Anesthesiology
66:433-435, 1987

The Dose Response of Fentanyl in Neonatal Anesthesia

MYRON YASTER, M.D.*

At equipotent doses (ED_{50}, MAC), most inhaled anesthetics cause a significant incidence of unacceptable side effects in neonates.[1,2] Because of these side effects, some anesthesiologists recommend no anesthesia as the technique of choice because of the cardiovascular, pulmonary, and neurologic immaturity of the newborn.[3] Robinson and Gregory[4] used heart rate and arterial blood pressure responses as an index of adequate anesthesia to demonstrate that human premature infants undergoing ductal ligation could be anesthetized with 30-50 μg/kg fentanyl, pancuronium, and oxygen. The anesthesia achieved demonstrated circulatory stability and has thereby generated interest in fentanyl as a preferred anesthetic technique in the newborn. This study prospectively determined the minimum effective dose of fentanyl required for neonates undergoing several types of surgery.

SUBJECTS AND METHODS

Twenty-five neonates, less than 7 days of age, ASA III & IV, and scheduled for emergency thoracic (tracheoesophageal fistula, diaphragmatic hernia), abdominal (omphalocele, gastroschisis, necrotizing enterocolitis, and intestinal obstruction), or genitourinary (bladder exstrophy) operations were studied. Approval from the Institution's Committee on Clinical Investigation was obtained. Twelve males and 13 females, averaging (±SD) 2.67 ± 0.67 kg (range 0.7-3.7 kg) and 36.5 ± 3.2 weeks (range 28-42 weeks) gestation were studied. All babies received 0.1 mg atropine, iv prior to awake intubation of the trachea. Following intubation, paralysis was achieved with metocurine (0.3 mg/kg) iv, and ventilation was controlled to maintain Pa_{CO_2} between 30-35 mmHg, as determined by repeated analysis of arterial blood gases and by use of an end-tidal CO_2 monitor. Heart rate, rhythm, arterial blood pressure (*via* radial artery catheterization), temperature, and end-tidal CO_2 were continuously monitored. Thirteen infants had central venous pressure monitoring (*via* internal or external jugular venous catheterization) as well. Cardiac output was measured in duplicate using the dye dilution technique[5] in 11 of the 13 patients with central venous catheters. Five per cent dextrose in 0.2% saline was infused in a peripheral vein at maintenance rates calculated according to a standard formula.[6] Lactated Ringer's solution was infused at a rate of 6-8 $ml \cdot kg \cdot hr^{-1}$ to replace third space fluid losses. Estimated blood volumes and allowable blood losses were calculated according to standard formulae.[6] Blood loss was measured by weighing sponges, measuring the volume of blood in suction bottles, and by hourly hematocrit determinations. Blood was replaced with 3 ml of lactated Ringer's solution for each milliliter of blood lost until the calculated allowable blood loss was reached at which point lost blood was replaced with an equal volume of transfused blood.

An escalating dosage schedule starting with the lowest probable effective and tolerable dose was used. Prospectively starting with 2.5 μg/kg, and then advancing in 2.5 μg/kg increments, five patients were to be studied in each treatment group until a dose of fentanyl was found that was effective in all patients. However, if more than two patients failed at any initial fentanyl dose, that dose was abandoned and the next fentanyl dose was begun. Using criteria similar to Robinson and Gregory,[4] we chose a definition of effective dose which involved physiologic responses to surgical stimulation. If a patient showed a hemodynamic response to surgical stimulus (*i.e.*, a rise in heart rate or arterial blood pressure greater than 20% above control), anesthesia was supplemented with 2.5 μg/kg fentanyl increments until heart rate and arterial blood pressure returned to presurgery levels. The need to supplement the original dose of fentanyl within 30 min of surgery was considered a failure of the initial dose of fentanyl to provide adequate anesthesia. Supplementation after 30 min was considered as a need to provide additional anesthesia, rather than a failure of the initial dose of fentanyl to provide adequate anesthesia. Data were analyzed using two-way analysis of variance split plot design in which time is a within-group factor and fentanyl dose is a between-group factor. Individual values within each group were compared by orthogonal contrast.[7] A P value of less than 0.05 was considered significant. All values are presented as averages ± standard deviation.

RESULTS

There was a significant decrease in heart rate (13%) following all fentanyl doses compared to control (182

* Assistant Professor, Anesthesiology/Critical Care Medicine.

Received from the Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205. Accepted for publication October 20, 1986.

Address reprint requests to Dr. Yaster.

Key words: Anesthesia: pediatric. Anesthetics, intravenous: fentanyl. Potency, anesthetic.

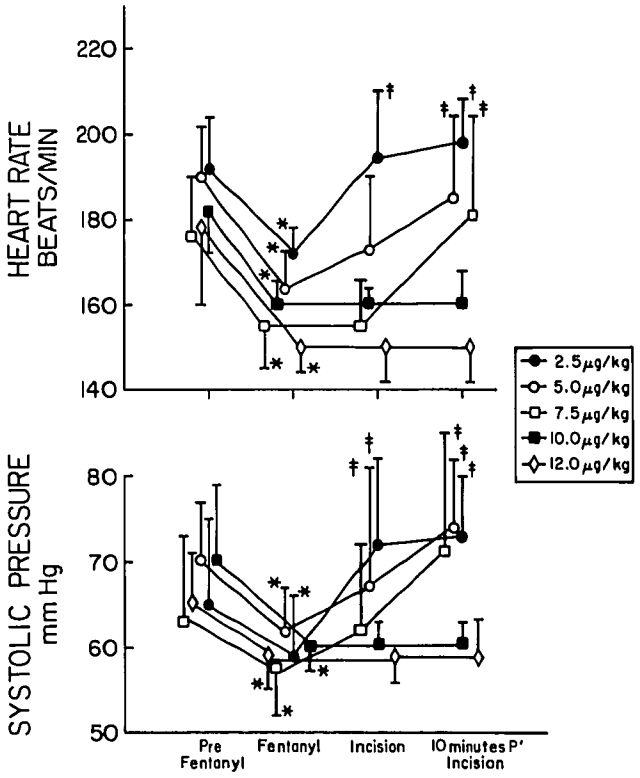

FIG. 1. The mean heart rate and systolic arterial blood pressure responses to the initial fentanyl dose and to surgical incision are depicted for each treatment group. Initial fentanyl dosage groups are represented by: a closed circle (2.5 μg/kg, n = 3), an open circle (5.0 μg/kg, n = 6), an open square (7.5 μg/kg, n = 6), a closed square (10.0 μg/kg, n = 5), and an open diamond (12.5 μg/kg, n = 5). Bars represent the standard deviation. Statistical significance, $P < 0.05$, is represented by an asterisk (*) for comparison of the initial fentanyl dose to control and by a cross (†) for comparison of incision (and time following incision) to fentanyl.

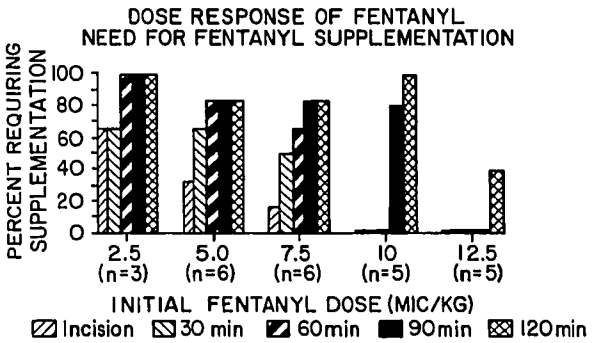

FIG. 2. The percentage of patients requiring fentanyl supplementation is depicted for each initial fentanyl treatment group at incision, and at 30, 60, 90, and 120 min following incision. Supplementation of the initial fentanyl dose was based on the hemodynamic response to surgical stimulus (*i.e.*, a rise in heart rate or arterial blood pressure greater than 20% above control). Fentanyl in initial doses of greater than 10 μg/kg uniformly provided stable heart rate and arterial blood pressure following surgical stimulation for as long as 75 min.

± 13 bpm, pre *vs.* 159 ± 12 bpm, post, $P < 0.001$). Similarly, arterial blood pressure decreased (9%) following all fentanyl doses compared to control (65 ± 11 mmHg, pre *vs.* 59 ± 7 mmHg, post, $P < 0.002$). The effect of fentanyl on heart rate and arterial blood pressure occurred regardless of the initial dose ($P < 0.002$) (fig. 1). Mean (±SD) cardiac index and systemic vascular resistance index did not change following fentanyl administration (2.22 ± 0.89 l · min · m^2, 886 ± 309 dyne · sec · cm^{-5}) as compared to control (2.29 ± 0.94 l · min · m^2, 1126 ± 652 dyne · sec · cm^{-5}) in the 11 patients in whom cardiac output was measured. The initial fentanyl dose significantly affected the time of onset and the magnitude ($P < 0.02$) of the heart rate and arterial blood pressure response to surgery. Fentanyl supplementation was required at incision or within 30 min of the initial dose in more than 50% of the patients who received initial doses ranging between 2.5–7.5 μg/kg (fig. 2). Among patients requiring fentanyl supplementation during the first 30 min, a total dose (initial dose plus supplemental doses) of 17.5 ± 2.5 μg/kg (n = 9) was required to restore heart rate and arterial blood pressure to presurgical levels. However, fentanyl, when given in initial doses of 10 μg/kg or greater, provided adequate anesthesia for as long as 75 min ($P < 0.02$) (fig. 2). Indeed, 80% of the neonates receiving an initial bolus of 10 μg/kg fentanyl did not require narcotic supplementation until 90 min of surgery had elapsed. Those receiving 12.5 μg/kg as an initial bolus did not require fentanyl supplementation until 120 min of surgery had elapsed.

DISCUSSION

The newborn who requires surgery poses special anesthetic challenges. Potent inhaled anesthetics can rarely be provided at MAC levels without producing unacceptable hypotension.[1,2] In this prospective study of fentanyl as the primary anesthetic agent in newborns, an initial dose of fentanyl greater than or equal to 10 μg/kg consistently provided adequate anesthesia. Indeed, initial fentanyl doses less than or equal to 7.5 μg/kg not only failed to achieve an adequate depth of anesthesia, but necessitated substantial fentanyl supplementation as well. Fentanyl in doses of 12.5 μg/kg produced a longer duration of anesthesia than 10 μg/kg (90 min *vs.* 75 min). Thus, at the higher initial levels, fentanyl produced a dose-dependent increase in the duration of anesthesia that may have been predicted on the basis of previous pharmacokinetic studies.[8,9]

The fentanyl-oxygen-relaxant technique first described in premature neonates undergoing ligation of the patent ductus arteriosus involved 30–50 μg/kg fentanyl, and showed that fentanyl was an effective anesthetic agent in

these infants.[4] The patients studied were seriously ill, fluid-restricted preterm infants, varying in age from 1 day to 6 weeks, and may not be representative of the majority of children undergoing neonatal surgery. Our data, therefore, extend the observations of Robinson and Gregory[4] to premature and term neonates undergoing a wide variety of major surgical procedures in the first week of life. Furthermore, fentanyl produces anesthesia at significantly lower doses (10–12.5 μg/kg) than previously reported, and is consistent with the decreased anesthetic requirements for infants less than 1 month of age reported for halothane by Lerman *et al.*[10]

The typical response to intubation in the neonate is profound bradycardia and an increased arterial blood pressure.[11] To prevent this bradycardia and the resultant decreased cardiac output,[12] we routinely pretreat our neonates with atropine[13] prior to endotracheal intubation. This explains the high initial heart rates (prefentanyl) reported in this study and why we chose to paralyze our patients with a relaxant (metocurine) that would not exacerbate the tachycardia and potentially mask the autonomic response to pain.

Induction of anesthesia with fentanyl produced only minor hemodynamic changes. The changes that did occur were of little clinical significance, and included mild slowing of the heart rate and small decreases in the systolic arterial blood pressure. Furthermore, in the 11 infants in whom cardiac outputs were obtained, there was no change in either cardiac index or systemic vascular resistance following fentanyl administration. Thus, the present study confirms the work of other investigators using this drug in neonates undergoing cardiac surgery.[4,14–16]

In summary, the fentanyl-oxygen-metocurine technique described above has been shown to be a safe and effective anesthetic technique in premature and full-term infants undergoing a wide variety of surgical procedures. Fentanyl in initial doses of 10–12.5 μg/kg produced insignificant hemodynamic changes and provided reliable anesthesia for 75 min.

The author wishes to acknowledge the editorial assistance of Randall C. Wetzel, M.D., and Kenneth Kubos, Ph.D., and the secretarial assistance of Sandra Burnley and Nancy Martin.

References

1. Friesen RH, Lichtor JC: Cardiovascular depression during halothane anesthesia in infants: A study of three induction techniques. Anesth Analg 61:42–45, 1982
2. Nicodemus HF, Nassiri-Rahimi C, Bachman L, Smith TC: Median effective doses (ED_{50}) of halothane in adults and children. ANESTHESIOLOGY 31:344–348, 1969
3. Ward RJ, Crawford EW, Stevenson JK: Anesthetic experiences for infants under 2,500 gram weight. Anesth Analg 49:767–772, 1970
4. Robinson S, Gregory GA: Fentanyl-air-oxygen anesthesia for patent ductus arteriosus in preterm infants. Anesth Analg 60:331–334, 1981
5. Rudolph AM: Cardiac catheterization and angiography, Congenital Diseases of the Heart. Edited by Rudolph AM. Chicago, Yearbook Medical Publishers, Inc, 1974, pp 49–162
6. Furman EB, Roman DG, Lemmer LAS, Hairabet J, Jasinska M, Laven MB: Specific therapy in water, electrolytes, and blood volume replacement during pediatric surgery. ANESTHESIOLOGY 42:187–193, 1975
7. Kirk RE: Experimental Design: Procedures for the Behavioral Sciences, 2nd Edition. Belmont CA, Wadsworth Inc, 1982, p 95
8. Murphy MR, Olson WA, Hug CC Jr: Pharmacokinetics of ^{3}H-fentanyl in the dog anesthetized with enflurane. ANESTHESIOLOGY 50:13–19, 1979
9. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ: Pharmacokinetics of fentanyl in neonates. Anesth Analg 65:227–232, 1986
10. Lerman J, Robinson S, Willis MM, Gregory GA: Anesthetic requirements for halothane in young children 0–1 month and 1–6 months of age. ANESTHESIOLOGY 59:421–424, 1983
11. Grogaard S, Sundell H: Effect of beta-adrenergic agonists on apnea reflexes in newborn lambs. Pediatr Res 17:213–219, 1983
12. Rudolph AM, Heymann MA: Cardiac output in the fetal lamb: The effects of spontaneous and induced changes of heart rate on right and left ventricular output. Am J Obstet Gynecol 124: 183–192, 1976
13. Kelly MA, Finer NN: Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. J Pediatr 105:303–309, 1984
14. Hickey PR, Hansen DD, Wessel DL, Lange P, Jonas RA: Pulmonary and systemic hemodynamic responses to fentanyl in infants. Anesth Analg 64:483–486, 1985
15. Hickey PR, Hansen DD: Fentanyl and sufentanyl—Oxygen pancuronium anesthesia for cardiac surgery in infants. Anesth Analg 63:117–124, 1984
16. Hickey PR, Hansen DD, Wessel DL, Lange P, Jonas RA, Elixson EM: Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 64:1132–1142, 1985