on the face and in the mouth, oropharynx, and trachea. In addition, the awake patient may assist in positioning and protect the unanesthetized limbs. Finally, contact with the awake patient may limit the number and intrusiveness of monitors required.

In summary, we have presented a case of an infant with EB simplex undergoing circumcision successfully managed with caudal epidural blockade. When surgical site, procedure, and patient condition permit, a regional technique can provide safe and effective anesthesia in patients with EB.

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Recurrent Respiratory Depression after Alfentanil Administration

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Recurrent respiratory depression after apparent recovery from the administration of fentanyl was first reported in 1976,[1] over 10 yr after its introduction. Subsequent reports have implicated secondary rises in plasma fentanyl concentration as the cause of many (but not all[2]) of these events.[3–6] Alfentanil is a new opioid analgesic, with a shorter terminal elimination half-time ($t_{1/2\beta}$) than fentanyl. This is due to its smaller steady-state volume of distribution, although its hepatic clearance is also less.[7] These pharmacokinetic differences may mean that recurrent respiratory depression is less likely after alfentanil,[8] and that secondary peaks in alfentanil plasma concentration should not occur by the same mechanism thought to cause secondary peaks in plasma fentanyl concentration: reuptake from tissue stores.[7] However, we now report an episode of recurrent respiratory depression after alfentanil administration and discuss the possible causes.

Case Report

A 49-yr-old, 60-kg man with squamous cell carcinoma of the posterior wall of the hypopharynx was scheduled for panendoscopy and biopsies for tumor mapping, and fine-needle aspiration of an enlarged left cervical lymph node. The patient complained only of mild dysphagia without hoarseness. Past medical history included 30 yr of heavy smoking and alcohol consumption. The patient was taking no medications. Examination showed a thin man, edentulous, without gross deformities of the upper airway. The trachea was in the midline and the cardiopulmonary examination was normal. Complete blood count, serum electrolytes, chest radiograph, and ECG were normal.

Without premedication, anesthesia was induced with alfentanil 75 $\mu g \cdot kg^{-1}$ iv and isoflurane 0.5% along with vecuronium 0.1 $mg \cdot kg^{-1}$ iv for muscle relaxation. Direct laryngoscopy was performed and the trachea intubated without difficulty. Alfentanil 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv, nitrous oxide 60%, and isoflurane 0.5% maintained anesthesia. During bronchoscopy, the $F_{I_{O_2}}$ was increased to 1.0, and ventilation controlled *via* the side arm of the bronchoscope. Forty-eight minutes after induction of anesthesia, thiopental 75 mg and additional vecuronium was given iv in response to movement, and the alfentanil infusion was

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slowed to 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The alfentanil infusion ended 93 min after its beginning, 30 min before tracheal extubation. Isoflurane was discontinued 15 min later, but nitrous oxide 60% and muscle relaxation were continued during the fine-needle aspiration. Neuromuscular blockade was reversed at the conclusion of the procedure with neostigmine 50 $\mu g \cdot kg^{-1}$ and glycopyrrolate 10 $\mu g \cdot kg^{-1}$. One hundred percent O_2 was then administered.

The patient rapidly became alert; when his trachea was extubated, his spontaneous respiratory rate was 16 min^{-1}, E_tCO_2 (end-tidal P_{CO_2}) 42 mmHg and E_tIsoflurane 0.04%. He moved to the stretcher without assistance. In the recovery room, he was alert and talking, with a respiratory rate of 16 min^{-1}. Fifteen minutes later, he was cyanotic, apneic, and unresponsive, with a heart rate of 84 bpm. Ventilation was controlled with 100% O_2 *via* face mask, and then his trachea was intubated without additional medication. Blood was noted in the posterior pharynx at the time of laryngoscopy and blood was present in the endotracheal tube after intubation, but no clots or causes of respiratory obstruction were seen. Shortly thereafter, he awoke and responded to commands. He breathed spontaneously, but $EtCO_2$ rose from 58 to 62 mmHg. His pupils were pinpoint. Following naloxone 0.2 mg iv, the E_tCO_2 decreased to 48 mmHg and pupil size increased. E_tIsoflurane was 0.02%. His trachea was extubated, and he had no further ventilatory difficulties.

Discussion

Immediately after the respiratory arrest, this patient, while responsive, had pinpoint pupils and a high, rising end-tidal CO_2 indicative of excessive opioid effect. That naloxone antagonized these signs is corroborating evidence of residual opioid effect.

Recurrent respiratory depression after alfentanil administration has not been reported, although the phenomenon is well described after the use of fentanyl.[1] Three theories of fentanyl associated recurrent respiratory depression are: gastroenterohepatic recirculation, reuptake from tissue stores, and interaction between degree of arousal, stimuli, and opioid-induced respiratory depression.

For gastroenterohepatic recirculation to cause a significant recurrent peak in plasma opioid concentration, these events must occur: accumulation and concentration in acidic gastric secretions as a result of ion trapping (conversion of unionized, diffusible drug at *p*H 7.4 to ionized form at low *p*H), movement of fluid from the stomach to duodenum with alkalinization by pancreatic secretions converting most of the drug back to unionized form, uptake into the portal circulation, and low first-pass extraction by the liver so that a significant amount of the drug escapes into the systemic circulation. Several authors[7,9,10] believe that fentanyl recurrent peaks are not a result of gastroenterohepatic recirculation. While the *p*Ka of 8.43[11] and the degree of ionization of 91% at *p*H 7.4 permit some ion trapping (and high concentrations can be measured in gastric fluid),[4] the total amount of trapped fentanyl is low and hepatic extraction is high.[9] In humans, fentanyl is primarily cleared by the liver (about 94% of the total dose)[12] at a rate nearly equivalent to normal hepatic blood flow, representing an estimated first pass extraction close to 100%.[7] Instillation of fentanyl into the stomach does not result in significant plasma concentrations of the unmetabolized drug, presumably as a result of this high extraction ratio.[10] Alfentanil has characteristics that make gastroenterohepatic recirculation more feasible. Approximately 0.4% of a dose of alfentanil is excreted unchanged by the kidneys, and the rest is presumably cleared by the liver.[8] The clearance of alfentanil is lower than fentanyl, and the hepatic extraction has been estimated at 33–40%.[7,8] Alfentanil has a *p*Ka of 6.50,[11] and 11% is ionized at *p*H 7.4, favoring ion trapping in the stomach. Indeed, in the rat the gastric concentration of alfentanil surpasses the plasma concentration 15 min after administration; after 1 h, it is ten times the plasma concentration. However, the amount of drug in the stomach (including metabolites) is less than 3% of the total dose, probably due to the low volume of fluid involved.‡ Gastroenterohepatic recirculation can theoretically cause a recurrent peak in plasma alfentanil concentration,[7] but the peak would not be clinically significant if the total amount trapped in gastric secretion is as low in humans as in rats.

Reuptake from tissue stores can cause a recurrent peak in plasma opioid concentration if these events occur: significant uptake in low blood-flow tissues with a later increase in blood flow to these same tissues, increasing efflux of accumulated drug from low blood-flow tissues to the central compartment. Fentanyl is highly lipid soluble and has a steady-state volume of distribution (Vd_{ss}) of 3.99 $l \cdot kg^{-1}$.[12] It is avidly taken up by muscle, and release from peripheral stores, not hepatic clearance, determines its terminal plasma concentration half-time ($t_{1/2\beta}$).[12] Sequentially decreasing and then increasing muscle blood flow after fentanyl administration does produce a recurrent plasma concentration peak.[10] Also, patients after cardiac surgery can experience recurrent peaks at the time they wake up and start moving voluntarily (and presumably increase previously depressed muscle blood flow).[2] Thus, fentanyl recurrent peaks appear to be the result of reuptake from tissue stores. Alfentanil, however, has a much smaller volume of distribution. Its Vd_{ss} is 0.86 $l \cdot kg^{-1}$,[13] and it is less lipid soluble: an octanol:water coefficient of 129:1 at *p*H 7.4, whereas for fentanyl it is 955:1.[11] Muscle uptake should be much less and a clinically significant increase in plasma concentration from redistribution into the central compartment appears unlikely.

‡ Schuermans V, Heykants J: Absorption, distribution, metabolism and excretion of alfentanil in animals. Preclinical research report 27246, 1982, Janssen research products information services.

Unlike the two mechanisms discussed above, the interaction of arousal and opioid-induced respiratory depression is not the result of secondary peaks in plasma opioid concentration. Sudden cessation of stimulation after arrival in the recovery room may contribute to recurrent respiratory depression if significant plasma concentrations of opioid are still present.[1] Also, the transition from awake to sleep markedly depresses the ventilatory response to CO_2 in a patient given an opioid.[14] Our patient was undisturbed for the 15-min period between conclusion of check-in to the recovery room and the respiratory arrest. We estimate that at the time of the event the patient's alfentanil plasma concentration was 63 $ng \cdot ml^{-1}$ (68% confidence limits of 27 to 99, and $t_{1/4\beta}$ of 94 min) by the method of Maitre *et al.*[15] For spontaneous ventilation, the Cp_{50} (plasma concentration for 50% response) is 223 $ng \cdot ml^{-1}$ (age range 23–54 yr, diazepam 10 mg premedication).[16] Using the logistic equation from that study, we calculate the probability of apnea to be 0.1% at 99 $ng \cdot ml^{-1}$, and 0% at both 63 and 27 $ng \cdot ml^{-1}$. The predicted alfentanil plasma concentration (assuming no recurrent peak) at the time of renarcotization appears to be too low to produce apnea when combined with lack of stimulation. However, if we extend to the 95% confidence limits, the plasma fentanyl concentration upper limit is 135 $ng \cdot ml^{-1}$, with an apnea probability of 1%.

We do not have a ready explanation for the apneic episode experienced by this patient. Recurrent respiratory depression after alfentanil can be caused by the combination of lingering opioid (especially in patients with prolonged $t_{1/4\beta}$, *e.g.*, the elderly or someone with atypical pharmacokinetics) and decreased stimulation or the onset of sleep. Recurrent respiratory depression might also be caused by gastroenterohepatic recirculation of alfentanil, although this has yet to be documented. Recurrent respiratory depression due to reuptake from tissue stores appears to be unlikely for alfentanil. In any case, patients recovering from alfentanil anesthesia may enter the recovery room awake, yet later experience somnolence and respiratory depression.

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