of gastrointestinal hormones which may in turn evoke the release of vasoactive mediators from carcinoid tumours. Some of the gastrointestinal hormones, which have been shown experimentally to produce flushing in susceptible patients, include gastrin, pentagastrin and cholecystokinin.¹⁵

Somatostatin,¹⁶ or growth hormone release inhibitory

hormone, has been demonstrated to inhibit the release and the activity of several gastrointestinal hormones and also to inhibit the release of vasoactive mediators from the carcinoid tumour including serotonin. Clinically, it has been used to reverse the flushing, bronchoconstriction and diarrhoea associated with carcinoid syndrome. Further, it has been very effective in correcting the hypotension associated with carcinoid crisis intraoperatively and perioperatively. Using this basic information, somatostatin analogue was administered (50 µg IV and 50 µg SC) prior to celiotomy and manipulation of the tumour. During the manipulation of the liver, jejunum and ileum, there was mild hypotension, associated with flushing and tachycardia. While it cannot be proven, we speculate that severe hypotension and carcinoid crisis might have been averted by pre-treatment with somatostatin. The therapeutic effects of somatostatin are limited because of its very short half-life which is two to three minutes. Several analogues have been prepared to overcome this disadvantage. These analogues have greater potency than the tetradecapeptide somatostatin but their duration of action is not significantly extended.¹⁷ Some somatostatin analogues have also shown selective inhibition of the secretion of one hormone with lesser effects on others. The short duration of somatostatin analogue also precludes its use as a regular pre-medicant. Instead, it is effective when administered IV to treat a patient with carcinoid crisis after the syndrome is already manifest. Alternatively, somatostatin may be administered prophylactically SC or IM either before induction of anaesthesia or before tumour manipulation. To delay biodegradation and to prolong duration of activity, somatostatin analogue ought to be administered subcutaneously.

General management principles for the patient with carcinoid syndrome include adequate preoperative hydration and the administration of the anti-histaminic agents (diphenhydramine 50 mg) and anti-serotonin agents¹⁸ (cyproheptadine and ketanserin) just before or during the induction of anaesthesia. However, it appears that somatostatin has made the use of these agents superfluous. Consequently, these measures were not used in this case. More clinical data is required before a firm recommendation can be made at the present time. The operative site should be prepared and draped gently to minimize mechanical stimulation and consequent hypersecretion of sensitive carcinoid tumours. Other specific measures used in this case to avert the onset of carcinoid crisis intraoperatively include the avoidance of thiopentone and the non-depolarizing muscle relaxants with histamine-releasing properties, e.g., atracurium and d-tubocurarine.^{4,19} The adrenergic agonists epinephrine, norepinephrine and dopamine are also contraindicated. Succinylcholine is best avoided since the fasciculations

produced may increase intra-abdominal pressure with resultant secretion of the vasoactive substances from the tumour.

During carcinoid crises, major fluid shifts may occur in the various body water compartments. Effective treatment is best rendered by haemodynamic monitoring of the patient perioperatively. Central venous pressure monitoring and pulmonary artery catheterization with cardiac output monitoring are desirable especially in patients with cardiac manifestations of carcinoid syndrome. Urinary output measurements, intra-arterial monitoring and frequent blood gas determinations are mandatory.

The major objectives in treating patients with carcinoid syndrome and carcinoid tumours are the reduction of the tumour mass²⁰ and control of the disabling symptoms. The first objective may be accomplished by surgical excision when possible. When metastases have occurred, complete excision may not be possible and debulking whenever practical may provide satisfactory palliation. This is particularly true of liver metastases. In our patient, the liver metastases demonstrated on CT scan and magnetic resonance imaging were not palpable on surgical manipulation and consequently, hepatic resection was not done.

Prior to surgery, the disabling symptoms associated with carcinoid syndrome are controlled by a variety of chemotherapeutic agents²¹ with varying degrees of success. Streptozocin and 5-fluorouracil are the agents most commonly used. Our patient was well controlled for eight years with 5-fluorouracil which was discontinued when she developed serious liver dysfunction. Like 5-fluorouracil, most of the chemotherapeutic agents are associated with substantial systemic toxicity.

In conclusion, we present a patient with carcinoid tumour associated with carcinoid syndrome scheduled for exploratory laparotomy and hepatic resection. Pre-treatment with somatostatin analogue appeared to have prevented the development of carcinoid crisis in this patient. More studies are needed to determine the prophylactic value of somatostatin in the intraoperative management of patients with carcinoid syndrome.

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Résumé

Le syndrome carcinoïde produit du "flushing," bronchoconstriction et hypermotilité gastro-intestinale secondaire à la libération de sérotonine, histamine, bradykinine et de prostaglandine. Une variété de médicaments, produits alimentaires et agents anesthésiques peut provoquer ce syndrome. Sous anesthésie, le "flushing" peut être associé à une hypotension aiguë et un collapsus cardiovasculaire; ce phénomène est connu comme étant la crise carcinoïde. Récemment un analogue de la somatostatine a été utilisé avec succès pour traiter cette crise carcinoïde en période peropératoire. On présente ici le cas d'une femme de 66 ans atteinte d'un syndrome carcinoïde et qui fut pré-traitée avec 50 mg d'un analogue de la somatostatine par voie intraveineuse et intramusculaire avant la manipulation chirurgicale. La conduite anesthésique et les suites postopératoires furent sans complication.