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LETTER TO THE EDITOR

Prolonged apnea, caused by remifentanil, during awakening from anesthesia for emergency ventriculoperitoneal shunt placement

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To the Editor:

Respiratory depression may occur after use of most opioid drugs, but only one case of prolonged apnea after intraoperative administration of the ultra-short-acting opioid, remifentanil, has been reported [1]. We present a neurosurgical patient with prolonged postoperative apnea that was probably caused by remifentanil. A 70-year-old man (height 168 cm, weight 50 kg) with a complicated history of multiple neurosurgical and radiation treatments for a parasellar chordoma underwent emergency ventriculoperitoneal shunting for acute hydrocephalus. Two weeks previously, he had undergone tracheostomy under general anesthesia with propofol, sevoflurane, and remifentanil, with no postoperative respiratory depression.

The anesthetic protocol used in the instance reported here was the same as the one used previously. Anesthesia was induced with propofol 60 mg, remifentanil 0.3 μg/kg per minute, and rocuronium 30 mg and was maintained with end-tidal sevoflurane concentration 1 vol% and remifentanil 0.05–0.1 μg/kg per minute. No opioids other than remifentanil were administered. The surgery lasted 60 min and was completed without complications, with normal blood pressure and bladder temperature throughout. On awakening from anesthesia, the patient had prolonged apnea that did not respond to sugammadex but was successfully reversed by naloxone.

Because of the naloxone-reversible nature of the apnea, absence of any opioids other than remifentanil, and absence of other common factors associated with delayed awakening, it is likely that the respiratory depression was caused by remifentanil. The pharmacogenetic variant suggested by Nelson et al. [1] as a cause of abnormal response to remifentanil could be excluded because there was no prolonged apnea after the previous administration of remifentanil. Pharmacokinetic simulation using the Minto model (Fig. 1) [2] indicated that the remifentanil effect-site concentration at the time of the first naloxone administration was about 0.1 ng/ml, which can be considered clinically negligible. We therefore believe that altered local pharmacokinetics of remifentanil in the brain was the most likely cause of respiratory depression in our patient rather than altered systemic pharmacokinetics.

Remifentanil is a highly lipid-soluble drug with an octanol/water partition coefficient ($Kp_{Octanol/Water}$) of 17.9 at pH 7.4 [3]. Because of its high lipid solubility, remifentanil can rapidly transfer across the blood–brain barrier (BBB). Membrane permeability does not limit the brain uptake of highly lipid soluble drugs, which is determined primarily by regional flow. Under these conditions, and assuming that the metabolism of remifentanil in the brain is negligible because of its very short pharmacokinetic/pharmacodynamic equilibration half-time, the half-time for brain turnover of remifentanil can be calculated as 0.693 × brain/plasma partition coefficient ($Kp_{Brain/Plasma}$)/brain plasma flow (Q_{Plasma}) [4]. In our patient, Q_{Plasma} could have been reduced by

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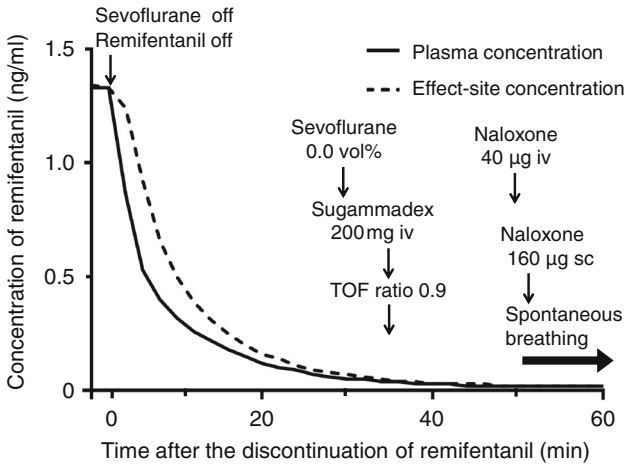

Fig. 1 Predicted decline in the concentration of remifentanil after termination of infusion, and related postanesthetic events. Thirty minutes after sevoflurane and remifentanil were discontinued, the patient was making no respiratory effort and had an end-tidal sevoflurane concentration of 0.0 vol%. His train-of-four (TOF) ratio recovered to 0.9 after sugammadex 200 mg. Fifty minutes after discontinuation of remifentanil, naloxone 40 μg was administered intravenously (*iv*), and spontaneous respiration resumed quickly. Additional naloxone 160 μg was administered subcutaneously (*sc*), and the patient was taken to the ward

hydrocephalus. Reduced Q_{plasma} could have slowed down the elimination of remifentanil from the brain, resulting in prolongation of its respiratory-depressant effects.

Further accumulation of clinical evidence regarding the ability of remifentanil to cause respiratory depression, the underlying mechanisms, and any potential relevance to neurosurgical procedures, is required.

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