ANAESTHESIA FOR THE CARCINOID SYNDROME: A REPORT OF NINE CASES*

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IT IS WELL RECOGNIZED that patients with the carcinoid syndrome are difficult to manage during anaesthesia.[1,2] Although the syndrome is rare, the number of such patients undergoing anaesthesia is increasing because long-term medical therapy is prolonging survival and surgical intervention either for resection of the primary tumor, excision of hepatic metastases, or hepatic dearterialization is becoming more common.[3] The total reported anaesthetic experience with the carcinoid syndrome is modest. Mason and Steane (1976) in a comprehensive review of the relevance of this syndrome to the anaesthetist found a total of only 40 anaesthetics described in nine papers.[1] They found that the incidence of complications, including hypotension, bronchospasm or hypertension was high, occurring in 27 of the reported cases. During the past two years nine patients with the carcinoid syndrome were anaesthetized in our own institution, seven of whom were managed by the authors. The hazards of anaesthesia in an unprepared and unrecognized patient are illustrated by one case, but the low incidence of significant complications in the remaining eight patients differs from the published experience of others and prompted the following brief case reports. Pre-operative laboratory data of interest are summarized in Table I.

Patient 1

A 35-year-old male was investigated for anaemia and weight loss.[4] There was no history of cutaneous flushing, wheezing, abdominal pain, or diarrhoea. Radiological studies indicated a polypoid gastric lesion which, following endoscopic biopsy was found to be a carcinoid tumor. Serum serotonin and urinary 5-Hydroxyindoleacetic acid (5HIAA) levels were within the normal range. Resection of the gastric tumor was planned. Pantopon and atropine were used for premedication. Anaesthesia was induced with Innovar and thiopentone. Tracheal intubation was facilitated with succinylcholine and thereafter anaesthesia and muscle relaxation were maintained with nitrous oxide and oxygen, fentanyl and pancuronium. Anaesthesia was initially uneventful but greatly increased peristalsis of the small bowel was observed. When the stomach was mobilized the blood pressure rose from 17.29/10.64 kPa (130/80 mm Hg) to 23.94/13.3 kPa (180/100 mm Hg) and the pulse rate from 80 to 160 beats per minute. Intense bronchospasm also developed and it became difficult to ventilate the patient. Blood gas analysis revealed a respiratory alkalosis and a metabolic acidosis. Halothane was added to the inspired mixture and hydrocortisone was administered intravenously without effect. No specific antiserotonin or antibradykinin agents were available in the operating room. Bronchospasm, hypertension and tachycardia persisted until a wide gastric resection of the tumor area had been performed, when the patient's condition dramatically improved. No further problems were encountered. Hepatic metastases were not found. Post-operatively 5HIAA levels were within normal limits.

Patient 2

A 44-year-old very apprehensive female with a history of severe facial flushing, facial swelling, urinary frequency and galactorrhoea was found to have increased bowel sounds, rapid transit of a barium meal through the small intestine and elevated urinary 5HIAA and serum 5 hydroxytryptophan levels. An exploratory laparotomy was scheduled. Premedication consisted of pantopon and scopolamine. Innovar and thiopentone were used for induction and succinylcholine given to facilitate intubation. Anaesthesia and relaxation were maintained with nitrous oxide oxygen, fentanyl and pancuronium. During induction of anaesthesia severe facial flushing occurred. Thereafter flushing occurred after each increment of fentanyl or pancuronium was administered throughout the procedure, the duration of which was two and three-quarter hours. There were no cardiovascular or respiratory complica-

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TABLE I

PRE-OPERATIVE LABORATORY DATA: NINE PATIENTS WITH CARCINOID SYNDROME

Patient	Serum µg/m		Plasma µg/ml	Urine mg/25 hours		Urine µg/24 hours	
	Serotonin (Normal 0.08–0.31)	5 Hydroxytryptophan (normal < 0.02)	Tryptophan (normal 9.5–16.0)	5 HIAA (normal 2–8)	Indoleacetic acid (Normal 3–8)	Tryptamine (Normal 25–125)	Histamine (normal 25–65)
1	0.11		10.0	5.5			
2	0.17	0.05		13.0	5.9	89	41
3	0.38	0.09	9.0	15.0			
4	0.77		5.2	211.0	5.1	416	37
5	1.15		3.6	17.8	4.9	165	
6	0.54		4.1	20.4	512	169	43
7	0.45		6.9	128	4.9	510	40
8	0.18		9.7	52.5	5.1	286	61
9	2.0		1.9	435	16.5	318	

tions. No primary tumor was found but liver biopsy revealed anaplastic adenocarcinoma.

Patient 3

A 76-year-old female with clinical features including abdominal pain, flushing, and hypermotility of small bowel, suggesting carcinoid syndrome, was investigated. Serum serotonin, five hydroxytryptophan and urinary 5HIAA levels were elevated and exploratory laparotomy was planned. Premedication consisted of secobarbitone and atropine. A thiopentone, pancuronium, nitrous oxide oxygen sequence was used to provide anaesthesia and relaxation. Following induction, a mean blood pressure of 14.63 kPa (110 mm Hg) was maintained, but on one occasion as the bowel was manipulated, the pressure rose to 26.6 kPa (200 mm Hg). Methotrimeprazine 2.5 mg was administered intravenously and the blood pressure returned to its former level after two or three minutes. Except for this brief hypertensive episode anaesthesia was uneventful. No tumor was found in the abdomen. Subsequently, a thyroid tumor was discovered. The nodule was "cold" on scan. The patient refused further surgery, was treated with chemotherapy and both her symptoms and the thyroid nodule subsided.

Patient 4

A 65-year-old female with proven carcinoid syndrome and a history of small bowel resection was admitted because of severe diarrhoea, flushing and weight loss, as a candidate for hepatic dearterialization. Serum serotonin and urinary 5HIAA levels were elevated.

She was maintained on steroids, lomotil and methysergide, but medical therapy was ineffective. She developed intestinal obstruction and signs of peritonitis which necessitated an emergency laparotomy with extensive lysis of adhesions. Numerous liver metastases were noted.

Premedication consisted of secobarbitone and atropine. Anaesthesia consisted of a thiopentone, pancuronium, nitrous oxide and oxygen sequence. During the three-and-a-half-hour operation no problems relating to the carcinoid syndrome occurred. The blood pressure remained consistently in the range 10.64/7.98 kPa (80/60 mm Hg) despite adequate fluid replacement but this problem was clearly related to septicaemia and hypovolaemia.

Five patients were anaesthetized for hepatic artery ligation. These patients were proven cases of the carcinoid syndrome with persistent elevations of serum serotonin and urinary 5HIAA excretion, unresponsive to medical therapy despite receiving a variety of therapeutic agents.[5]

Pre-operatively they were maintained on steroids and cyproheptadine. Neomycin orally and fructose 10 per cent intravenously were administered for three days pre-operatively.

Aprotonin (Trasylol) 200,000 units was given intravenously immediately before induction of anaesthesia or during induction.

Aprotonin, methotrimeprazine, angiotensin amide, methoxamine, and hydrocortisone were held ready in the operating rooms.

In addition to routine monitoring aids, the mean arterial pressure was recorded through a catheter placed in a radial artery and arterial blood was withdrawn at intervals for blood gas analysis.

The same anaesthetic technique was used for all five patients. Premedication consisted of secobarbitone and atropine. Thiopentone, pancuronium, nitrous oxide and oxygen were the only agents used. All patients were ventilated mechanically and a moderate respiratory alkalosis was maintained. Reversal of neuromuscular blockade was achieved with atropine and prostigmine.

Patient 5

A 52-year-old female with severe flushing, diarrhoea, and a history of a small bowel resection for a carcinoid tumor of Meckels diverticulum with elevated serotonin and 5HIAA levels underwent three hours of anaesthesia for hepatic artery ligation. Facial flushing was noted on several occasions. The mean blood pressure rose on two occasions from 12 to 16 kPa (90 to 120 mm Hg) but these hypertensive episodes were successfully treated with 2.5 mg of methotrimeprazine intravenously and were of brief duration. Postoperatively the patient was awake after five minutes but appeared drowsy for several hours.

Patient 6

A 66-year-old male with a history of small bowel carcinoid, flushing, diarrhoea, and weight loss, underwent three hours of anaesthesia for hepatic artery ligation. Two modest hypertensive episodes occurred when mean blood pressure rose from 14.63 to 21.28 kPa (110 to 160 mm Hg) and these were treated with methotrimeprazine. No other problems were encountered.

Patient 7

A 54-year-old female with severe symptoms of

the carcinoid syndrome, increased serotonin and 5HIAA levels and decreasing response to chemotherapy for biopsy-proven carcinoid tumor underwent two hours of anaesthesia for hepatic artery ligation.[6] Fifteen minutes after intubation bronchospasm developed. Hydrocortisone 200 mg and aprotonin 20,000 units were given with some improvement. Aprotonin 100,000 units and hydrocortisone 100 mg were given intravenously during the next hour, during which bronchospasm gradually diminished. At the end of the operation the chest was clear. In the recovery room she was drowsy for one hour postoperatively.

Patient 8

A 51-year-old female with a history of lung resection for bronchial carcinoid and persistent flushing, diarrhoea and weight loss, underwent four hours of anaesthesia for hepatic artery ligation. On three occasions the mean blood pressure rose from 13.3 to 21.28 kPa (100 to 160 mm Hg) but was easily restored with methotrimeprazine 2.5 mg intravenously.

Patient 9

A 65-year-old male was admitted with surgically proven carcinoid of small bowel, extensive hepatic metastases, carcinoid heart disease with congestive failure and organic mental syndrome suffering from severe flushing, diarrhoea and weakness unresponsive to chemotherapy. Serotonin and urinary 5HIAA levels were elevated. He received diazepam and Innovar for sedation while undergoing angiography with local anaesthesia. No problems occurred. This patient had an abnormal response to cyproheptadine, sleeping for 12 hours after a single dose and this drug was subsequently withheld. There were no complications during two and a half hours of general anaesthesia for hepatic artery ligation.

Discussion

Excluding one patient, the complications occurring during anaesthesia were minor in nature. Hypertensive episodes occurred in four additional patients and bronchospasm in one, but the degree of bronchospasm and vasomotor instability was only life-threatening in the patient with a gastric carcinoid tumor (Patient 1). This patient was atypical as there were no pre-operative symptoms of the carcinoid syndrome, nor were abnormal levels of serotonin or its metabolites detected. Other vasoactive substances sometimes associated with the carcinoid syndrome were not assayed. The combination of hypertension and bronchospasm is unusual since bronchospasm is usually associated with hypotension and thought to be due to bradykinin release.[1,2] Hypertension and tachycardia are thought to be due to an outpouring of serotonin.[1,2] Foregut carcinoid tumors are of neuro-ectodermal origin and in addition to serotonin may secrete a variety of hormonal agents including histamine, adrenaline, adrenocorticotrophic hormone, melanocyte stimulating hormone, insulin, glucagon, gastrin and secretin. Gastric carcinoid tumors in particular are sometimes associated with increased histamine secretion.

Foregut carcinoids may also secrete 5-hydroxytryptophan, a serotonin precursor, and histamine; such tumors are known to be associated with severe atypical carcinoid syndrome. Furthermore, prostaglandins are frequently produced by carcinoid tumors and may be responsible for flushing and bronchospasm.[8]

In patient 2 the clinical features suggesting carcinoid syndrome and the modest elevation of urinary 5HIAA levels in the presence of metastatic adenocarcinoma may indicate aberrant hormone production from a non-carcinoid tumor, also resulting in an atypical carcinoid syndrome.

Hypotension was not a problem in this group of patients.

Delayed awakening occurred in two patients without leading to any untoward sequelae. In most cases drug administration was limited to secobarbitone, atropine, thiopentone, pancuronium, and nitrous oxide. The technique used was essentially that described by Mason and Steane who, however, also used fentanyl.[9] We chose to exclude fentanyl because this agent may occasionally cause ventilatory difficulties due to muscle rigidity.[10]

Most agents used during anaesthesia may be associated with histamine or serotonin release and, therefore, it would seem prudent to limit the number of drugs used. The use of morphine for premedication in two patients and succinylcholine for intubation in three patients was inappropriate. Morphine may provoke serotonin or histamine release.[11] The increase in intra-abdominal pressure occurring after succinylcholine[12] may precipitate a carcinoid crisis.

Steroids, aprotonin and methotrimeprazine have been considered helpful in the anaesthetic management of patients with the carcinoid syndrome.[1]

Steroids are sometimes very effective in con-

trolling severe prolonged flushing and probably act by blocking kinin release. Though useful prophylactically they are probably ineffective once kinins have been liberated.[13]

Aprotonin inhibits tumor kallikrein *in vitro* but its intravenous administration has not been effective in controlling spontaneous or provoked flushing.[14]

Aprotonin is not universally available. It may, however, be helpful as an antikinin agent when bronchospasm occurs.[2] In those cases undergoing hepatic artery ligation, informed consent was obtained for the use of aprotonin, but whether the administration was beneficial is unclear. Certainly no ill effects were associated with aprotonin administration. The recommended vasopressors,[15] angiotensin and methoxamine, were not used; but from the experience of others it is clearly necessary to have one of these agents available.

Methotrimeprazine is a potent antiserotonin agent and was very effective in controlling hypertension. On every occasion when methotrimeprazine was administered to treat a hypertensive episode, the episode was aborted. There were no dramatic changes in pulse rate during the brief periods of hypertension. It is possible that these hypertensive episodes were not hormonal in origin but due to inadequate anaesthesia; methotrimeprazine is also a potent analgesic and would be expected to be effective in such circumstances.

Unfortunately, neither aprotonin nor methotrimeprazine were available in the operating room for patient I.

Over-all, our clinical experience indicates that anaesthesia for patients with the carcinoid syndrome may not be as hazardous as previously reported, provided that patients are adequately prepared and antiserotonin and antikinin agents are available.

Summary

Anaesthesia for nine patients with the carcinoid syndrome is described. With the exception of one case in which severe bronchospasm and hypertension occurred, complications were minor. Steroids, aprotonin and methotrimeprazine appear to be useful agents in the management of such patients. An anaesthetic technique employing thiopentone, pancuronium and nitrous oxide proved satisfactory.

Résumé

Les auteurs rapportent leur expérience anesthésique de neuf cas de malades présentant un syndrome carcinoïde. A l'exception d'un cas où est survenu un bronchospasme important avec hypertension, ils n'ont observé que des complications mineures. Les stéroïdes, l'aprotonine et la méthoxymeprazine sont des agents qui peuvent contribuer à la bonne marche de ces interventions. Comme méthode d'anesthésie, l'emploi de thiopenthal, de protoxyde d'azote et de pancuronium s'est avéré une technique satisfaisante.

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