8. Fox RH, Solman AJ: A new technique for monitoring the deep body temperature in man from the intact skin surface. J Physiol (Lond) 212:8P–10P, 1971
9. Fox RH, Solman AJ, Isaacs R, Fry AJ: A new method for monitoring deep body temperature from the skin surface. Clin Sci 44:81–86, 1973
10. Kobayashi T, Nemoto T, Kamiya A, Togawa T: Improvement of deep body thermometers for man. Ann Biomed Eng 3:181–188, 1975
11. Singer B, Lipton B: Monitoring of core temperature through the skin: A comparison with esophageal and tympanic temperatures. Bull NY Acad Med 51:947–952, 1975

Anesthesiology
58:275–277, 1983

Postoperative Rigidity Following Fentanyl Anesthesia

CHARLES M. CHRISTIAN II, M.D., PH.D.,* JOHN L. WALLER, M.D.,† C. CRAIG MOLDENHAUER, M.D.‡

Postoperative respiratory depression occurs after the intravenous injection of fentanyl. Becker *et al.*[1] demonstrated the biphasic nature of this response; Adams and Pybus[2] cited three patients in whom postoperative respiratory depression followed an apparently normal recovery from fentanyl–nitrous-oxide anesthesia; McQuay *et al.*[3] demonstrated a second peak of plasma fentanyl which occurred after surgery. Stoeckel *et al.*[4] postulated an entero-systemic recirculation to explain these phenomena. Hall[5] expressed concern about the impact of the recent trend to high-dose (50–150 μg/kg) fentanyl anesthesia on the problem of a secondary or biphasic episode of respiratory depression.

We describe three patients who developed rigidity several hours after fentanyl administration which may be attributable to a secondary peak of fentanyl in the plasma.

REPORTS OF THREE PATIENTS

Patient 1. A 56-year-old, 78-kg man with coronary occlusive disease scheduled for coronary artery bypass grafting (CABG) was premedicated with 30 mg propanolol, po, 10 mg diazepam, po, and 15 mg morphine, im. Systemic and pulmonary arterial and peripheral venous lines were established, and electrocardiographic and electroencephalographic monitoring were initiated prior to induction of anesthesia.

Induction of anesthesia was accomplished with 35 μg/kg fentanyl and 150 μg/kg pancuronium; the patient breathed 100% oxygen through a semi-closed system. Truncal rigidity was not seen during induction of anesthesia and no hemodynamic response to endotracheal intubation occurred. Ventilation was controlled to maintain Pa_{CO_2} between 33 and 37 mmHg.

Additional fentanyl (15 μg/kg) failed to ablate hemodynamic responses to skin incision and a sodium nitroprusside infusion was begun. Additional doses of 10 μg/kg fentanyl were given prior to sternotomy and prior to initiation of cardiopulmonary bypass. Neuromuscular blockade was maintained by incremental doses of pancuronium bromide titrated to produce the loss of the last twitch of a train-of-four. During the course of surgery, the patient received a total dose of fentanyl of 70 μg/kg (5.46 mg) and 16 mg pancuronium, iv.

The anesthetic and surgical course was otherwise unremarkable. At the termination of the procedure, four hours after induction of anesthesia, neuromuscular train-of-four had returned to control value although no antagonist had been given. Ventilation was spontaneous. He was responsive to voice and would move all four extremities on command. His rectal temperature was 35.4° C.

The patient was taken to the cardiovascular acute care unit where ventilation was controlled with a volume ventilator which delivered an FI_{O_2} of 0.6, a tidal volume of 12 ml/kg at an intermittant mandatory vantilatory rate of six breaths/min. Analysis of arterial blood gases revealed a pH_a of 7.47, a Pa_{O_2} of 113 mmHg, and a Pa_{CO_2} of 37 mmHg. The patient was placed under a radiant heater and sodium nitroprusside infusion was used to control hypertension.

Approximately 45 min later, five hours after the initial injection of fentanyl, the patient became obtunded and his extremities, chest, and abdominal musculature became rigid. His rectal temperature at this time was 36.7° C. Analysis of blood gases revealed a Pa_{CO_2} of 65 mmHg, a pH_a of 7.23, and a Pa_{O_2} of 98 mmHg. The peak inspiratory pressure (PIP) was 47 cmH_2O. His pupils were 2 mm and reactive to light. His cardiac index was 4.7 $l \cdot min^{-1} \cdot m^{-2}$, mean arterial pressure 111 mmHg, pulmonary artery occlusion pressure 17 mmHg, and central venous pressure 10 mmHg.

Within three minutes after 40 μg naloxone, iv, the patient was responsive, moved all extremities upon command, and complained of mild incisional discomfort. Rigidity disappeared completely. After readjustment of the ventilator, analysis of blood gases revealed a Pa_{CO_2} of 42 mmHg, a pH_a of 7.42, and Pa_{O_2} of 123 mmHg. Cardiac index was 3.9 $l \cdot min^{-1} \cdot m^{-2}$, mean arterial pressure 84 mmHg, pulmonary artery occlusion pressure 16 mmHg, and central venous pressure 11 mmHg.

* Assistant Professor, Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Duke University Medical Center.
† Associate Professor, Section of Anesthesiology, Cardiothoracic Division, Emory University Clinic.
‡ Cardiac Fellow, Section of Anesthesiology, Cardiothoracic Division, Emory University Clinic.

Received from the Departments of Anesthesiology, the Duke University Medical Center, Durham, North Carolina, and the Emory University Clinic, Atlanta, Georgia. Accepted for publication September 16, 1982.

Address reprint requests to Dr. Christian: Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710.

Key words: Analgesics: fentanyl. Anesthetics, intravenous: fentanyl. Complications: rigidity. Pharmacokinetics: distribution.

Patient 2. A 51-year-old, 75.3-kg man was admitted for CABG. He was premedicated with 20 mg propranolol, isosorbide dinitrate, and 10 mg diazepam, po, and 8 mg morphine and 0.4 mg scopolamine, im, one hour preoperatively. Anesthesia was induced with 75 μg/mg fentanyl infused at 300 μg/min. Diazepam, 15 mg, was given iv to insure unconsciousness and succinylcholine was given iv in 20-mg increments when truncal rigidity compromised ventilation. During the course of a three-hour anesthetic, the patient received a total of fentanyl 74 μg/kg (5.650 mg), 30 mg diazepam, 160 mg succinylcholine, and 13 mg pancuronium.

The patient was admitted to the cardiac surgical ICU 195 min after induction of anesthesia and his rectal temperature was 35.6° C. Two hours and 45 minutes postoperatively, he developed board-like rigidity of the abdominal and thoracic musculature, increased peak inspiratory pressure (PIP) readings on the ventilator, and a respiratory acidosis. The rigidity was eliminated completely by 20 mg succinycholine, iv. No wheezes were heard.

Four hours and 30 minutes after admission to the ICU (7 hours and 45 minutes after induction of anesthesia), the patient again experienced truncal rigidity with board-like tensing of the abdominal muscles and peak inspiratory pressures of 35 cmH_2O. Despite being ventilated with a tidal volume (V_T) of 950 ml, an IMV of 7 min, and a FI_{O_2} of 0.6, analysis of arterial blood gases revealed a Pa_{CO_2} of 64 mmHg, pH_a of 7.22, and Pa_{O_2} of 108 mmHg. His rectal temperature was 37.7° C. Succinylcholine, 20 mg, completely eliminated his rigidity and decreased his peak inspiratory pressure to 25 mmHg l/min. His plasma fentanyl level at that time was 8 ng/ml.§

Patient 3. A 62-year-old man, admitted to the hospital following his resuscitation from an episode of hypotension and circulatory collapse, was brought to the operating room in stable condition the following morning for CABG. Anesthesia was induced with 75 μg/kg fentanyl infused at the rate of 300 μg/min. The patient became rigid despite his pretreatment with 2 mg pancuronium 2 min before the initiation of the fentanyl infusion. The intraoperative course was uneventful. The total dose of fentanyl was 115 μ/kg.

The patient was receiving sodium nitroprusside and had adequate circulatory dynamics 5.5 hours after the induction of anesthesia. Ventilation was controlled at a rate of 12 breaths/min with a FI_{O_2} of 0.7 and V_T of 900 ml. Analysis of arterial blood gases revealed a Pa_{O_2} of 86 mmHg, Pa_{CO_2} 46 mmHg, and a pH_a of 7.36. One hour later, analysis of arterial blood gases revealed a Pa_{O_2} of 88 mmHg, Pa_{CO_2} of 57 mmHg, and pH_a of 7.27. Peak inspiratory pressures of 45 cmH_2O were required to deliver 900 ml tidal volume, and palpation revealed board-like rigidity of the abdominal musculature.

Pancuronium, 2 mg, was administered iv. Fifteen minutes later, the Pa_{O_2} was 103 mmHg, Pa_{CO_2} 45 mmHg, and pH_a 7.39. Ventilator peak inspiratory pressure was 25 cmH_2O, and no further rigidity was encountered.

Discussion

Fentanyl anesthesia have been associated with postoperative biphasic respiratory depression.[1,3,4] Based on a pharmacokinetic analysis, Stoeckel *et al.*[4] proposed an enterosystemic recirculation for fentanyl similar to that described for methadone and meperidine.[7] Fentanyl is transferred rapidly into the peripheral compartment.[9]

McClain and Hug[14] investigated the kinetics of tritiated fentanyl in humans, and reported a prolonged secondary half-life ($t_{1/2\beta}$ = 219 min) and an apparent secondary peaking of fentanyl in plasma which occurred five to seven hours after injection. They postulated that this secondary fluctuation may be due to an increased perfusion of the peripheral compartment or to an increased plasma uptake of fentanyl from skeletal muscle as perfusion increases with spontaneous movements by the patients.

The stomach wall stores fentanyl and secretes it into the gastric juice.[4] The gastric fentanyl may then be reabsorbed from the alkaline medium of the small intestine and appear 30 to 60 minutes later in the vascular compartment. This is a possible explanation for the secondary acute respiratory depression that may occur up to four hours following fentanyl injection.[1] Immediate muscular rigidity associated with rapid injection of fentanyl is not uncommon[10,11] and is thought to be due to central nervous system stimulation by narcotics.[12] However, late development of this rigidity has not been reported previously. We believe our patients' late muscular rigidity was due to fentanyl.

The delay in the effect seen in patient 1 could be attributed to the moderate hypothermia seen on transfer to the acute care unit. Gastric emptying of sequestered fentanyl and perfusion of peripheral tissues would be delayed by central hypothermia. Active warming and pharmacologic vasodilation in the postoperative period would be expected to increase reabsorption of sequestered fentanyl and produce the delayed appearance of the secondary fentanyl peak.

Finally, the complete ablation of all symptoms in one case by 0.04 mg naloxone supports our belief that the described phenomena were related to fentanyl. Naloxone antagonizes both central and peripheral fentanyl-induced effects.[12] Since all available data suggest that all of our patients had some fentanyl in plasma and brain tissue, the postulation of an increase in fentanyl concentration, from whatever cause, suggests a threshold concentration in plasma and brain that will cause truncal rigidity.

The facilitated passage through biologic membranes and the nonspecific tissue binding of fentanyl are related to the lipophilia of the drug. Fentanyl exhibits increased lipophilia as *p*H decreases; Ainslie *et al.*[13] have demonstrated increased brain levels of fentanyl during alkalosis.

Unfortunately, plasma fentanyl levels were measured in only one case, after rigidity had been treated with neuromuscular blockers. The plasma fentanyl level at this time was 8 μg/ml. The "rigidity threshold" for fentanyl apparently is at or above this concentration, but this remains speculative at this time.

In summary, truncal rigidity upon induction of general anesthesia with fentanyl is a well-documented phenomenon. However, truncal rigidity postoperatively has

§ RIAA Assay, Courtesy of C. C. Hug, Jr., M.D., Ph.D.

not been reported previously. Earlier reports dealing with secondary fentanyl peaks occurring postoperatively have dealt with the dangers associated with respiratory depression in the spontaneously ventilating patient. We have described the occurrence of another side effect of fentanyl that could seriously compromise the mechanically ventilated patient, particularly when hypothermia is superimposed. Treatment with naloxone or neuromuscular blockers was effective attenuating the rigidity.

References

1. Becker LD, Paulson BA, Miller RD, Severinghaus JW, Eger EI II: Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. ANESTHESIOLOGY 44:291–296, 1976
2. Adams AP, Pybus DA: Delayed respiratory depression after use of fentanyl during anesthesia. Br Med J 1:278–279, 1978
3. McQuay HJ, Moore RA, Patterson GMC, Adams AP: Plasma fentanyl, fentanyl concentrations and clinical observations during and after operation. Br J Anaesth 51:543–550, 1979
4. Stoeckel H, Hengstmann JH, Schuttler J: Pharmacolokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Br J Anaesth 51:741–744, 1979
5. Hall GM: Fentanyl and the metabolic response to surgery. Br J Anaesth 52:561–562, 1980
6. Schanker LS, Tocco DT, Brodie BB, Hagben CAM: Absorption of drugs from the rat small intestine. J Pharmacol Exp Ther 123:81–88, 1958
7. Lynn RK, Olsen GD, Leger RM, Gorden EP, Smith RG, Gerber N: The secretion of methadone and its major metabolic in the gastric juice of humans. Drug Metab Dispos 4:504–509, 1976
8. Trudnowski RJ, Gessner T: Gastric sequestration of meperidine following intravenous administration. Abstract ASA Meeting, Chicago, 1975, p 327
9. Hengstmann JH, Stoeckel H, Schuttler J: Pharmacokinetics of fentanyl-evaluation of an infusion nodel. Naunyn Schmiedebergs Arch Pharmacol (Suppl) 302: Abstract 252, 1972
10. Comstock MK, Scamman FL, Carter JG, Moyers JR, Stevens WC: Rigidity and hypercarbia on fentanyl oxygen induction. ANESTHESIOLOGY 51:S28, 1979
11. Waller JL, Hug CC, Nagle DM, Craver JM: Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. ANESTHESIOLOGY 55:212–217, 1981
12. Sockoll MD, Hoyt JL, Gergis SD: Studies in muscular rigidity, nitrous oxide, and narcotic analgesic agents. Anesth Analg (Cleve) 51:10–20, 1972
13. Ainslie SG, Elsels JH, Corkill G: Fentanyl concentrations in brain and serum during respiratory acid-base changes in the dog. ANESTHESIOLOGY 51:293–297, 1979
14. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106–114, 1980
15. Jaffe JH, Martin WR: Narcotic Analgesics and Antagonists. Edited by Goodman LS, Gilman A. New York, Macmillan Publishing Co, Inc, 1975, pp 267–268

Anesthesiology
58:277–280, 1983

Estimating Allowable Blood Loss: Corrected for Dilution

JEFFREY B. GROSS, M.D.*

Several formulas have been derived for estimating allowable pre-transfusion blood loss.[1,2] One such formula is:

$$V_L = EBV \times \frac{H_O - H_F}{H_O} \quad (1)$$

where V_L = allowable blood loss; EBV = patient's estimated blood volume; H_O = patient's initial hematocrit (or hemoglobin concentration); and H_F = patient's minimum allowable hematocrit (or hemoglobin concentration). This "linear" formula implies that the fractional decrease in hemoglobin or hematocrit is equal to the fraction of the total blood volume that has been lost. This would be true if all of the shed blood had the initial hematocrit. However, intravascular volume usually is maintained prior to blood transfusion by administration of crystalloids; hematocrit therefore should decrease gradually. Because each milliliter of shed blood contains progressively less hemoglobin, the above formula overestimates the hemoglobin loss. Inconsistencies may result. For example, formula 1 predicts that if blood losses exceed the total blood volume, the resulting hemoglobin concentration will be negative!

Bourke and Smith discussed this problem in 1975,[1] and described the problem of isovolemic hemodilution in terms of the differential equation:

$$\frac{dH}{dV_L} = -\frac{H}{EBV}$$

The solution of this equation with initial $H = H_O$ and initial $V_L = O$ is:

* Assistant Professor of Anesthesia.

Received from the Departments of Anesthesia, University of Pennsylvania, and Philadelphia Veterans Administration Medical Center, Philadelphia, Pennsylvania. Accepted for publication September 17, 1982.

Address reprint requests to Dr. Gross: Department of Anesthesiology, Philadelphia V.A.M.C., University and Woodland Avenues, Philadelphia, Pennsylvania 19104.

Key words: Blood: loss; hemodilution; replacement. Hemorrhage. Transfusion: stored blood.