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Oral clonidine relieved postoperative pain after pheochromocytoma resection

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Introduction

Clonidine is a selective agonist for α2-adrenoceptors, with a ratio of 200:1 (α2:α1). Many desirable effects in anesthesia have been studied extensively: sedation, anxiolysis, perioperative hemodynamic stability, and a reduction in the requirements for opioid and anesthetic agents [1]. We present a patient whose postoperative pain management after pheochromocytoma resection was difficult and who obtained complete pain relief by oral administration of clonidine.

Case report

A 47-year-old woman, weight 43 kg and height 152 cm, was admitted to our hospital for resection of a left adrenal tumor. She had first experienced general fatigue and edema 6 months previously and then had paroxysmal hypertensive attacks. The diagnosis was confirmed by endocrine examinations and computed tomography (CT) at another hospital. Endocrinological findings included plasma catecholamine levels of epinephrine (E): 134 $pg \cdot ml^{-1}$ (normal range: up to 80 $pg \cdot ml^{-1}$), norepinephrine (NE): 34 200 $pg \cdot ml^{-1}$ (normal range: 90–420 $pg \cdot ml^{-1}$) and dopamine: 56 $pg \cdot ml^{-1}$ (normal range: up to 30 $pg \cdot ml^{-1}$). CT findings of the abdomen demonstrated a mass 5 cm in diameter at a left suprarenal lesion. These findings indicated an NE-secreting type of pheochromocytoma.

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The patient was premedicated with oral diazepam 5 mg and ranitidine 150 mg 2 h before induction of anesthesia. An epidural catheter was inserted at the T9–10 interspace and was placed 5 cm cephalad. Anesthesia was induced with thiamylal 150 mg and fentanyl 0.1 mg IV, and the trachea was intubated following the administration of vecuronium 6 mg IV. Anesthesia was maintained with 60% nitrous oxide in oxygen and 0.5%–1.5% isoflurane, and with intermittent fentanyl 0.1 mg IV while muscle relaxation was obtained with vecuronium. Standard monitoring was used for anesthetic management. The surgery was performed by the thoracoabdominal approach at the 8–9 intercostal space. At the end of the surgery, morphine 2 mg was administered epidurally and continuous epidural administration of 0.25% bupivacaine 2 $ml \cdot h^{-1}$ was initiated for postoperative pain relief. Anesthesia and surgery were uneventful. Surgery was completed in 5 h 46 min without any problem and the blood loss measured was 50 g. The patient was postoperatively transferred to the intensive care unit (ICU) with her trachea intubated, and was extubated after 6 h.

Figure 1 shows the outline of postoperative pain management for the patient. The patient complained of wound pain 2 h after her arrival at the ICU while 0.25% bupivacaine 2 $ml \cdot h^{-1}$ was being administered epidurally. We administered 0.25% bupivacaine 5 ml epidurally every 4 h subsequently. She complained frequently of pain on the 1st postoperative day. We administered local anesthetics epidurally every hour. We gave buprenorphine 0.2 mg with 0.25% bupivacaine 5 ml epidurally, but her pain relief was insufficient. Because of the short duration of blockade and the insufficiency of analgesic effect, a new catheter was inserted at the T10–11 interspace and was placed 7 cm cephalad. We administered butorphanol 1 mg IV just before the epidural catheterization, but no analgesic effect was obtained. We administered 1% lidocaine with 1:200 000 epinephrine [1% lidocaine(E)] 7 ml through the epidural catheter. Pain relief was obtained 15 min later with

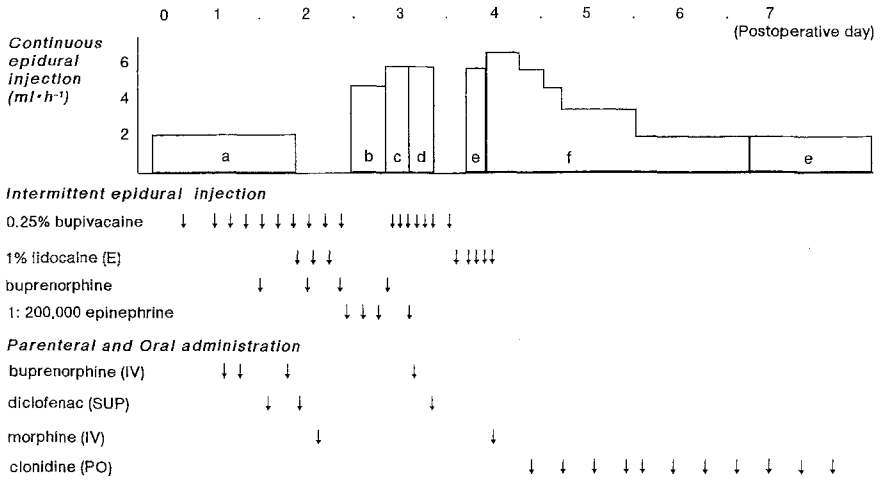

Fig. 1. Postoperative pain management in the intensive care unit. *a*, bupivacaine 2.5 mg·ml^{-1}; *b*, bupivacaine 1 mg·ml^{-1} + fentanyl 10 μg·ml^{-1}; *c*, epinephrine 2.5 μg·ml^{-1}; *d*, epinephrine 5 μg·ml^{-1}; *e*, lidocaine 10 mg·ml^{-1} + epinephrine 5 μg·ml^{-1}; *f*, lidocaine 8 mg·ml^{-1} + epinephrine 5 μg·ml^{-1} + fentanyl 10 μg·ml^{-1}. *IV*, intravenous; *PO*, per oral; *SUP*, suppository; *E*, with 1:200 000 epinephrine

blockade extending from T5 to L2 bilaterally. We administered the local anesthetic epidurally at the patient's request. The analgesic effect of 1% lidocaine(E) seemed to be superior to that of 0.25% bupivacaine, but the effect of both local anesthetics lasted less than an hour. We administered buprenorphine 0.2 mg IV and diclofenac 50 mg by suppository, but this combination did not give a sufficient analgesic effect. Because morphine 5 mg IV and 5 mg IM were effective for her pain, we initiated continuous epidural administration with fentanyl and 0.125% bupivacaine (Fig. 1b). Analgesia was insufficient and we administered local anesthetics intermittently. Because 1% lidocaine(E) was more effective than 0.25% bupivacaine and the tumor of the patient was an NE-secreting type, a dramatic decrease in the postoperative NE blood level was suspected. It was proved that the plasma level of NE decreased from 34 200 to 419 pg·ml^{-1} a week later. We thought that this case had a connection with α2-adrenoceptors which mediate antinociception. We tried administering normal saline 10 ml with 1:200 000 epinephrine epidurally. Complete pain relief was obtained 15 min later and the analgesic effect lasted about 90 min. Subsequently, we began continuous epidural administration of normal saline with 1:400 000 or 1:200 000 epinephrine (Fig. 1c,d). However, she needed intermittent administration of local anesthetics. There was some doubt as to the veracity of her pain, so we administered normal saline 7 ml epidurally to exclude the placebo effect, but it did not relieve her pain at all. Her pain became more severe notwithstanding continuous and intermittent epidural administration of lidocaine(E). Accordingly, we administered morphine 10 mg IV and started continuous epidural administration of 1% lidocaine(E) and fentanyl (Fig. 1f). The patient got sufficient pain relief by this modality, but it was accompanied by respiratory depression ($Paco_2$: 55 mmHg and a respiratory rate 8·min^{-1}). Accordingly, we administered clonidine 150 μg orally to decrease the dose of epidural administration of local anesthetics. She no longer needed intermittent epidural injections, opioids, and non-steroidal anti-inflammatory drugs (NSAID) once oral administration of clonidine was started. First, clonidine 150 μg three times daily was used and her systolic blood pressure decreased to 80 mmHg. We changed to clonidine 75 μg four times daily, and her pain was successfully relieved without hypotension. The patient was transferred to the ward with continuous epidural administration of 1% lidocaine(E) 2 ml·h^{-1} and oral clonidine on the 7th postoperative day.

Discussion

Points of management of pain for the patient are as follows: (1) epidural administration of local anesthetics had an analgesic effect which lasted less than an hour; (2) opioid agonist-antagonists and NSAID had no analgesic effect; (3) epidural administration of normal saline with 1:200 000 epinephrine showed an analgesic effect; (4) a placebo effect was ruled out by epidural administration of normal saline; (5) opioid produced a sufficient analgesic effect but with respiratory depression; and (6) oral administration of clonidine produced a sufficient analgesic effect. Although the patient had severe postoperative pain due to the surgical procedure (thoracoabdominal approach) and postoperative anxiety, points (3) and (6) above suggest that the dramatic decrease in the NE blood level after the resection

of the pheochromocytoma also contributed greatly.

NE is a neurotransmitter of the descending monoaminergic systems. An increase in the activity of the bulbospinal noradrenergic systems produces an antinociceptive effect mediated by the α2-adrenoceptor, located postsynaptically in the dorsal horn of the spinal cord [2–5]. In the present case, 1% lidocaine(E) was more effective than 0.25% bupivacaine. It is specific in this case that epidural administration of normal saline with 1:200 000 epinephrine produced analgesia. We speculate that the levels of NE produced by the pheochromocytoma were drastically lowered and that analgesic action mediated by α2-adrenoceptors was decreased. Taking this into consideration, we used an α2-agonist, clonidine. Epidural or intrathecal administration is reasonable as a route of clonidine administration because the dorsal born of the spinal cord is the primary site of analgesic action. However, oral or parenteral administration or clonidine has been shown to relieve postoperative pain [1,6,7] and to have an analgesic action at the supraspinal site [8]. Because only oral tablets are available in Japan, we administered clonidine orally.

Clonidine produces many desirable effects in anesthesia: sedation, anxioysis, perioperative hemodynamic stability, and a reduction in the requirements for other anesthetic agents, but it is generally used as an antihypertensive drug in Japan. It provides postoperative analgesia without nausea, pruritus, or respiratory depression observed by systemic or intraspinal opioid administration. Our patient obtained complete pain relief by oral clonidine without intermittent epidural administration of local anesthetics and was free from opioid-induced adverse effects. Hypotension appeared as a side effect and was controlled by decreasing the dose of oral clonidine.

The bioavailability of clonidine in cerebrospinal fluid (CSF) following epidural and intravenous injection was 14% and 0.02%, respectively [9]; CSF clonidine concentrations more effectively predict the degree of analgesia than do plasma concentrations [5,9]. In the present case, CSF clonidine concentrations may not exceed its therapeutic concentration because it was administered orally. The analgesic action of clonidine may appear even below the normal therapeutic CSF concentrations because the epidural administration of normal saline with 1:200 000 epinephrine showed an analgesic effect. Not only the spinal cord but also the supraspinal sites for clonidine analgesic action may have been involved in pain relief in our patient and may be emphasized by the dramatic decrease in the NE plasma level after phechromocytoma resection.

We conclude that clonidine is effective for pain relief in patients following resection of NE-secreting type pheochromocytoma.

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