Remifentanil and anaesthesia for carcinoid syndrome

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Carcinoid syndrome creates many challenges during anaesthesia, including hypertension, hypotension and bronchospasm. These challenges are less common and less severe after the routine use of octreotide. We describe the use of remifentanil as part of the anaesthetic management of a 67-yr-old man undergoing resection of a carcinoid tumour of the terminal ileum. The combination of perioperative octreotide administration, intraoperative remifentanil infusions and sevoflurane anaesthesia, with postoperative epidural analgesia proved satisfactory. We review the recent literature and suggest that remifentanil is a useful addition to the armamentarium of the anaesthetist in the management of a patient with carcinoid syndrome.

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Carcinoid tumours are rare neoplasms of neuroendocrine tissue derived from enterochromaffin or Kulchitsky cells. The annual incidence is approximately 0.28 per 100 000 population. Carcinoid syndrome results from the direct release of vasoactive amines and peptides into the systemic circulation, usually from liver metastases associated with mid-gut carcinoids, or from bronchial or ovarian primary tumours. Patients with carcinoid syndrome may require anaesthesia for resection of the primary tumour, and for excision or radiofrequency ablation of hepatic metastases. Remifentanil has been used during resection of other rare endocrine tumours, but this is the first report of its use in a patient with carcinoid syndrome.

Case report

A 67-yr-old man was referred to the endocrine physicians with a 6-week history of severe hot flushes. These occurred three times a day, particularly in the morning and after food. He also complained of rectal bleeding but colonoscopy and upper gastrointestinal endoscopy revealed no abnormality. He had a 3-yr history of unstable hypertension, treated with bendrofluazide 2.5 mg daily. Cardiac examination was normal, and two finger-breadths of liver were palpable below the right costal margin.

Twenty-four hour urine collection revealed normal catecholamines but raised concentrations of 5-hydroxyindoleacetic acid of 236 \( \mu \text{mol} \) 24 h\(^{-1}\) (normal range 10–47 \( \mu \text{mol} \) 24 h\(^{-1}\)). The concentration of liver enzymes was slightly elevated. Computerized tomography and an octreotide-somatostatin receptor study indicated liver metastases. A liver biopsy, guided by ultrasound, was consistent with carcinoid tumour and a bone scan identified involvement of the thoracic cage and sacrum. No focal lesion was identified by a small bowel series but capsule endoscopy, a new investigation that provides direct endoscopic visualization of the small bowel with computerized imaging, indicated a small polyp in the ileocaecal region. The plasma concentration of the gastrointestinal hormone neurokinin A was significantly elevated at 150 ng litre\(^{-1}\) (normal range 0–20 ng litre\(^{-1}\)). This finding was in keeping with a diagnosis of a mid-gut carcinoid tumour.

Subcutaneous octreotide 200 \( \mu \text{g} \) three times per day relieved the symptoms of diarrhoea and flushing so the longer acting somatostatin analogue, lanreotide, 120 mg monthly by i.m. injection, was prescribed for ongoing control of symptoms. The patient was scheduled for laparotomy, liver biopsy and probable small bowel resection.

Pre-anaesthetic history and examination confirmed the previous findings. Anaesthetic history included an uneventful appendicectomy 30 yr previously and mastoidectomy 20 yr previously. Haemoglobin, urea, electrolytes and chest radiograph were normal. The ECG showed sinus bradycardia with first-degree AV block but no evidence of valvular heart disease.

Premedication included subcutaneous octreotide 100 \( \mu \text{g} \) and oral temazepam 20 mg. I.V. access was established and an epidural catheter was placed at the T12–L1 interspace with 8 cm of catheter left in the epidural space. A 3 ml test dose of bupivacaine 0.25% was injected to exclude intrathecal placement, but no further epidural bupivacaine was injected until towards the end of the procedure. An arterial line was inserted and vasopressors (phenylephrine and ephedrine), vasodilators (including sodium nitroprusside) and octreotide were readily available. An infusion of remifentanil was commenced at 0.2 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \). Anaesthesia was induced with propofol 150 mg and neuromuscular blockade was provided by vecuronium 10 mg with incremental doses of 2 mg throughout surgery. Anaesthesia was maintained by an infusion of remifentanil 0.2 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) and sevoflurane 1% in an air/oxygen mixture. A central venous line was placed in the right internal jugular vein and a urinary catheter and nasogastric tube inserted. A test dose of morphine 2 mg was given before surgery started without any haemodynamic disturbance or urticaria. After 35 min, the remifentanil infusion was reduced from 0.2 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) to 0.15 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \). No bolus doses of remifentanil were required.

Additional drugs included ondansetron 8 mg, cefuroxime 1.5 g and metronidazole 500 mg. Octreotide 100 \( \mu \text{g} \) diluted into 10 ml with sodium chloride 0.9% was prepared for management of any intraoperative carcinoid crisis, but was not required. During the operation, there was an episode of flushing when the tumour was handled, but no evidence of bronchospasm.

The entire procedure lasted 4 h; arterial pressure, heart rate and central venous pressure remained virtually unchanged throughout the procedure. Laparotomy confirmed multiple large metastases throughout the liver, one of which was biopsied. A small, mobile, intraluminal tumour was resected from the terminal ileum, followed by an end-to-end anastomosis. Blood loss was minimal and intravenous fluids consisted of Ringer lactate 1 litre and saline 0.9% 1 litre.

Towards the end of the operation, epidural anaesthesia was established with a titrated injection of bupivacaine 0.25% 10 ml, and continued after surgery with a continuous infusion, via an Abbott pain management provider pump, of
bupivacaine 0.1% with fentanyl 5 \( \mu \text{g} \ \text{ml}^{-1} \) at a rate of 8–10 ml h\(^{-1} \). Octreotide, antibiotics and enoxaparin were continued. Postoperative recovery was uneventful. Histological examination of the resected specimen confirmed the diagnosis of carcinoid tumour.

**Discussion**

Anaesthetic considerations in patients with carcinoid syndrome include the prevention of mediator release, avoiding triggering factors and preparation for the management of perioperative carcinoid crises.\(^4\) Premedication with an anxiolytic that does not have histamine-releasing properties is recommended to reduce the release of catecholamines as a result of preoperative stress, and it is logical to add an antihistamine. We chose to add ondansetron, an anti-serotonin, since patients with gastrointestinal motility disorders, including carcinoid syndrome, have shown some improvement when treated with this drug.\(^5\)

Preoperative treatment with the somatostatin analogue octreotide has been shown to improve the perioperative course of these patients.\(^6\) Premedication with subcutaneous octreotide 100 \( \mu \text{g} \) suppresses serotonin and kinin activity during surgery.\(^6\) Additional factors in the operative setting that trigger the release of carcinoid mediators include the response to intubation, inadequate analgesia, hypotension, the use of drugs that release histamine, intraoperative tumour handling and hypertension, which causes the release of bradykinin. In a recent series, 43% of patients received vasopressors, either phenylephrine or ephedrine, and 38% of patients required intraoperative octreotide. The median dose of octreotide was 350 \( \mu \text{g} \).\(^6\)

Unlike morphine and pethidine, remifentanil has very little potential for histamine release. While little has been written on this topic, remifentanil has been suggested to reduce the likelihood of histamine release in patients with mastocytosis.\(^7\) Severe hypotension after administration of morphine has been reported in such a patient.\(^8\) Remifentanil infusion has the advantages of good suppression of the intubation response, adequate analgesia, rapid titratability and the ability to control any intraoperative hypertension. These attributes are useful in the management of a patient with carcinoid syndrome. A potential disadvantage is the occurrence of hypotension, especially at higher infusion rates. At an infusion rate of 0.15–0.2 \( \mu \text{g} \ \text{kg}^{-1} \ \text{min}^{-1} \), the haemodynamic variables were virtually unchanged in this patient. Other narcotics that have been used in the management of carcinoid syndrome include sufentanil and fentanyl.\(^9,10\)

There is a risk that epidural anaesthesia could cause hypotension, triggering mediator release and a carcinoid crisis.\(^11\) However, the successful use of epidural anaesthesia for transurethral resection of the prostate in a patient with carcinoid syndrome has been reported,\(^12\) although it is worth noting that the tumour was not being manipulated in this case.

In our patient, epidural analgesia was adequate and did not produce any adverse haemodynamic consequences during the postoperative period of 72 h, after which the catheter was removed. The use of epidural analgesia is only advised in carcinoid patients who have been adequately treated before surgery with octreotide and provided that local anaesthetic is administered in a graded manner with careful haemodynamic monitoring. A diluted concentration of bupivacaine 0.1% is advised in the postoperative period.

A test dose of i.v. morphine was administered after induction without any haemodynamic consequences. This was given to find whether patient controlled analgesia (PCA) with morphine was an option in the postoperative period, if epidural analgesia failed or caused significant hypotension. Those wishing to completely avoid the potentially harmful effects of morphine may choose PCA with fentanyl as a safer option.\(^6\)

In summary, the combination of intraoperative remifentanil infusion and postoperative epidural analgesia is a helpful addition to the recommended technique for the anaesthetic management of a patient with carcinoid syndrome.

**References**