Neurolept anesthesia using fentanyl and droperidol supplemented by nitrous oxide and oxygen was pioneered in Europe between 1959 and 1961. It gained popularity in the United States due to its "profound analgesia, minimal hypotension, probable protection against epinephrine induced ventricular arrhythmias and a smooth postoperative course." Recent concern over pollution of operating rooms has also enhanced its popularity. At the time of its introduction, the respiratory depressant effects of fentanyl were reported to be shorter than those produced by other narcotics and were thought to be outlasted by its analgesic properties. This proved to be a misconception which has led to some near catastrophies following fentanyl's use in general anesthesia.

In 1967, Dunbar noted the respiratory response to a challenge of CO₂ to be diminished to 50% of control 60 minutes after fentanyl/droperidol was induced to supplement nitrous oxide anesthesia. He judged its respiratory depressant effects to parallel those of 2.5 MAC fluothane. Then, in 1976, Becker serendipitously observed biphasic respiratory depression after fentanyl/droperidol or fentanyl alone was used to supplement nitrous oxide anesthesia. In the patients studied, CO₂ response curves had reached a mean of 103% of control 30 minutes after arrival in the recovery room. However, in 90% of the patients studied, the response then diminished to 55% of control. The CO₂ response curves returned to only 86% of control 230 minutes after the last injection of fentanyl.

McQuay and associates measured a significant biphasic increase in plasma fentanyl levels which correlates well with the observations of biphasic respiratory depression noted by Baker and his colleagues. Vejlsted measured diminished CO₂ response curves of up to six hours in patients who had undergone neurolept anesthesia after premedication with pethidine (meperidine). Adams and Pybus reported three cases of delayed respiratory depression following administration of fentanyl, one of which occurred four hours after the last injection. The patient had been transferred from the recovery room to the ward after an uneventful recovery from anesthesia. He then suffered profound respiratory depression which responded rapidly to intravenous naloxone. Of the cases they reported, none of the patients had received any postoperative medication. Thus, clinical observation that a patient has recovered from
neurolept or fentanyl/nitrous oxide anesthesia can be misleading. It can lead the anesthetist to refrain from using naloxone when such use may be necessary to restore ventilatory adequacy after a postoperative recurrence of respiratory depression.

The case
A 20-year-old, 80 kg, 175 cm Caucasian male classified as ASA I presented for iliac bone grafting for a right scaphoid fracture. Premedication, consisting of meperidine 75 mg, promethazine 50 mg and glycopyrrolate 0.5 mg, was given intramuscularly one hour prior to induction. Defasciculation was accomplished with d-Tubocurarine 3 mg and preoxygenation was carried out with 100% oxygen by mask utilizing the circle absorption system.

Induction was satisfactorily accomplished with 2.5% thiopental 325 mg. Adequate ventilation was established and the trachea was intubated following the administration of succinylcholine 100 mg. Maintenance anesthesia was initiated utilizing enflurane 0.5%, supplemented with nitrous oxide 2 L/min and oxygen 1 L/min. The level of anesthesia was deepened by assisting ventilation and gradually increasing the concentration of enflurane every few breaths.

At an inspired concentration of approximately 1.5%, the patient suddenly developed a nodal rhythm with intermittent unifocal premature ventricular contractions. The heart rate (HR) rapidly dropped from 84 to 58 beats per minute (BPM). Enflurane was discontinued and a normal sinus rhythm with an HR of 68 BPM was restored through administration of atropine 0.4 mg.

Through auscultation of equal bilateral breath sounds, it was ascertained that the patient was well ventilated. The decision was then made to convert to fentanyl/droperidol with nitrous oxide 2 L/min and oxygen 1 L/min. Pancuronium was used for relaxation in three incremental doses totaling 4 mg.

Stability of heart rhythm is, by and large, a remarkable and consistent feature of enflurane anesthesia. However, a host of arrhythmias, albeit rare, has been reported including transient nodal rhythms and premature ventricular contractions. It cannot, of course, be categorically proven that enflurane was the causative factor in this particular instance. However, even though the heart rate and rhythm had returned to normal, it was decided that the conservative approach would be to change the anesthetic technique, especially since the arrhythmias had occurred concurrently. Fentanyl, droperidol and nitrous oxide offered the patient a wider margin of safety as far as cardiac stability was concerned. This technique also offered adequate depth of anesthesia for the increased pain of ischemia resulting from the use of a tourniquet.

Ventilation was controlled with a minute volume of 7500 cc. Arterial blood gases showed a pH of 7.50; pCO2 of 30; pO2 of 126; HCO3 of 23.5; B.E. of +1 and O2 saturation of 98.9%. The case proceeded uneventfully for 125 minutes. Increments of fentanyl averaging 1.8 cc were employed based on increases in HR and blood pressure. On first termination of the case, the x-ray showed an improper placement of K-wires, thus requiring further surgical time of 20 minutes. A sustained tetanus with full train of four was noted on the blockade monitor; however, no further muscle relaxants were used because the estimated surgical time that would be required for placement of K-wires was very short. And, in anticipation of patient movement, an additional 2 cc increment of fentanyl was administered prior to repositioning the K-wires.

Anesthesia time lasted 20 minutes after realignment of K-wires, allowing for an additional x-ray and the application of a splint. A total of 18 cc of fentanyl and 5 mg of droperidol were administered over 150 minutes. Sustained tetanus persisted on the blockade monitor and the pancuronium was reversed with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. Adequate ventilation and the patient's ability to lift his head and form a hand grip were demonstrated upon cessation of nitrous oxide and the patient was extubated uneventfully.

He was transferred to the recovery room breathing oxygen by a non-rebreathing mask at 10 L/min. The patient was drowsy but maintained his own airway without difficulty and responded appropriately and purposefully to verbal command. Vital signs on arrival in the recovery room were: Temperature-95 orally; HR-88; respirations-12; BP 118/70. Fifteen minutes after arrival in the recovery room, the patient's respiratory rate dropped precipitously to 4-6/min and he became unresponsive. No change was noted in BP or HR.

Naloxone 0.2 mg was administered intravenously. The patient became readily arousable and respirations returned to 12-14/min. An additional 0.2 mg of naloxone was administered intramuscularly to extend the reversal of respiratory depression. The patient was transferred to the ward one and a half hours later with no changes noted from his initial recovery room assessment. He required no analgesics following the administration of naloxone.

Discussion
Our patient received 10 incremental doses of
fentanyl for an average of 0.075 mcg/kg/min of anesthesia time. In comparison, McQuay and associates studied three groups of patients utilizing different dosages for the administration of fentanyl. Each group was induced with thiopental. Group A then received a 10 mcg/kg bolus followed in 20 minutes by a 2 mcg/min drip. Group B also received a 10 mcg/kg bolus followed by two incremental doses of fentanyl, and group C simply received a one time bolus of 25 mcg/kg. Their extrapolated doses averaged over time are: Group A–0.145 mcg/kg/min; group B–0.125 mcg/kg/min; group C–0.22 mcg/kg/min.

Due to the fact that the anesthetic technique was converted from enflurane/nitrous oxide and that the odor of residual enflurane could be detected in the anesthesia bag, it was decided that our patient did not require a large initial loading dose of fentanyl. However, 5 mg of droperidol were given initially to facilitate the anesthetic technique. No odor of residual enflurane was detectable at the end of surgery.

The mcg/kg/min dose of fentanyl received by this patient falls within the range of many fentanyl/nitrous oxide and fentanyl/droperidol/nitrous oxide anesthetics which have been empirically noted to require no reversal at our institution (0.05-0.10 mcg/kg/min). However, in retrospect, had thiopental been substituted for the final increment of fentanyl, the delayed respiratory depression may not have occurred.

The delayed respiratory response manifested by this patient occurred 60 minutes after the last dose of fentanyl, 40 minutes after cessation of surgical stimulation, and 20 minutes after emergence. This seems to be in harmony with the findings of McQuay, who measured second peaks in plasma fentanyl concentrations within 45 minutes of the end of surgery.

In consideration of the possible contributing factors to the biphasic response, Becker surmised the following: (1) lowered sympathetic activity in the postoperative period; (2) varying intensity of stimulation during the recovery period; and (3) sequestration of fentanyl in the acidic environment of the stomach and then passage into the alkaline environment of the small intestine where it can be reabsorbed.

McQuay and associates measured plasma cortisol levels throughout their study and found them to continue increasing well into the postoperative period. Therefore, sympathetic activity appears to be unaffected by moderate doses of fentanyl. Another observer who employed five times the amount of fentanyl as in McQuay's study found plasma cortisol levels to be significantly diminished. The stimulation given our patient should have been adequate to encourage ventilation. In fact, the nurses were continuing their initial assessment when he became unresponsive. The third possibility, that fentanyl was reabsorbed, seems reasonable, especially since a second peak has now been measured. However, further research is needed to verify this conclusion.

It might also be surmised that the addition of droperidol to the anesthetic technique may have been a factor in the recurrent postoperative respiratory depression seen in this patient. However, two independent teams of observers have found exactly the opposite to be true. Becker and associates concluded that "droperidol adds to neither the anesthetic nor the respiratory depressant effects of fentanyl...and may actually decrease it." Harper and associates found that "slope depression dissipated slightly more rapidly with fentanyl plus droperidol than with fentanyl at equivalent narcotic doses." They postulated that the cause of this was the consistent restlessness and agitation they observed in patients following neurolept anesthesia. No restlessness or agitation was observed postoperatively in our patient.

Whatever the reason, the clinical significance is obvious—a patient having undergone fentanyl/nitrous oxide or fentanyl/droperidol/nitrous oxide anesthesia that is inadequately reversed or not reversed with naloxone can undergo a second stage of respiratory depression after uneventful recovery from anesthesia. This could be especially significant in several postoperative situations commonly encountered by nurse anesthetists in modern anesthetic practice, including the following.

1. Patients who have undergone abdominal surgery with subsequent field block or thoracic or renal surgery with subsequent intercostal block are free from postoperative pain and may lack a noxious stimulus to facilitate breathing.

2. Considering the complications reported by Adams and Pybus, time allotted for recovery from fentanyl/nitrous oxide anesthesia in outpatient surgery deserves thorough individual attention.

3. The common practice of supplementing inhalation anesthesia with intermittent doses of fentanyl could also prove significant postoperatively, especially since as little as 0.1 MAC (0.178%) of enflurane or 0.1 MAC (0.075%) of fluothane has been shown to decrease the ventilatory response to hypoxia. The awake MAC of enflurane is approximately 1% and 0.42% for fluothane. A patient in the recovery room could have the necessary concentrations of these agents in his system to blunt the hypoxic ventilatory response. This effect, coupled with a biphasic response of fentanyl, could
cause profound respiratory depression and problematic airway obstruction.

All of the above mentioned categories of patients need postoperative oxygen in the recovery room. Naloxone should always be considered as a means to avoid the biphasic respiratory depression.

Anderson had to administer naloxone to 26.8% of patients following moderate doses of fentanyl. A mean dose of 2 mcg/kg intravenous naloxone was found to be adequate for maintaining ventilation without reversing postoperative analgesia afforded by the use of fentanyl. The patients required no postoperative analgesia for the first five and three quarter hours following surgery.17 Our patient received 2.5 mcg/kg intravenously and an equal amount intramuscularly without attenuating postoperative analgesia.

Due to the time variation over which the biphasic respiratory depression can occur in some patients, it is probably wise to follow an intravenous dose of naloxone with an intramuscular dose when it is elected to reverse fentanyl-induced respiratory depression. Cullen states that naloxone attenuates narcotic-induced respiratory depression for 30-60 minutes. He recommends following an initial intravenous dose 15 minutes later with an intramuscular dose that is double the initial dose.18 This can extend the period of reversal for many hours.

Summary

The recovery of patients following neurolept or fentanyl/nitrous oxide anesthesia is extremely variable due to variations in drug dosage, biotransformation and excretion idiosyncrasies among individuals.19 The respiratory depressant effects of fentanyl or fentanyl/droperidol can far outlast the analgesic duration and can recur after having dissipated. The level of consciousness and the quality of breathing can be misleading indicators of complete recovery from neurolept anesthesia. Respiratory rate has been observed to return to control levels when simultaneous response to CO2 re-breathing was reduced and resting PeCO2 was increased.13 Naloxone can be used in dosages which will help ensure adequate ventilation without attenuating postoperative analgesia.

REFERENCES


AUTHOR

Capt. James M. Rich, CRNA, BSN, ANC, received his BSN from Ball State University in Muncie, Indiana. He is a graduate of the Walter Reed Intensive Care Nursing Course and the Anesthesiology for ANC Officers Course at Walter Reed Army Medical Center. He is currently a staff nurse anesthetist at General Leonard Wood Army Community Hospital at Fort Leonard Wood, Missouri. This paper was developed when the author was at Walter Reed Army Medical Center.

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