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Postoperative Respiratory Depression and Elevated Sufentanil Levels in a Patient with Chronic Renal Failure

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Sufentanil citrate is a new opioid analgesic analog of fentanyl. Due to its ability to suppress hemodynamic and hormonal responses to surgery, it has been recommended for cardiac surgery, neurosurgery, and major surgical procedures.[1–4] Its use has also been advocated in "balanced anesthesia" as an alternative to fentanyl, morphine, or meperidine.[5–7] The pharmacokinetics of sufentanil have been studied in healthy adult, geriatric, and obese patients.[8,**] We report a case of prolonged postoperative respiratory depression associated with abnormally elevated plasma sufentanil levels in a patient with chronic renal failure.

REPORT OF CASE

A 68-year-old, 80-kg man was scheduled for insertion of a peritoneal dialysis catheter while under general anesthesia. His medical history included end-stage renal disease due to chronic pyelonephritis, right middle lobe pneumonia resolved 6 weeks before admission, atherosclerotic heart disease, and a history of congestive heart failure and ventricular ectopy. His medications included quinidine 300 mg po qid, dihydrotachysterol 0.125 mg po tid, folate 1 mg po qd, iron sulfate 325 mg po qd, and calcium carbonate 650 mg po tid. The patient had undergone multiple previous general and regional anesthetics for dialysis shunt revisions, cystoscopies, and a cholecystectomy without apparent anesthetic complications. Physical examination revealed no cardiac or pulmonary abnormalities. Preoperative laboratory evaluation revealed a hematocrit of 33.3%, hemoglobin 11.5 g/dl, serum calcium 8.2 mg/dl, total protein 5.4 g/dl, albumin 3.4 g/dl, AG ratio of 1.7, sodium 143 mEq/l, potassium 4.3 mEq/l, chloride 109 mEq/l, CO_2 of 22 mol/l, glucose 137 mg/dl;, blood urea nitrogen 22 mg/dl, and creatinine 10.9 mg/dl. Preoperative chest roentgenogram showed a small right basilar pleural effusion and a right middle lobe peripheral infiltrate. The preoperative ECG showed normal sinus rhythm.

After 3 min, general anesthesia was induced with a single bolus injection of sufentanil 120 μg (1.5 μg/kg) and thiopental, 100 mg (1.25 mg/kg), given iv. Neuromuscular blockade was achieved with vecuronium, 0.1 mg/kg iv. The trachea was intubated, and ventilation controlled. Anesthesia was maintained with 65% N_2O/35% O_2. Vital signs were stable throughout the anesthetic, with the systolic blood pressure ranging from 90 to 120 mmHg and the diastolic blood pressure varying between 55 and 80 mmHg. The heart rate ranged from 60 to 85 beats/min. Neuromuscular blockade was assessed with the use of peripheral nerve stimulator. The patient required no additional narcotics, vasoactive drugs, or neuromuscular blockers throughout the 120-min course of the operation. At the conclusion of the procedure, 100% oxygen was delivered, and neuromuscular blockade was reversed with atropine 2.0 mg and neostigmine 5.0 mg iv. The patient demonstrated full return of twitch and responded to commands, and his trachea was extubated in the operating room. He was taken immediately to the recovery room.

On admission to the recovery room the patient was awake and responding to commands. Vital signs included an arterial blood pressure of 99/54 mmHg, heart rate of 74 beats/min, and a respiratory rate of 16 breaths/min. His breathing was spontaneous and unlabored, and ECG showed normal sinus rhythm.

Approximately 10 min after arrival in the recovery room (130 min after induction of anesthesia), the patient complained of dyspnea. There was no clinical evidence of muscle rigidity. Inspired oxygen was increased to 100% by face mask, and nasal and oral airways were inserted. Approximately 35 min after admission to the recovery room (155 min after induction of anesthesia), the patient demonstrated decreased mentation. Naloxone 0.4 mg was given without results. A peripheral nerve stimulator was applied, which demonstrated an intact train-of-four; however, an additional 45 mg of edrophonium was given anyway, with no apparent effect. Analysis of arterial blood gases revealed a pH_a of 7.14, a Pa_{CO_2} of 63.4 mmHg a Pa_{O_2} of 96.2 mmHg (94% saturation), and a bicarbonate of 20.9 mEq/l. The trachea was reintubated, and mechanical ventilatory support was instituted. He appeared awake, was breathing spontaneously, opened his eyes to command, and responded appropriately to "yes-and-no" questions. Bedside spirometry demonstrated a mean inspiratory force of minus 30 cmH_2O with a vital capacity of 850 ml. His trachea was extubated after 1 h. He was initially awake, responsive, and breathing adequately. While breathing 100% O_2 via a mask, pH_a was 7.34, Pa_{CO_2} 40 mmHg, Pa_{O_2} of 387 mmHg, and bicarbonate 21 mEq/l.

One-half hour later (250 min after induction of anesthesia), the patient again became dyspneic, less arousable, and complained of nausea; pH_a was 7.16, Pa_{CO_2} was 63 mmHg, Pa_{O_2} was 72 mmHg, and bicarbonate was 22 mEq/l on 100% O_2 by mask. The trachea was reintubated, and mechanical ventilatory support was provided overnight in the intensive care unit. The trachea was extubated the following day, and no further ventilatory support was required.

Sufentanil levels were determined postoperatively with the use of a gas chromatographic method, using a fused silica capillary column with a nitrogen–phosphorous detector. Extraction of sufentanil from the blood samples was as previously described, except reconstitution was in toluene.[10] Temperature programming was used to increase resolution and detection abilities of the system. Limits of detection of sufentanil were 20 pg/ml of serum. The coefficient of variation is 5% for 50 pg/

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ml of sufentanil in a 4-ml serum sample. The blood sample drawn at 5 h after dosing showed a sufentanil level of 2.6 ng/ml along with a large associated peak that we believe to be a sufentanil metabolite. At 9 h and 13 h after dosing, the sufentanil level was found to be 1.2 and 0.6 ng/ml, respectively. No sufentanil was detected in blood samples drawn at 17 h or later. The associated peak, possibly a metabolite, gradually decreased over the sampling period.

Discussion

This case demonstrates prolonged respiratory depression associated with abnormally high plasma sufentanil in a patient with chronic renal failure. Using pharmacokinetics for sufentanil in healthy subjects,[9] the terminal elimination half-life is 164 min and the serum sufentanil levels at 5 h should be 0.09 ng/ml instead of the 2.6 ng/ml level detected. By 9 and 13 h, the sufentanil level should be below 0.03 ng/ml and almost below the limits of detection for our analytic assay. However, at 9 and 13 h substantial levels of sufentanil were still present. It was not until 17 h that the plasma sufentanil levels were beyond detection. Although samples were drawn at only three time points, the terminal elimination half-life obviously was elevated in this patient. A lack of sufficient data points does not allow us to accurately calculate any pharmacokinetic parameter for this patient.

It is curious that naloxone (0.4 mg iv) did not reverse the respiratory depression seen in this patient. One can only speculate that too small a dose was given and that the patient may have benefitted from additional naloxone.

Although there are no published reports of sufentanil metabolism in humans, Janssen Pharmaceutica has found that sufentanil is metabolized rapidly in laboratory animals by N-dealkylation at the piperidine nitrogen and O-demethylation.†† The products of N-dealkylation are pharmacologically inactive. However, the desmethyl metabolite has approximately 10% of the activity of sufentanil. In rats 87% of a sufentanil tracer dose was excreted in 24 h, with only approximately 1% excreted as unchanged sufentanil. The sufentanil metabolites are excreted almost equally in the urine and feces, with 30% appearing as conjugates, presumably conjugates of desmethyl sufentanil. The role that the kidney has in clearing sufentanil and its metabolites from the body has not been established. However, the production of a possibly active metabolite, desmethyl sufentanil, and the substantial amount of conjugated metabolite formation imply the possible importance of normal renal function necessary for the clearance of sufentanil.

Don *et al.*[10] reported three cases of prolonged narcotic action in patients with renal failure. These effects were antagonized by naloxone up to nearly 7 days after the narcotics were administered. They postulated these results were due to high systemic levels of morphine or its breakdown products, which accumulated in these patients with renal disease, release of the drug or its metabolites from tissues, or from enterohepatic recirculation.

Kang *et al.*[11] found that there may be significant extrahepatic biotransformation of fentanyl. The same may be true for sufentanil. If the extrahepatic biotransformation of sufentanil is decreased or absent in renal-failure patients, the prolonged elevated levels of sufentanil observed in this patient would be explained. In addition, since sufentanil is extensively metabolized in laboratory animals and the resulting conjugates are, in part, cleared by the kidney, the decreased renal function of our patient may have resulted in an increase of circulating "active metabolites."

McDonnell *et al.*[12] have reported evidence for the polymorphic metaolism of alfentanil. Since sufentanil and alfentanil undergo identical metabolic pathways, polymorphic oxidation of sufentanil also may occur. Thus, the patient reported in this study may have a deficiency in one route of metabolism or an enhancement of another, either of which may result in a higher level of the "active" desmethyl sufentanil or a slower overall clearance of the parent compound.

There may be other factors that contributed to the respiratory depression and elevated sufentanil levels seen in this patient that we have not considered. Release of the drug and its metabolites from protein binding, redistribution from tissues, or enterohepatic recirculation may have contributed to the respiratory depression and elevated sufentanil levels seen in this patient. There was no evidence of hepatic disease in this patient, suggesting that alteration of hepatic biotransformation was not the cause of the prolonged respiratory depression. Thus, we conclude that the clinician must anticipate the possibility of respiratory depression several hours following sufentanil administration, especially in patients with respiratory depression.

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Acute Respiratory Arrest and Rigidity after Anesthesia with Sufentanil: A Case Report

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Sufentanil, an analog of fentanyl, is a recently approved narcotic that is five to 10 times as potent as fentanyl.[1] It may have some advantages over fentanyl, reportedly having a more rapid onset of action,[2] being more effective in preventing intraoperative hypertension and tachycardia,[2,3] and resulting in less cumulative respiratory depression.[4] We report a case of acute respiratory arrest associated with muscular rigidity following apparently satisfactory recovery from anesthesia supplemented with sufentanil.

REPORT OF ACASE

The patient was a 35-year-old, 85-kg man presenting for fusion of his left wrist. He had undergone uncomplicated general anesthesia in the past, and a review of systems and medical history were unremarkable. Routine laboratory tests were normal.

No premedication was administered. After routine monitors were placed, 1 mg of pancuronium and 75 μg of sufentanil were given iv while the patient breathed oxygen. Although apnea followed, the patient was still responsive and would breath on command. Anesthesia was induced with thiopental, 250 mg iv; succinylcholine, 100 mg iv, was administered, and the trachea was intubated. The patient was ventilated with nitrous oxide (66%) and oxygen (34%), and a further 5 mg of pancuronium was administered iv. Thirty minutes later, before surgical incision, 50 μg of sufentanil was administered iv. The surgical procedure lasted a further 150 min; four additional bolus doses of 25 μg of sufentanil to a total dose of 225 μg (2.6 μg/kg) were administered iv during this time in response to increases in arterial blood pressure, the last dose being given 40 min before the end of anesthesia. Despite these additional doses of sufentanil, 30 min after the start of the surgical procedure isoflurane (0.3%) was required for approximately 40 min to control hypertension. A further 2 mg of pancuronium was administered iv during the procedure to maintain muscle relaxation. Thiopental (75 mg) was given iv to control patient movement 15 min before the end of surgery.

At the end of the procedure, neostigmine (3 mg) and glycopyrrolate (0.6 mg) were administered iv, and the nitrous oxide discontinued. The patient immediately awakened and the trachea was extubated. The patient sat up on the operating table and attempted to move across to the guerney without assistance. He was asked to lie down and was moved with the aid of a roller. During this time he was totally cooperative and was breathing well. He was taken to the recovery room, a distance of 40 yards. Upon arrival he was totally unresponsive. Despite stimulation, he remained apneic and comatose. Controlled ventilation was attempted via a mask, but the airway was very difficult to maintain due to rigidity of the jaw muscles. The patient's abdomen was also rigid to palpation. With two anesthesiologists maintaining the airway, some oxygen was entering the lungs, but the patient did not awaken or respond to further stimulation. Naloxone, 0.4 mg, was administered iv and within 30 s the patient was easy to ventilate. Fifteen seconds later, he was again wide awake, breathing spontaneously, and responding appropriately. His subsequent course was totally uneventful, and he required no postoperative narcotic analgesia.

DISCUSSION

Respiratory depression in the postoperative period after anesthesia with a narcotic is a well-recognized phenomenon, appropriately dubbed "silent death" by Cascorbi and Gravenstein.[5] The rapidity with which this patient became apneic and comatose did not match their description. We believe that there are several possible explanations for what happened to our patient. A relative overdose of narcotic could have produced this picture of apnea and unconsciousness. However, our supplemental administrations of sufentanil were in response to signs of sym-

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