Anesthesiology 2003; 98:1005–7

Subdural Spread of Local Anesthetic Agent following Thoracic Paravertebral Block and Cannulation

Ignacio Garutti, M.D., Monica Hervias, M.D.,* Jose Maria Barrio, M.D.,* Fernando Fortea, M.D.,† Jesus de la Torre, M.D.†*

THORACIC paravertebral block has been shown to be effective for surgical anesthesia when the afferent pain input is predominantly unilateral from the chest. We describe a patient scheduled for right thoracotomy with combined paravertebral–general anesthesia who had abnormal responses to local anesthetic injection administered *via* the paravertebral catheter. The catheter subsequently was found to be in the subdural space. To our knowledge, this is the first report to be published in the anesthesia literature of a subdural blockade occurring during intended cannulation to paravertebral space.

Case Report

A 49-yr-old woman with a lung bronchogenic carcinoma was scheduled for a medial lobectomy. Her medical history included asthma treated with inhaled bronchodilators; there was no history of medication allergies.

No premedication was given. In the operating room, a 16-gauge intravenous access was obtained and the usual monitoring (electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring) was initiated without any remarkable findings. Five hundred milliliters of Ringer's lactate solution was infused, and induction of anesthesia was initiated with 120 mg propofol, 150 μg fentanyl, and 50 mg rocuronium. A double-lumen tube was then inserted (Robertshaw, left side, no. 39). Anesthesia was maintained with a 0.8–1.2% concentration of sevoflurane and a rocuronium perfusion (0.6 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}), and her lungs were ventilated with a fraction of inspired oxygen of 1.

After induction of anesthesia, the patient was placed on her left side in order to perform a right paravertebral block with cannulation for management of the perioperative pain (surgery and postoperative pain). An 18-gauge Tuohy needle (Perisafe® Plus; Becton-Dickinson, Warwickshire, Switzerland) was inserted 2.5 cm lateral to the aspect of the spinous process of T6 and advanced perpendicular to the skin in all planes. After encountering the costotransverse ligament, we advanced the needle approximately 1.5 cm further until there was loss of resistance to the injection air.

After negative aspiration, 3 cm of the epidural catheter (closed-end round catheter, 20 gauge) was inserted into the paravertebral space. The catheter was then checked with the negative aspiration test, and 3 ml bupivacaine, 0.5%, with epinephrine (1:200,000) was injected. There were no hemodynamic changes during the next 10 min, and another 12 ml of bupivacaine, 0.5%, without epinephrine was injected. Fifteen minutes after this second bolus, the patient's blood pressure decreased substantially (to 70/40 mmHg), as did the heart rate (48 beats/min). There were no wide variations on the arterial pressure curve area related to mechanical ventilation. All lung auscultation findings, airway pressures, and pressure–volume curves were absolutely normal during the period between intubation and the beginning of one-lung ventilation.

Sevoflurane administration was discontinued, followed by the rapid infusion of 500 ml of a colloid and the administration of 10 mg ephedrine intravenously. The dosing of ephedrine was repeated twice but did not increase the systolic blood pressure to higher than 100 mmHg, so a 0.1-μg $\cdot$ kg^{-1} $\cdot$ min^{-1} infusion of norepinephrine was initiated, with good results. During the next 60 min the norepinephrine infusion rate was progressively reduced, and the infusion was finally stopped due to hemodynamic stabilization. The thoracotomy was started in this left lateral position, and sevoflurane administration was reinitiated then. The heart rate did not change for the rest of the surgery (180 min total). No other analgesic administration was needed during the rest of the surgery until the thoracic wall closure, when a slight increase in the heart rate and blood pressure suggested some pain, and 100 μg fentanyl was given intravenously.

At the end of surgery (40 min after this fentanyl administration and 10 min after the end of sevoflurane administration) the patient was awake and helpful, and the ventilation pattern was good, so she was extubated. She was moved to the intensive care unit. The patient did not have any sensory or motor blockade. Once the patient had been monitored and no hemodynamic, ventilatory, or any other changes were noted, we decided to check the placement of the catheter, with the patient's permission. After a negative aspiration test, 15 ml of the contrast medium Iopamiro-300 (Iopamidol, 300 mg/ml; Rovi, Madrid, Spain) was injected through the catheter with the patient seated. Two chest radiographs were obtained: lateral (fig. 1) and posterior–anterior. The lateral view (fig. 1) showed the characteristic "railroad tracks" from the lumbar region to the cervical region. Furthermore, computed tomography thoracic–abdominal imaging (fig. 2) was performed to confirm the contrast extension. The contrast circumferentially outlined the thecal sac (subdural spread sign).

The catheter was removed immediately. A postoperative intravenous analgesia infusion (meperidine and ketorolac) was initiated and was continued for the next several days in the wards. The patient was discharged from the wards 7 days later, with no other incidents during her hospitalization.

Discussion

Subdural cannulation has been described as a complication of intended anesthetic blocks (epidural, dural, and even interscalene block), but there are no published reports of a subdural block with an intended paravertebral block. However, some cases of total spinal block[1] have been described, and a postpuncture headache has been reported as a possible complication of paravertebral block.[2]

The subdural space is a potential space located between the dura mater and the arachnoid mater. The dura mater extends laterally some "cuffs" along the nerve

* Medical doctor, Department of Anesthesiology and Reanimation, † Medical doctor, Department of Radiology.

Received from the Department of Anesthesiology and Reanimation, Hospital General Universitario Gregorio Maranon, Madrid, Spain. Submitted for publication November 5, 2001. Accepted for publication June 26, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Garutti: c/o Dr. Esquerdo 46, Madrid 28007, Spain. Address electronic mail to: ngarutti@inicia.es.

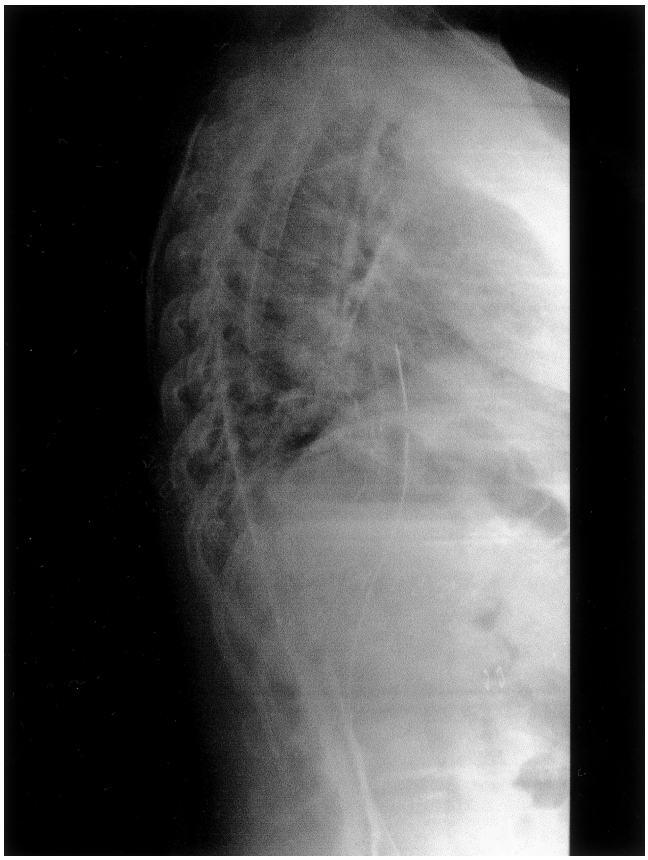

Fig. 1. Chest radiograph, lateral view: the contrast medium injected through the paraspinal catheter appears anterior and posterior to the spinal cord, along the dorsal and lumbar spinal levels.

roots at the spinal level, which are in contact with the spinal ganglion. Sometimes these dural cuffs are prolonged to the paravertebral space as a normal anatomic variation. Abnormal variations (meningocele, perineural cysts) are possible and can be discovered in image studies with contrast medium. The radiologic studies of our patient could not completely eliminate the possible existence of these abnormal anatomic variations that would have facilitated the subdural block. Another possibility could be that the needle advancement was anterior–medial instead of directly anterior, which would greatly increase the chances of a dural cuff injury and/or entry in the subdural space.

Lubenow *et al.*[3] described the two major and the three minor clinical criteria for the diagnosis of subdural block. Our patient met one of the major criteria (negative aspiration), and the other—unsuspected widespread sensory block—was probably present but masked by the simultaneous general anesthesia. The minor criteria included delayed onset and massive sympatholysis (hypotension and possibly pupil dilatation), which was out of proportion to the dose of local anesthetic agent injected. The third minor criterion described by Lubenow *et al.*[3], which may have been present but masked by the general anesthesia, was variable motor block. This last minor criterion is an issue with intended epidural anesthesia but is not a consideration with intended thoracic paravertebral block.

The contrast medium injected through the paraspinal catheter surrounded the spinal cord except for the site of the spinal ganglia, a circumstance that was related to the extraarachnoid location of the contrast medium, but it was impossible to determine where the tip of the catheter was. The extension of the contrast medium along several vertebral bodies—near the complete dorsal and lumbar spine, as was shown in the lateral view of the chest radiograph—points out the contrast in the subdural space; if it had been in the epidural space, the contrast would have been limited to a smaller extension.[4]

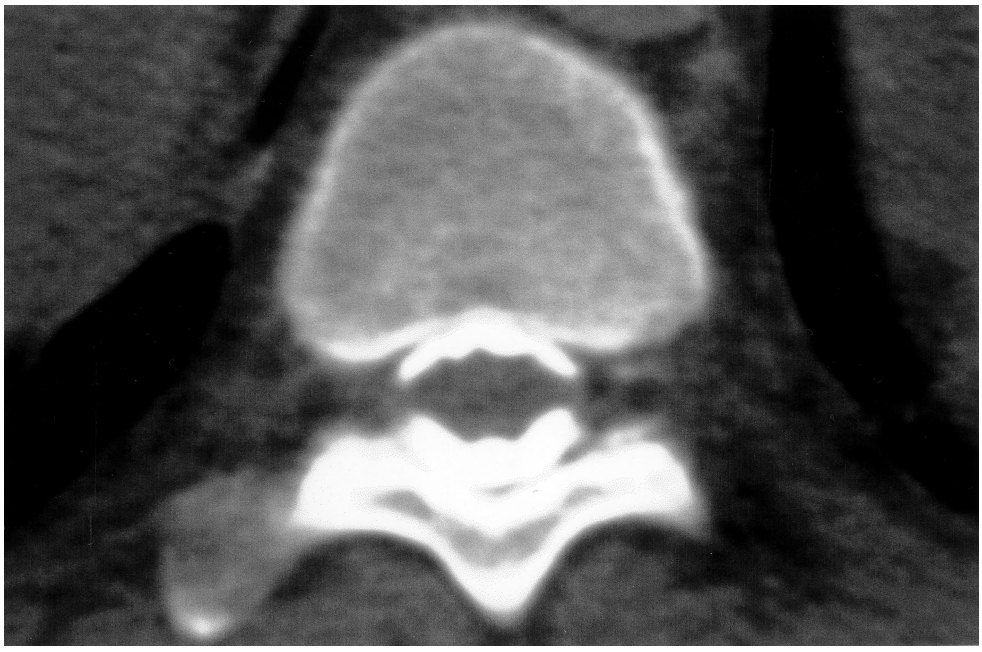

Fig. 2. Computed tomographic image of the spine, axial view: the contrast medium injected through the paraspinal catheter is surrounding the spinal cord, except at the site of spinal ganglia (subdural spread sign).

The occurrence of hypotension with paravertebral blocks usually is related to hypovolemia by unilateral vasodilation,[5] but the paravertebral volume injected in this patient was too small (15 ml) to produce an extended sympathetic block, which could have explained the profound hypotension. Recently, Saito *et al.*[6] showed an increase in blood pressure when 22 ml lidocaine was injected into the paravertebral space. In our patient, the extreme hypotension was the clue that made us suspect a block other than a paravertebral one.

Four different blocks had to be considered: thoracic paravertebral block, thoracic epidural block, subarachnoid block, and subdural block. Clinical manifestations of a subdural block at the thoracic level range from hypesthesia of the affected dermatomes to full respiratory arrest with severe hypotension or cardiac arrest.[3] Definitive diagnosis requires radiologic studies with contrast medium injected through the catheter.

The low incidence of severe complications associated with paravertebral blocks makes anesthesiologists confident about this technique. A good knowledge of the anatomy of the paravertebral space is important to understanding possible severe complications. The number of paravertebral catheters being placed for management of postoperative pain is great, but the incidence of complications, such as malpositioning of catheters, is unknown. Abnormal behavior of local anesthetics administered in a paravertebral catheter should lead one to suspect a subdural block; its early detection can prevent serious consequences. The removal of these catheters is necessary due to the unpredictable behavior of anesthetics in the subdural space.

References

1. Lekhak B, Bartley C, Conacher ID, Nouraei SM: Total spinal anaesthesia in association with insertion of a paravertebral catheter. Br J Anaesth 2001; 86: 280–2
2. Sharrock NE: Postural headache following thoracic somatic paravertebral nerve block. ANESTHESIOLOGY 1980; 52:360–2
3. Lubenow T, Keh-Wong E, Kristof K, Ivankovich O, Ivankovich AD: Inadvertent subdural injection: A complication of an epidural block. Anesth Analg 1988; 67:175–9
4. Lamasters DL, De Groot J, Autchon V, Williams AL: Normal thoracic spine, Computed Tomography of the Spine and Spinal Cord. Edited by Newton TH, Potts DG. San Anselmo, California, Clavadel Press, 1983, pp 74–92
5. Richardson J, Sabanathan S: Thoracic paravertebral analgesia. Act Anesthesiol Scand 1995; 39:1005–15
6. Saito T, Den S, Cheema SP, Tanuma K, Carney E, Carlsson C, Richardson JA: Single-injection, multi-segmental paravertebral block-extension of somatosensory and sympathetic block in volunteers. Acta Anaesthesiol Scand 2001; 45:30–3

Anesthesiology 2003; 98:1007–11

Somatostatin Does Not Prevent Serotonin Release and Flushing during Chemoembolization of Carcinoid Liver Metastases

Christian Zimmer, M.D., Peter Kienbaum, M.D.,† Richard Wiesemes, M.D.,† Jürgen Peters, M.D.‡*

CARCINOID tumors are rare neoplasms of the neuroendocrine amine precursor uptake and decarboxylation cell system, with an incidence of 1 to 2 cases per 100,000.[1] They originate from different embryonic divisions of the gut, most commonly the appendix and small bowel and rarely from the rectum or lung.[2] These tumors usually produce a variety of hormones and biogenic amines, such as serotonin (5-HT), but also potentially produce histamine, substance P, prostaglandins, or kallikrein.[2]

The carcinoid syndrome is characterized by flushing with facial telangiectasia, diarrhea, and bronchospasm and is caused by insufficient hepatic metabolism or direct release of 5-HT and biogenic amines into the systemic circulation, due to liver metastases or extraportal primary carcinoid tumors. The heart may be affected by tricuspid insufficiency, endocardial fibrosis, or pulmonary valve stenosis.[3] Patients with nonresectable liver metastases may benefit from chemoembolization, which may achieve good symptom control and improved quality of life.[4]

However, tumor manipulation may, by massive release of mediators, trigger an acute, potentially lethal carcinoid crisis. According to a standard textbook of anesthesia, perioperative administration of somatostatin is the "therapy of choice for the management of carcinoid symptoms and crisis," because somatostatin is a "powerful inhibitor of release of peptides."[5]

However, this recommendation, although widely considered a clinical standard, is based on case reports and a small series of patients.[6] In a recently published retrospective analysis of 119 patients undergoing abdominal surgery for metastatic carcinoid tumors between 1983 and 1996, the authors stated that without intraoperative octreotide treatment, 8 of 73 patients developed complications compared with 0 of 45 patients treated with octreotide intraoperatively.[7] Accordingly, we examined the effectiveness of prophylactic somatostatin infusion on suppressing 5-HT concentrations during three succes-

* Resident in Anesthesiology, † Staff Anesthesiologist, ‡ Professor of Anesthesiology and Intensive Care Therapy and Chairman.

Received from the Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany. Submitted for publication April 19, 2002. Accepted for publication August 20, 2002. Support was provided solely from departmental sources.

Address reprint requests to Dr. Zimmer: Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Hufelandstr. 55, D-45122 Essen, Germany. Address electronic mail to: christian.zimmer@uni-essen.de.

sive chemoembolizations performed in the same patient with carcinoid syndrome during monitored anesthesia care.

Case Report

A 48-yr-old woman (163 cm, 54 kg) with carcinoid syndrome due to nonresectable liver metastases (two bulky metastases in the right lobe and diffuse small metastases in the left lobe) from an ileum carcinoid resected 2 yr previously was scheduled for a series of chemoembolizations *via* the hepatic artery during monitored anesthesia care. With indium-111-octreotide scintigraphy (150 MBq), bulky nuclide enhancements were detectable in the right liver lobe and in the central liver, demonstrating an octreotide receptor–positive carcinoid tumor.

Except for flushing of the face three or four times daily, the patient was free of symptoms for 1.5 yr after her first operation. The symptoms worsened (flushing and diarrhea) 6 months ago, and the serum 5-HT concentration (1,430 μg/l; reference range, 110–330 μg/l) and urinary excretion of 5-hydroxyindole acetic acid (265 mg/24 h; reference range, 2–9 mg/day) were markedly increased. Therefore, octreotide acetate treatment was started and diminished the tumor-related symptoms, especially diarrhea. However, to achieve better and longer-lasting symptom control, chemoembolization of the bulky metastases was planned.

On the day of the preanesthetic examination the patient presented in slightly reduced physical condition and reported a history of intermittent flushing of the face, hypotension during flushing, and diarrhea. Findings of chest radiography, echocardiography, and laboratory tests were normal except for an increased serum 5-HT concentration (583 μg/l), an increased 5-hydroxyindole acetic acid urinary excretion (83 mg/day), and a slight increase in γ-glutamyl transferase (26 U/l; reference range, 4–18 U/l). The patient's medication for symptom control (200 μg octreotide acetate three times daily subcutaneously) was continued until the morning of chemoembolization.

For pressure measurements, arterial and central venous catheters were inserted *via* the right internal jugular vein and left radial artery during local anesthesia before each chemoembolization, and the electrocardiogram (lead II) was monitored. Central venous blood was withdrawn for measurements of 5-HT concentrations in both whole blood and plasma. For measurements in whole blood, blood was withdrawn in an EDTA tube, immediately cooled in crushed ice, and stored at −20°C until analysis. For measurements in plasma, sampling tubes with EGTA and glutathione were used and centrifuged, and the plasma was stored at −20°C until analysis.

Prior to chemoembolization, the patient received prednisolone (250 mg intravenously), as well as the histamine H1 and H2 receptor antagonists clemastine (120 mg intravenously) and cimetidine (400 mg intravenously). Furthermore, somatostatin was infused continuously ($0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$), as recommended for prophylaxis of carcinoid crisis. The patient was then brought to the angiography suite.

For pain control, the patient received the long-acting opioid piritramide (7.5 mg intravenously), metamizol (2.5 g intravenously), and a remifentanil infusion adjusted to deliver 40–120 μg/h as needed. 5-HT concentrations were measured during specified stages of the procedure (*e.g.*, at catheter placement in the hepatic artery and at embolization) and particularly during flushing.

Despite somatostatin infusion, hemodynamic conditions were quite unstable, and the patient showed severe flushing several times during the first session of chemoembolization of the bulky metastases in the right liver lobe. To treat hypotension, phenylephrine and theoadrenalin–caffedrine were injected. Furthermore, 2.5–5 mg ketanserin, a specific 5-HT_2-receptor antagonist, was repeatedly injected to control hypertension.

5-HT concentrations in whole blood were markedly increased even before intervention, but, despite flushing episodes, they varied little throughout the procedure (fig. 1). In contrast, 5-HT concentrations in plasma showed an almost sixfold fluctuation, between 205 and 1,578 μg/l (fig. 1). However, no apparent correlation was observed between 5-HT concentrations in plasma and either flushing episodes or hypotension.

The same prophylaxis was administered before the subsequent two chemoembolizations. While hemodynamic conditions during the second intervention (repeated embolization of the metastases in the right lobe 6 weeks later) were much more stable than in the first procedure, 5-HT concentrations in whole blood were also much increased at baseline and varied in a similar range (982–1,250 μg/l). Again, plasma 5-HT concentrations varied widely (85–1,072 μg/l). Although vasoconstrictor therapy was not necessary, ketanserin was used to control hypertensive episodes. Again, no apparent correlation was seen between 5-HT plasma concentrations and blood pressure alterations.

Before the third chemoembolization 4 months later, the patient's condition had much improved, octreotide had been withdrawn, flushing episodes were rare, and the diarrhea had stopped. Embolization of a small metastasis in the left liver lobe was hemodynamically uneventful. Initial 5-HT concentrations in whole blood, however, were even higher (1,352–1,640 μg/l) than at the previous baseline before interventions, but they did not change much during the procedure. Although 5-HT concentrations in plasma increased immediately from 240 to 330 μg/l after the start of embolization to 677 and 558 μg/l, no hypotension or bronchospasm occurred, despite the nausea reported by the patient.

Discussion

Since patients with carcinoid syndrome undergoing tumor manipulation are prone to develop carcinoid crisis, avoidance of mediator release is an important goal.

Somatostatin and its longer-acting analog, octreotide, are commonly used for symptom control in patients with carcinoid syndrome.[8] Perioperative administration of somatostatin or octreotide is recommended as intravenous prophylaxis for carcinoid crisis, either at a dosage of 100 μg/h or as a 50-μg single dose, in addition to preoperative administration of corticosteroids and antihistaminic drugs.[5,8] Although the cellular mechanism of the action of somatostatin is still unclear, five subtypes of somatostatin G-protein-coupled receptors (sstr 1–5) have been identified. Most midgut carcinoid tumors express at least one somatostatin receptor subtype, and many express all five subtypes.[9] Octreotide may bind to any of the five subtypes, but there is evidence that its action regarding the prevention of mediator release is strongly associated with sstr-2.

Among 25 carcinoid patients, all 7 patients with a positive octreotide scan but without expression of sstr-2 mRNA failed to respond to octreotide treatment.[10] A missing sstr-2 is therefore probably responsible for about 20% of cases involving a positive octreotide scan without successful response to octreotide treatment.[10] Polyclonal antibodies against sstr-2 for immunohistochemical studies, together with octreotide scintigraphy, may help to identify patients suitable for somatostatin analog treatment.[11]

However, our patient's octreotide scintigraphy results were positive, and good initial symptom control was

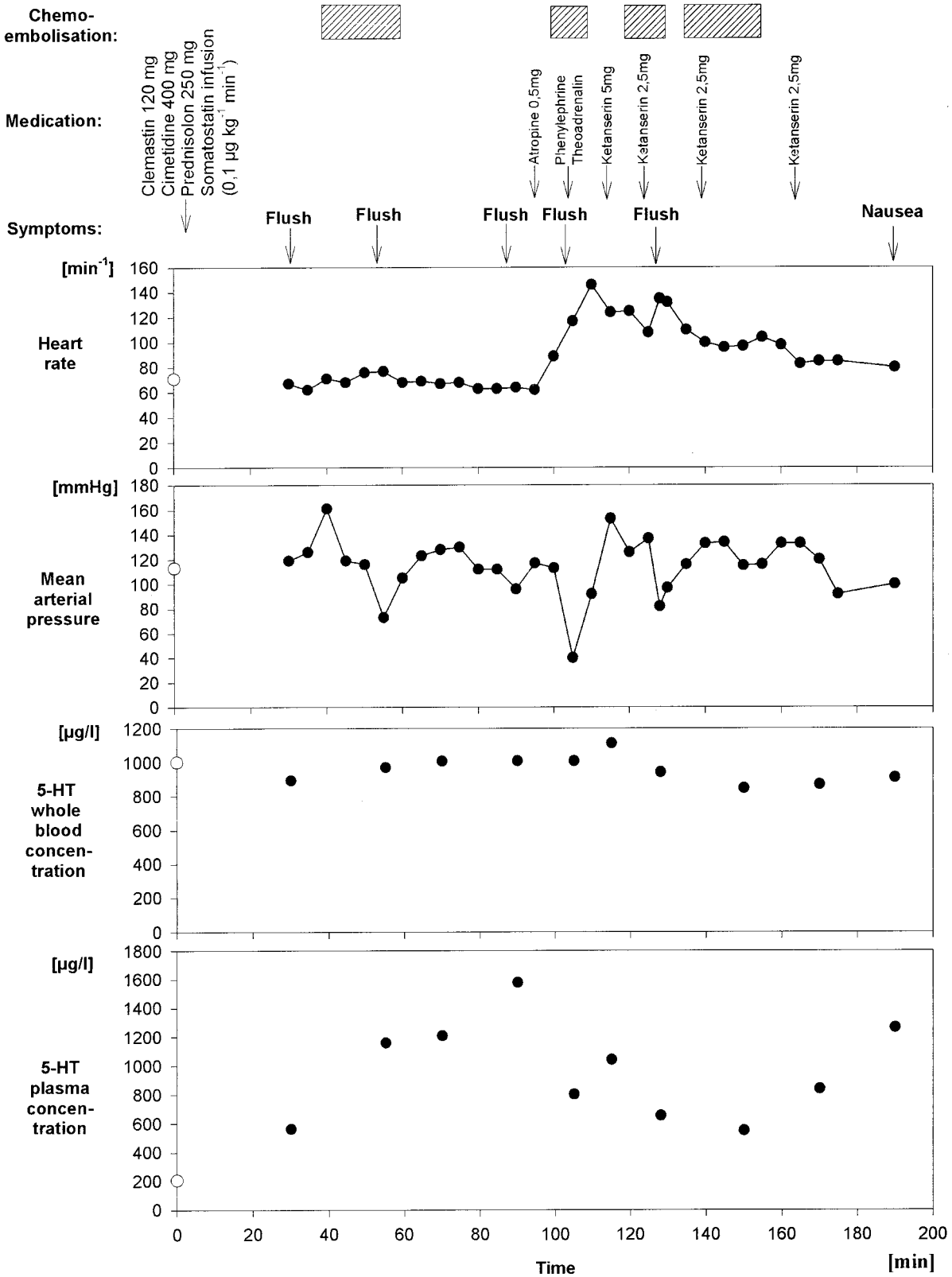

Fig. 1. Hemodynamic measurements and serotonin (5-HT) concentrations in whole blood and plasma before and during chemoembolization of carcinoid liver metastases. Flushing episodes and pharmacologic interventions are marked by arrows, and chemoembolizations are marked by bars. Several flushing episodes with either hypertension or hypotension occurred, mostly during or shortly after embolization. Whereas 5-HT whole blood concentrations were stable, 5-HT plasma concentrations increased after the first embolization and markedly fluctuated. Atropin was given at the request of the radiologists for a better embolization result with higher heart rate.

achieved after the beginning of octreotide treatment, most likely indicating a sstr-2–positive tumor. Nonetheless, somatostatin failed to prevent 5-HT release during chemoembolization. Despite somatostatin infusion at an even higher dosage (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 330 $\mu g/h$) than recommended, high baseline 5-HT concentrations in whole blood, increasing slightly from the first to the third procedure despite chemoembolization, failed to decrease. Furthermore, somatostatin failed to suppress the increase in 5-HT plasma concentrations occurring during each chemoembolization (*i.e.*, the 5-HT release from the tumor).

Different mechanisms of mediator release may explain the failure of somatostatin during chemoembolization of carcinoid tumors. Physiologic mechanisms of 5-HT release from enterochromaffin cells and carcinoid tumors include exocytosis of secretory granules, in which 5-HT and other mediators are stored. This process is influenced by a complex pattern of receptor-mediated mechanisms, including the inhibition of 5-HT release by somatostatin.[12]

During chemoembolization of carcinoid tumors, other mechanisms are likely involved, such as tissue hypoxia with loss of functional cell membrane integrity or mechanically induced cell damage, leading to a massive and fast mediator release and not preventable by somatostatin. On the other hand, recent investigations suggest that mechanically induced 5-HT release from carcinoid tumor cells is mediated *via* a G-protein–coupled mechanoreceptor, and 5-HT release so evoked can be inhibited by somatostatin in a concentration-dependent manner.[13]

Despite marked increases in plasma 5-HT concentrations, clinical signs (*e.g.*, flushing and hemodynamic instability) did not correlate with 5-HT increases during chemoembolization. 5-HT release may mediate diarrhea, hypertension, and bronchoconstriction but not flushing and hypotension.[8] Substance P and tachykinins, in turn, may be important for flushing, but their release is only partially suppressed by somatostatin.[14]

The observed discrepancy between 5-HT plasma and whole blood concentrations during chemoembolization is interesting and is most likely due to the fact that secreted serotonin is actively absorbed from plasma and mainly stored in platelets.[15] The increase in baseline 5-HT whole blood concentration during the course of therapy might be caused by tumor necrosis following each embolization, with ensuing release of 5-HT, which is then stored in platelets. Accordingly, evaluation of rapid concentration changes as relevant to vascular receptors should be performed in plasma.

Different kinetics of 5-HT in whole blood and plasma and no apparent correlation between 5-HT concentrations and flushing or hypotension were also suggested by measurements in patients with carcinoid tumors undergoing surgery during neurolept anesthesia.[16] However, we were able to demonstrate a relative reduction in the fluctuation of 5-HT concentrations in plasma during the chemoembolizations from the first to the third procedure, indicating a reduction of active tumor mass, but we were not able to show an absolute decrease in the basal concentrations before each procedure. Accordingly, the absolute plasma 5-HT concentration as an indicator of tumor mass reduction is doubtful.

To our knowledge, this is the first report of simultaneous 5-HT concentration measurements in plasma and whole blood in a patient with carcinoid syndrome undergoing somatostatin prophylaxis for chemoembolization. Despite prophylactic medication with somatostatin infusion, corticosteroids, and H_1- and H_2-histamine receptor antagonist treatment, hemodynamic instability and flushing developed, and increased 5-HT plasma concentrations indicated substantial 5-HT release. Although 5-HT release was still detectable, the second and third chemoembolizations were less eventful hemodynamically, possibly because of tumor mass reduction evoked by the first embolization.

In contrast to our findings, 4-day pretreatment with octreotide, 100–200 μg subcutaneously daily, caused a significant decrease in baseline 5-HT whole blood concentrations and decreased their increase after pentagastrin stimulation.[17] 5-HT concentrations in whole blood showed only minor variations during the succeeding chemoembolization in four patients with intraoperative prophylaxis (octreotide, 100 μg subcutaneously 4 times daily, and ketanserin, 20 mg intravenously 2 times daily), consistent with our findings, and hemodynamic variables were influenced little. However, the more sensitive 5-HT plasma concentrations were not measured.[17]

Fatal mediator release despite somatostatin prophylaxis is also suggested by a lethal carcinoid crisis, despite prophylactic administration of somatostatin (500 μg subcutaneously preoperatively and intravenously intraoperatively) in a patient undergoing tricuspid valve replacement. However, this patient did not receive steroids and antihistaminic drugs preoperatively, and 5-HT concentrations were not measured.[18]

In conclusion, prophylactic perioperative somatostatin infusion in a recommended dose of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not prevent serotonin release during chemoembolization of octreotide receptor–positive carcinoid metastases, despite successful preoperative octreotide treatment. Accordingly, sudden hemodynamic instability due to massive mediator release should be expected in patients with carcinoid syndrome, despite the use of currently recommended prophylactic medications.

References

1. Modlin JM, Sandor A: An analysis of 8305 cases of carcinoid tumors. Cancer 1997; 79:813–29
2. Kulke HM, Mayer R: Carcinoid tumors. N Engl J Med 1999; 340:858–68
3. Thorson A, Biörck G, Björkmann G, Waldenström J: Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side

of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis: a clinical and pathological syndrome. Am Heart J 1954; 47:795–817

4. Drougs JG, Anthony LB, Blair TK, Lopez RR, Wright JK Jr, Chapman WC, Webb L, Mazer M, Meranze S, Pinson CW: Hepatic artery chemoembolization for management of patients with advanced metastatic carcinoid tumors. Am J Surg 1998; 175:408–12

5. Roizen MF: Anesthetic implications of concurrent diseases, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 982–4

6. Veall GRQ, Peacock JE, Bax ND, Reilly CS: Review of the anaesthetic management of 21 patients undergoing laparotomy for carcinoid syndrome. Br J Anaesth 1994; 72:335–41

7. Kinney MAO, Warner ME, Nagorney MD, Rubin J, Schroeder DR, Maxson PM, Warner MA: Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. Br J Anaesth 2001; 87:447–52

8. Holdcroft A: Hormones and the gut. Br J Anaesth 2000; 85:58–68

9. Nilsson O, Kölby L, Wängberg B, Wigander A, Billig H, William-Olsson L, Fjälling M, Forsell-Aronson E, Ahlman H: Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy, and response to octreotide treatment in patients with carcinoid tumours. Br J Cancer 1998; 77:632–7

10. Janson ET, Gobl A, Kälkner KM, Öberg K: A comparison between the efficacy of somatostatin receptor scintigraphy and that of in situ hybridisation for somatostatin receptor subtype 2 messenger RNA to predict therapeutic outcome in carcinoid patients. Cancer Res 1996; 56:2561–5

11. Janson ET, Stridsberg M, Gobl A, Westlin JE, Öberg K: Determination of somatostatin receptor subtype 2 in carcinoid tumors by immunhistochemical investigation with somatostatin receptor subtype 2 antibodies. Cancer Res 1998; 58:2375–8

12. Racke K, Reimann A, Schwörer H, Kilbinger H: Regulation of 5-HT release from enterochromaffin cells. Behav Brain Res 1996; 73:83–7

13. Kim M, Javed NH, Yu JG, Christofi F, Cooke HJ: Mechanical stimulation activates Gαq signalling pathways and 5-hydroxytryptamine release from human carcinoid BON cells. J Clin Invest 2001; 108:1051–9

14. Conlon JM, Deacon CF, Richter G, Stöckmann F, Creutzfeld W: Circulating tachykinins (substance P, neurokinin A, neuropeptide K) and the carcinoid flush. Scand J Gastroenterol 1987; 22:97–105

15. Kema IP, de Vries EGE, Schellings AMJ, Postmus PE, Muskiet AJ: Improved diagnosis of carcinoid tumors by measurement of platelet serotonin. Clin Chem 1992; 38:534–40

16. Törnebrandt K, Nobin A, Ericsson M, Thomson D: Circulation, respiration and serotonin levels in carcinoid patients during neurolept anaesthesia. Anaesthesia 1983; 38:957–67

17. Ahlman H, Ahlund L, Dahlström A, Martner J, Stenquist O, Tylen U: SMS 201–995 and provocation tests in preparation of patients with carcinoids for surgery or hepatic arterial embolization. Anesth Analg 1988; 67:1142–8

18. Ockert DBM, White RD: Anesthetic management of patients with carcinoid heart disease undergoing cardiac surgery: two case reports and a review of previous experience. J Cardiothorac Anesth 1988; 2:658–65

Anesthesiology 2003; 98:1011–3

Skin Burn Caused by Operating Light during a Long Operation after Photodynamic Therapy

Taiga Itagaki, M.D., Matsuyuki Doi, M.D.,† Shigehito Sato, M.D.,‡ Shigeru Kato, M.D.**

PHOTODYNAMIC therapy (PDT) is becoming a popular treatment for early-stage esophageal, bronchial, stomach, and head and neck cancers.[1–3] However, PDT has a major side effect: skin photosensitivity. The mechanism of the effectiveness of PDT is explained as the combined effects of a photosensitizing agent (photosensitizer) and visible light. Dougherty *et al.*[4] reported that skin photosensitivity could last up to 2 months after the administration of a photosensitizer, but it is usually uncommon if there is no exposure to direct light and concentrated light. Only two cases of finger skin burn associated with a pulse oximeter during PDT have been reported.[5,6]

We present the case of a patient who showed a severe facial burn caused by an operating light during a long operation undergone 52 days after PDT.

Case Report

The patient is a 79-yr-old man (154 cm, 45 kg) with squamous cell carcinoma in the right maxillary sinus. He had a history of hypertension and had been treated with spironolactone medication since he was 60 yr old. He underwent partial maxillectomy after chemotherapy and radiation therapy. Six months after the first operation, PDT was scheduled for confirmed recurrence.

Forty-eight hours before PDT, the patient was given 96.7 mg porfimer sodium (Photofrin®; Wyeth Lederle Japan Co., Tokyo, Japan) intravenously. The patient then spent time in a dimly lit room (100–200 lux) to avoid induced skin photosensitivity. Three weeks after PDT, a dermatologist evaluated the patient's skin photosensitivity by exposing the back of the hand to sunlight for 5 min. The patient's skin reaction to this test was evaluated as negative. He was released from the dimly lit room and put in a normal hospital ward while using a sunscreen cream and avoiding the direct rays of the sun. Thereafter, the patient did not show any signs of skin photosensitivity during his hospital stay until an operation 52 days after PDT. He had a radical operation for maxillary cancer, with restoration of the forearm's free flap. The patient was premedicated with 0.5 mg atropine and 20 mg famotidine intramuscularly. During anesthesia, standard patient-monitoring devices, including a pulse oximeter, were applied. General anesthesia was induced with 5 mg/kg thiopental and 2 μg/kg fentanyl. Vecuronium, 0.15 mg/kg, was used to facilitate tracheal intubation. Anesthesia was maintained by inhalation of 67% nitrous oxide, 33% oxygen, and 1 to 2% sevoflurane. Intraoperatively, alprostadil alfadex and dopamine were continuously infused, and cefazolin sodium was administered as an antibiotic. Operating time was 14 h and 51 min. Two sets of operation room lights, Outer Space 9® (9-lamp type) and Outer Space 4® (4-lamp type; Yamada Shadowless Lamp Co., Tokyo, Japan), were used. These are standard lights used at our institution, and their average illuminations are 135,000 lux and 96,000 lux, respectively. Both operating lights were placed at a distance of about 120 cm from the patient. No lighting (*e.g.*, headlights) that illuminated the patient was used besides the operating lights.

After the operation, the patient showed severe swelling and erythema of the face, which was the site of surgery, and a dermatologist diagnosed a second-degree burn injury (fig. 1). There was also a slight reddening around the right forearm, which was the operating site for the donor of the graft. All other parts of the body were covered with

* Staff Anesthesiologist, † Assistant Professor, ‡ Professor and Chairman.

Received from the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. Submitted for publication June 17, 2002. Accepted for publication November 13, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Itagaki: Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, 431-3192, Japan. Address electronic mail to: taiga@mail.wbs.ne.jp.

clothing, and no burns were observed there. In addition, there was no burn injury on the left index finger, which is where the pulse oximeter probe was placed. Because the planted free flap became necrotic after surgery, the flap was removed on the fifth postoperative day in the same operating room. The time needed for flap removal was 1 h and 38 min. Although the same operating lights as for the first operation were used, the patient did not show any aggravation or new burn during this operation. After the second operation, the burn began to heal gradually, and the patient left the intensive care unit on the 13th postoperative day.

Discussion

In this case report, we describe a serious burn caused by an operating light during a long operation, which was performed 52 days after PDT, despite an evaluation of skin photosensitivity producing a negative result. As far as we know, there have been no reports of burn injury due to an operating light after the administration of a photosensitizer, and only two cases of burn injury associated with a pulse oximeter during PDT have been reported.[5,6]

In the two case reports of burns caused by a pulse oximeter, each patient had received PDT during general anesthesia for medical treatment of esophageal cancer or parietal malignant ependymoma.[5,6] The two burn injuries were induced by exposure to light from pulse oximeters at between 24 and 96 h after injecting the photosensitizer. However, our patient showed a serious burn injury 4 weeks after the definitively negative result of the photosensitivity evaluation. Before anesthesia, we considered that the porfimer sodium concentration in normal tissue had already decreased to a concentration that was much less than that at the photosensitivity evaluation and there would be no possibility of an abnormal pharmacologic response. However, in this case, burn injury was caused by the activation of extant porfimer sodium injected.

When 2 mg/kg porfimer sodium, a photosensitizer having an affinity to tumor cells, is injected intravenously, the concentration in normal tissue is about one fourteenth of that in tumor tissue at 48–72 h after injection. This difference between normal tissue and tumor tissue is maximized at this time. PDT is a selective treatment by which a laser beam is irradiated at the focus according to this period to destroy tumor cells using a photochemical reaction.[7] Porfimer sodium is in an excitation state and produces energy if it receives light of the proper wavelength. It activates oxygen in tissue, produces super oxide, and, finally, demonstrates an antitumor function.[8] The most frequent side effect of porfimer sodium is photosensitivity. Its incidence was 20.6% at the time the drug was recognized in Japan in October 1994. Therefore, patients must avoid direct light and concentrated light for at least 1 month after porfimer sodium injection and be kept under observation in a dimly lit room. An evaluation of skin photosensitivity is performed at 1 month after medication. The test involves exposing the back of the hand to the direct rays of the sun for 5 min. If the test result is negative, patients may be moved to a general ward; if it is positive, patients continue to be protected for an additional 2 weeks, after which the same test is repeated.

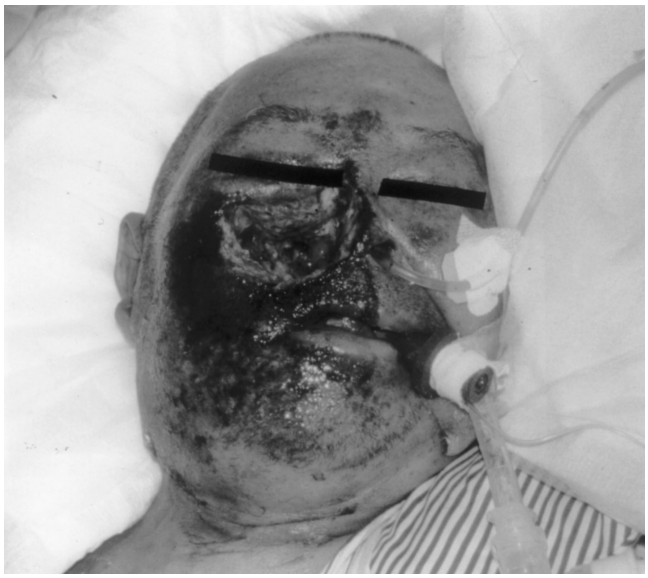

Fig. 1. Wound with a crust around the defective region due to maxillary cancer (fifth postoperative day).

Porfimer sodium has its highest absorption peak in the area of 405 nm (blue–violet). However, this wavelength overlaps with the absorption band of hemoglobin *in vivo*. Because of its low tissue permeability, it is not used as an excitation light. We generally use the Excimer Dye Laser® (PDT EDL-1; Hamamatsu Photonics K.K., Hamamatsu,Japan) for PDT, which is a pulse laser that radiates 630-nm red light and has good tissue permeability despite its much lower absorption than 405-nm blue light.[2,8] One of the wavelengths of the pulse oximeter that Radu *et al.*[5] used was also 630 nm. We measured the wavelength of our operating light, and it had a spectrum ranging from 250 to 800 nm, with a peak of 600 nm. Both the pulse oximeter and the operating light emit light that can excite porfimer sodium.

Some agents have been reported to be photosensitizing drugs: antibiotics (tetracyclines, fluoroquinolones, and sulfonamides), nonsteroidal antiinflammatory drugs, thiazide diuretics, antimitotic drugs, psychiatric drugs, calcium channel blockers, fibric acid derivatives, and so forth.[9,10] Our patient had not received such photosensitizing agents besides porfimer sodium prior to anesthesia. There is no report in the literature of skin photosensitivity induced by anesthetic agents. Therefore, there is a very small possibility that agents besides porfimer sodium participated in causing the burns.

The evaluation of photosensitivity is a qualitative evaluation to determine whether a patient can be moved to

Table 1. Characteristics of Photosensitizers

Photosensitizer	Light Conditions, nm	Optimal Time of Irradiation, h	Duration of Skin Photosensitivity
Porfimer sodium	630	24–72	4–6 weeks
Tin ethyl etiopurpurin	660	4–6	2 weeks
Benzoporphyrin	692	3	1 week
Meta-tetra(hydroxyphenyl)chlorin	650–664	36–168	1 week
Mono-l-aspartyl chlorine 6	664	48	3 days
Aminolevulinic acid	630	3–6	24 h

a normal ward. It is not intended to determine whether patients can bear a special state, such as long exposure to light during an operation. We think that a quantitative measurement of photosensitizer in tissue is more effective for estimating the risk of burn injury and also for determining the possible exposure time to operating light. Based on our experience with the present case, we recommend the following: (1) the method of evaluation of photosensitivity should be reevaluated; (2) the operating time should be shortened as much as possible; and (3) second-generation photosensitizers that have a shorter duration of photosensitivity than porfimer sodium, such as those that are now used throughout Europe and the United States, should be used.[2,3,11] The duration of skin photosensitivity caused by such drugs is shown in table 1. The high clearance rate of these drugs results in a very short light-shielding time. Using a filter that can cut wavelengths that show a high absorbance to a photosensitizer should be adopted as a fourth measure. There is a case report of a patient who had photosensitivity because of erythropoietic protoporphyria, and in perioperative management, an operation was performed using light sources in the operating room covered with yellow acrylate filters to avoid exposure of sensitive skin near the 400 nm spectrum.[12] Consideration of these factors will serve to prevent burn injury during post-PDT operation and PDT during general anesthesia.

In the future, together with the popularization of PDT, there may be an increase in surgical cases of patients with potential photosensitivity, including cases of PDT during general anesthesia. To prevent the occurrence of burn injury during these procedures, in addition to evaluating the patient's skin photosensitivity and recording the time elapsed after injection of photosensitizer, it is also important to check the wavelengths of any lighting facilities in the operating room.

References

1. Dougherty TJ: Photodynamic therapy. Photochem Photobiol 1993; 58:895–900
2. McCaughan JS Jr: Photodynamic therapy: A review. Drugs Aging 1999; 15:49–68
3. Merrill AB: Photodynamic therapy and the treatment of head and neck neoplasia. Laryngoscope 1998; 108:1259–68
4. Dougherty TJ, Cooper MT, Mang TS: Cutaneous phototoxic occurrences in patients receiving Photofrin. Lasers Surg Med 1990; 10:485–8
5. Radu A, Zellweger M, Grosjean P, Monnier P: Pulse oximeter as a cause of skin burn during photodynamic therapy. Endoscopy 1999; 31:831–3
6. Farber NE, McNeely J, Rosner D: Skin burns associated with pulse oximetry during perioperative photodynamic therapy. ANESTHESIOLOGY 1996; 84:983–5
7. Kato H, Aizawa K, Ono J, Konaka C, Kawate N, Yoneyama K, Kinoshita K, Nishimiya K, Sakai H, Noguchi M, Tomono T, Kawasaki S, Tokuda Y, Hayata Y: Clinical measurement of tumor fluorescence using a new diagnostic system with hematoporphyrin derivative, laser photoradiation, and a spectroscope. Lasers Surg Med 1984; 4:49–58
8. Weishaupt KR, Gomer CJ, Dougherty TJ: Identification of singlet oxygen as cytotoxic agent in photo-activation of murine tumor. Cancer Res 1976; 36: 2326–9
9. Moore DE: Drug-induced cutaneous photosensitivity: Incidence, mechanism, prevention and management. Drug Saf 2002; 25:345–72
10. Marguery MC: Drug-induced photosensitivity. Rev Prat 2000; 50:1315–9
11. Razum N, Balchum OJ, Profio AE, Carstens F: Skin photosensitivity: Duration and intensity following intravenous hematoporphyrin derivates, HpD and DHE. Photochem Photobiol 1987; 46:925–8
12. Asokumar B, Kierney C, James TW, Amato J, Tumanmd KJ: Anaesthetic management of a patient with erythropoietic protoporphyria for ventricular septal defect closure. Paediatr Anaesth 1999; 9:356–8

Anesthesiology 2003; 98:1014–5

Inadvertent Spinal Anesthesia during Continuous Epidural Anesthesia in an Infant

*Andreas H. Taenzer, M.D., F.A.A.P.**

SPINAL anesthesia is a known complication of epidural and caudal catheters. We report a case involving a 3-month-old infant in whom a spinal level from a caudal-to-thoracic catheter (threaded to the T4 level) was detected despite normal results of an epidurogram.

Case Report

A 7-kg, 3-month-old infant underwent repair of a congenital right diaphragmatic hernia. After an unremarkable early infancy, the diagnosis of diaphragmatic hernia was made on the basis of typical findings on a chest radiograph obtained for symptoms of upper respiratory infection at the age of 2 months.

Following mask induction and intubation, the patient was placed in the lateral decubitus position. A 20-gauge stiletted catheter (Abbott Laboratories, North Chicago, IL) was threaded from the sacral hiatus 15 cm up the epidural space *via* an 18-gauge Insyte catheter (Becton-Dickinson Infusion Therapy Systems, Sandy, UT). The catheter has a terminal opening with no side pores. Insertion was uneventful; the catheter was threaded in a continuous, steady motion. It neither met resistance nor was partially withdrawn or rethreaded. Following aspiration of the catheter, which was negative for blood or cerebrospinal fluid (CSF), a test dose of 0.7 ml (0.1 ml/kg) lidocaine, 1.5%, with epinephrine (1:200,000) was administered without signs of intravascular injection. General anesthesia was maintained with isoflurane in oxygen. In addition, regional anesthesia was maintained with intermittent boluses of 0.25% bupivacaine *via* the epidural catheter. No opioids were administered intraoperatively.

Following an uneventful right thoracotomy and diaphragmatic hernia repair, the patient was extubated in the operating room. Prior to transport to the PACU, 0.7 ml Isovue M200 (Bracco Diagnostics, Princeton, NJ) was injected through the caudal catheter and yielded a typical epidurogram, with the catheter tip at the T4. A continuous epidural infusion of 2% chloroprocaine at a rate of 1 ml/h was started and maintained postoperatively. The infant was comfortable and did not require any other analgesics.

The patient was evaluated by an anesthesiologist prior to transfer to a close observation unit and had normal motor function of all extremities 4 h after the operation.

The next morning it was noted that the infant did not move his legs. His respiratory rate had remained in the low 30s (breaths/min), and the oxygen saturation remained greater than 95% throughout the night. The patient was immediately evaluated; vital signs were normal. Neither the respiratory rate nor effort had changed. He appeared comfortable, with no sign of distress or pain from the incision site. A spinal level with complete lower extremity motor and sensory block below the umbilicus and a sensory block two interspaces above and below the thoracotomy site (tested by exposure to ice) was found. The infusion was discontinued. The caudal catheter was easily aspirated, yielding 2 ml of clear fluid, which tested positive for glucose at 102 mg/dl.

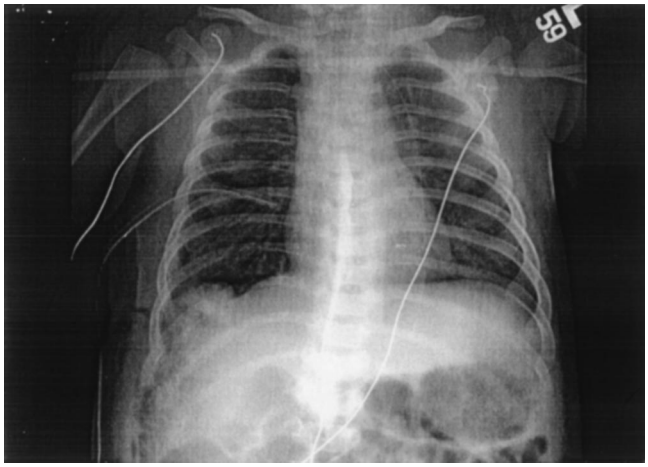

Fig. 1. Epidurogram obtained at the time of complete lower extremity motor block.

Again, 0.7 ml Isovue M200 was injected through the caudal catheter and yielded normal epidurogram results (fig. 1), with the position of the catheter tip unchanged at the T4 level. The caudal catheter was removed, and the infant had an uneventful postoperative course, with return of normal sensation and lower extremity muscle tone.

Discussion

Epidural anesthesia has been used for decades[1] in infants and children with an overall impressive safety record. The French-Language Society of Pediatric Anesthesiology collected data on a total of 17,837 central nervous system blocks, consisting of 15,013 caudal blocks (single shot), 293 sacral epidural blocks, 2,396 lumbar epidural blocks, and 135 thoracic epidural blocks. Dural penetration occurred a total of eight times.[2]

We commonly use thoracic epidural catheters placed *via* the caudal approach[3] and continuous infusion of chloroprocaine for epidural analgesia in infants.[4–7] We confirm placement of the catheter intraoperatively by fluoroscopy. In this case we obtained an epidurogram after surgical repair and before transfer to the PACU. After we were able to aspirate CSF, we injected contrast medium into the catheter, expecting to find a myelogram, but again found a pattern consistent with epidural

* Associate Director of Pediatric Anesthesia and Research Director. Current position: Assistant Professor, Department of Anesthesiology, University of Vermont, Burlington, Vermont.

Received from the Department of Anesthesiology, Maine Medical Center, Portland, Maine. Submitted for publication August 12, 2002. Accepted for publication December 9, 2002. Support was provided solely from institutional sources.

Address reprint requests to Dr. Taenzer: Maine Medical Center, Department of Anesthesiology, 22 Bramhall Street, Portland, Maine 04102. Address electronic mail to: taenza9@spectrummg.com.

injection. Both films were reviewed subsequently by two different radiologists at different institutions (Maine Medical Center, Portland, ME, and Children's Hospital Boston, Boston, MA) and were deemed to show normal epidurogram results.

As a mechanism, we suggest that the stiletted catheter caused a rent in the sacral or lumbar dura at the time of placement, causing chloroprocaine to enter the spinal space and CSF to enter the epidural space. Leakage of chloroprocaine into and CSF out of the spinal space would have caused a low spinal level and positivity of the CSF aspirated from the epidural catheter while maintaining a functional epidural catheter with very good analgesia in the thoracic region. Since the infant remained in supine position postoperatively, the isobaric chloroprocaine did not cause a total spinal block secondary to the thoracic kyphosis. We cannot prove that the infant did not have a dense epidural lower extremity block, as well as a therapeutic thoracic level with a window of cold sensation in between, in addition to a false-positive result of the glucose test on the aspirate. However, this would be an unlikely combination of events with a single terminal orifice catheter.

Neither chloroprocaine nor any of the intravenous solutions contained glucose and could easily explain an aspirate glucose concentration of 102 mg/dl. We do not think that the 18-gauge intravenous catheter punctured the dura at the time of placement since we would have expected return of CSF, but it cannot be ruled out entirely.

This case report emphasizes the importance of close monitoring for motor and sensory block and of respiratory rate and effort in nonverbal infants undergoing epidural anesthesia to detect an inadvertent dense motor block, even when the results of an epidurogram are normal.

References

1. Ruston FG: Epidural anaesthesia in paediatric surgery. Can Anaesth Soc J 1961; 11:12–34

2. Giaufre E, Dalens B, Gombert A: Epidemiology and morbidity of regional anesthesia in children: A one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. Anesth Analg 1996; 83:904–12

3. Boesenberg AT, Bland BAR, Schulte-Steinberg O, Downing JW: Thoracic epidural anesthesia via caudal route in infants. ANESTHESIOLOGY 1988; 69:265–9

4. Gunter JB, Watcha MF, Forestner JE, Hirshberg GE, Dunn CM, Connor MT, Ternberg JL: Caudal epidural anesthesia in conscious premature and high-risk infants. J Pediatr Surg 1991; 26:9–11

5. Henderson K, Sethna NF, Berde CB: Continuous caudal anesthesia for inguinal hernia repair in former pre-term infants. J Clin Anesth 1993; 5:129–33

6. Tobias JD, Rasmussen GE, Holcomb GW, Brock JW, Morgan WM: Continuous caudal anesthesia with chloroprocaine as an adjunct to general anesthesia in neonates. Can J Anaesth 1996; 43:69–72

7. Gunter JB: Benefits and risks of local anesthetics in infants and children. Paediatr Drugs 2002; 4:649–72