Anesthesiology
73:1136–1140, 1990

Tolerance and Dependence in Neonates Sedated with Fentanyl during Extracorporeal Membrane Oxygenation

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We undertook a retrospective chart review of 37 neonates who received fentanyl by continuous infusion while undergoing extracorporeal membrane oxygenation (ECMO) between May 1986 and October 1988. We quantified the doses of all sedatives utilized, determined the incidence of neonatal abstinence syndrome (NAS), and identified risk factors associated with NAS. We determined peak fentanyl infusion rate, mean fentanyl infusion rate, total fentanyl dose, and duration of ECMO therapy. NAS was observed in 21 of 37 neonates (57%). In both the NAS and non-NAS neonates, mean infusion rate increased steadily during ECMO therapy, from a mean of 11.6 ± 6.9 (SD) $\mu g \cdot kg^{-1} \cdot h^{-1}$ on day 1 to a mean of 52.5 ± 19.4 (SD) $\mu g \cdot kg^{-1} \cdot h^{-1}$ by day 8. Total fentanyl dose and duration of ECMO were significantly greater in neonates with NAS. We found that neonates with a total dose > 1.6 mg/kg or an ECMO duration > 5 days had a significantly greater incidence of NAS (chi-squared test, $P < 0.01$ and $P < 0.005$; odds ratios = 7.0 and 13.9, respectively). With multiple logistic regression, ECMO duration was found to be the most powerful predictor of the occurrence of NAS. We also measured plasma fentanyl concentrations in a separate group of 5 neonates receiving fentanyl by continuous infusion for sedation. Fentanyl concentrations increased steadily during the period of infusion, suggesting the development of tolerance to the sedating effects. We conclude that continuous administration of fentanyl for sedation is associated with the uniform development of tolerance and a significant incidence of dependence. Alternative approaches to sedation should be investigated. (Key words: Anesthesia: neonate. Analgesics, opioid: fentanyl. Complication, opioid: tolerance, dependence, withdrawal.)

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) is widely used in the treatment of neonates with life-threatening respiratory failure.[1] At our institution, ECMO is used in the management of some neonates with meconium aspiration, sepsis, pneumonia, birth asphyxia, congenital diaphragmatic hernia, and idiopathic persistent pulmonary hypertension.[2] Intravenous sedation in these patients is essential to provide hemodynamic stability and compliance with mechanical ventilation and to limit movement that might result in accidental dislodgement of the vascular cannulae. We chose fentanyl sedation for these patients because of the absence of significant hemodynamic effects,[3] the increased survival in neonates with congenital diaphragmatic hernia sedated with fentanyl in the postoperative period,[4] and the ablation of pulmonary vascular responsiveness induced by fentanyl.[5]

We observed that neonates undergoing ECMO often require unexpectedly large doses of fentanyl to achieve adequate sedation. Furthermore, these neonates often exhibit the neonatal abstinence syndrome (NAS)[6,7] when they are weaned from fentanyl infusion. We therefore undertook a retrospective chart review of all neonates treated with ECMO to quantify the doses of all sedatives utilized, to determine the incidence of NAS, and to identify risk factors associated with NAS. In addition, to clarify the basis for the high dose of fentanyl administered, we measured plasma fentanyl concentrations in five additional neonates.

Materials and Methods

After exclusion of neonates with congenital diaphragmatic hernia, 50 neonates were treated with ECMO between May 1986 and October 1988. We excluded neonates with congenital diaphragmatic hernia because of their high mortality, which precluded adequate follow-up for the detection of NAS. Thirty-seven records were available for review. The study group included 22 neonates with meconium aspiration syndrome, 8 with pneumonia, 3 with idiopathic persistent pulmonary hypertension, 2 with hyaline membrane disease, 1 with blood aspiration, and 1 with amniotic fluid aspiration.

After an initial bolus of fentanyl (10–20 μg/kg) during surgical placement of vascular cannulae, fentanyl was administered by continuous infusion. The fentanyl infusion rate was adjusted by the patient's physician to render the neonates sedated but arousable. Adequate sedation was indicated by minimal movement or discomfort in response to routine patient care, including tracheal suctioning. Benzodiazepines frequently were added for their additional sedative effect.[8] In order to permit periodic neurologic examination, these neonates did not receive mus-

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Received from the Department of Anesthesia, The Children's Hospital and Harvard Medical School, the Department of Biostatistics, Harvard School of Public Health, and the Division of Clinical Pharmacology, Tufts–New England Medical Center, Boston, Massachusetts. Accepted for publication August 2, 1990. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

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TABLE 1. Neonatal Abstinence Scoring System

Signs and Symptoms	Score	Signs and Symptoms	Score
Cry		Generalized convulsions	5
Excessive	2	Sweating	1
Continuous	3	Fever	
Sleep (h) after feeding		<101°	1
<1 h	3	>101°	2
<2 h	2	Mottling	1
<3 h	1	Nasal stuffiness	1
Moro reflex		Sneezing (>3 or 4 times/interval)	1
Hyperactive	2	Nasal flaring	2
Markedly hyperactive	3	Respiratory rate	
Tremors		>60/min. (with retractions)	1
Mild disturbed	1	>60/min	2
Moderate–severe disturbed	2	Excessing sucking	1
Mild undisturbed	3	Poor feeding	2
Moderate–severe undisturbed	4	Regurgitation	2
Increased muscle tone	2	Projectile vomiting	3
Frequent yawning (> 3 or 4 times/interval)	1	Stools	
Excoriation	1	Loose	2
Myoclonic jerks	3	Watery	3

Modified from Finnegan LP: Neonatal abstinence, Current Therapy in Neonatal and Perinatal Medicine. Edited by Nelson NM. St. Louis, CV Mosby, 1985, pp 262–272.

cle relaxants. After removal of the vascular cannulae, the fentanyl infusion rate was decreased as tolerated to allow separation from mechanical ventilation and to facilitate enteral feeding. Nonopioid sedatives, including benzodiazepines, chloral hydrate, and phenobarbital were maintained until the opioids were discontinued, after which the dose was gradually decreased.

We examined patient records for the following variables: peak fentanyl infusion rate, defined as the highest infusion rate during treatment with ECMO; mean fentanyl infusion rate for each ECMO day; total fentanyl dose for the entire ECMO period; and duration of ECMO therapy. For neonates who received sufentanil in addition to fentanyl (n = 5), a 7:1 potency ratio with fentanyl was assumed for subsequent data analysis. All neonates were examined for signs of the NAS according to the abstinence scoring system of Finnegan *et al.*¶ (table 1). Neonates with an abstinence score of 8 or greater were considered to have NAS and received pharmacologic intervention, including oral or intravenous opioids, as described previously.[7] The opioid dose was adjusted upward or downward based on serial abstinence scoring, with progressive decrease of the opioid dose as the abstinence score decreased.

We also measured plasma fentanyl concentrations in a similar but separate group of five neonates undergoing ECMO between July and September 1989. Informed consent was obtained prior to blood sampling in accordance with guidelines established by The Children's Hospital Committee on Clinical Investigation. These neonates were sedated in the same manner as outlined above. Heparinized samples were collected in glass tubes and protected from contact with rubber or plasticizer. Plasma was separated by immediate centrifugation and the samples were stored at −20° C until analysis. Plasma fentanyl concentration was determined with gas chromatography using nitrogen–phosphorus detection with a lower limit of detection of 0.5 ng/ml and a 6.9% coefficient of variation at a concentration of 1.0 ng/ml.

Peak infusion rate, mean infusion rate, total dose, and duration of ECMO in patients with and without NAS were compared by unpaired *t* tests as well as by Wilcoxon's rank sum tests. Two-by-two contingency tables and chi-squared tests were used to define thresholds for the total dose and the ECMO duration that significantly increased the likelihood of NAS. Multiple logistic regression was used to identify risk factors for the development of NAS.

Results

The study group included 25 males (68%) and 12 females (32%) with a mean birth weight of 2892 ± 699 (SD) g. All neonates in the study group survived for at least 2 weeks after ECMO therapy. The average duration of ECMO therapy was 5.2 ± 1.7 (SD) days. For the entire group of neonates, peak infusion rate was 33.1 ± 22.5 (SD) $\mu g \cdot kg^{-1} \cdot h^{-1}$. NAS was observed in 21 neonates (57%). In both the NAS and non-NAS neonates, mean infusion rate increased steadily during ECMO therapy, from a mean of 11.6 ± 6.9 (SD) $\mu g \cdot kg^{-1} \cdot h^{-1}$ on day 1

¶ Finnegan LP, Connaughton JF, Jr, Kron RE, Emich JP: Neonatal abstinence syndrome: Assessment and management. Addictive Diseases 2:141–158, 1975

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TABLE 2. Group Mean Data

	NAS (n = 21)	no-NAS (n = 16)	*P*
PFIR $\mu g \cdot kg^{-1} \cdot hr^{-1}$	37.9 ± 26.0	26.9 ± 15.5	NS
TFD (mg/kg)	3.4 ± 2.5	1.8 ± 1.5	0.03
ED (days)	6.0 ± 1.4	4.2 ± 1.7	0.001

Mean ± SD.

Peak fentanyl infusion rate (PFIR), total fentanyl dose (TFD) and ECMO duration (ED) compared in the NAS and no-NAS patients.

to a mean of 52.5 ± 19.4 (SD) $\mu g \cdot kg^{-1} \cdot h^{-1}$ on day 8. Five neonates (3 in the NAS group and 2 in the non-NAS group) received, in addition to fentanyl, sufentanil by continuous infusion. Midazolam or lorazepam or both were administered to all neonates except 1 in the NAS group.

Total dose and ECMO duration were significantly greater in neonates with NAS (table 2). Peak infusion rate did not differ significantly between the two populations. When mean infusion rate was plotted against ECMO day, there was no significant difference between the NAS and non-NAS neonates (see fig. 1).

Using two-by-two contingency tables, we defined thresholds for the total dose and the ECMO duration that significantly increased the likelihood of NAS. We found that neonates with a total dose > 1.6 mg/kg (fig. 2) or an ECMO duration > 5 days (fig. 3) had a significantly greater incidence of NAS (chi-squared test, $P < 0.01$ and $P < 0.005$; odds ratios = 7.0 and 13.9, respectively). Total fentanyl dose predicted the occurrence of NAS with a sensitivity of 76% and specificity of 69%, whereas ECMO duration described the population with a sensitivity of 76% and specificity of 81%.

By multiple logistic regression, ECMO duration was found to be the most powerful predictor of the occurrence

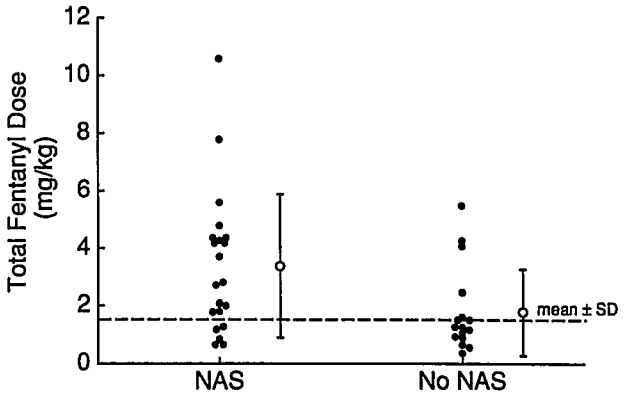

FIG. 2. Total fentanyl dose in the NAS and no-NAS groups. Total fentanyl dose >1.6 mg/kg (dashed line) detected the occurrence of NAS (odds ratio 7.0) with a sensitivity of 76% and specificity of 69%.

of NAS. Total dose was a statistically significant predictor of NAS when considered alone in the model, but did not add to the predictive value of ECMO duration in the multivariate model (table 3).

Plasma fentanyl concentrations were measured in a separate group of five neonates undergoing ECMO. This group included three females and two males with a mean birth weight of 3056 ± 529 (SD) g. The average duration of ECMO therapy for these neonates was 7.8 ± 4.5 days. Fentanyl was administered to this group of neonates by the same protocol described above. By the unpaired *t* test, there were no significant differences in peak infusion rate (16.0 ± 4.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$), total fentanyl dose (2.5 ± 1.8 mg/kg), or daily mean fentanyl infusion rate between this group of neonates and the study group described above. Fentanyl concentrations increased steadily during the course of ECMO therapy (fig. 4).

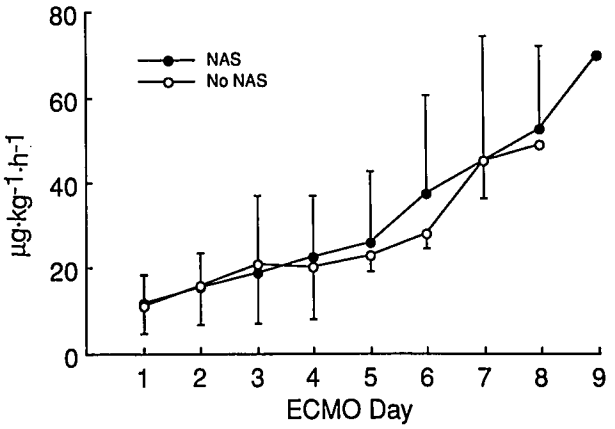

FIG. 1. Mean fentanyl infusion rate *versus* ECMO day for NAS and no-NAS patients (mean ± SD). There were no significant differences between the groups for any ECMO day.

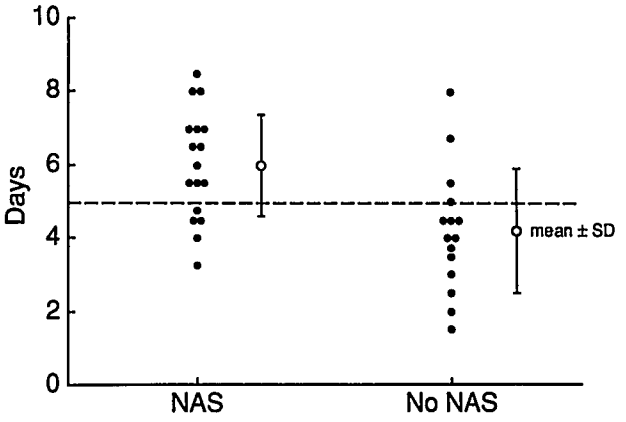

FIG. 3. ECMO duration in the NAS and no-NAS groups. ECMO duration >5 days (dashed line) detected the occurrence of NAS (odds ratio 13.9) with a sensitivity of 76% and specificity of 81%.

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Discussion

We report the uniform development of tolerance and a high incidence of opioid dependence in neonates receiving prolonged fentanyl infusion during ECMO. Tolerance was demonstrated by the steady increase in fentanyl infusion rate in combination with increasing plasma fentanyl concentrations required to maintain the desired clinical effect. Opioid dependence was evidenced by a high incidence of NAS as the fentanyl dose was decreased during weaning from mechanical ventilation.

The retrospective nature of this study implies that there was no prospectively determined endpoint of clinical effect and that a variety of observers were responsible for changes made in the sedation regimen. Nevertheless, the clinical practice of medicating these neonates until they exhibited minimal movement or discomfort in response to routine patient care, including tracheal suctioning, was sufficiently precise to indicate a clear escalation in the dose of fentanyl required.

During the period of ECMO therapy and fentanyl sedation, patients were arousable and in many cases breathing spontaneously. Since measured plasma fentanyl concentrations were similar to concentrations documented to produce anesthesia in newborn infants when fentanyl is used as the sole anesthetic,[9] we conclude that these patients exhibited tolerance to the sedating properties of fentanyl.

Tolerance to the analgesic effects of morphine[10,11] and fentanyl[12] can develop as rapidly as 3 h after a large initial dose. Several animal studies suggest that duration of receptor occupancy is the most important factor in the development of tolerance and dependence[13,14] and that continuous administration of opioids produces tolerance more rapidly than does intermittent administration.[15–17]

TABLE 3. Multiple Logistic Regression

Model	Predictors*	Coefficient	Significance Level	Odds Ratio (95% Confidence Interval)
1†	ED	0.870	0.035	2.4 (1.1, 5.3)
	TFD	0.048	0.857	0.95 (0.56, 1.6)
2‡	ED >5	2.2	0.033	9.0 (1.2, 71.5)
	TFD >1.6	0.61	0.545	1.8 (0.25, 13.5)

Multiple logistic regression examining ECMO duration (ED) and total fentanyl dose (TFD) as continuous and discrete predictors of the occurrence of NAS.

Model 1: ED and TFD treated as continuous predictors.

Model 2: ED discretized to ≤5 or >5 days, and TFD discretized to ≤1.6 or >1.6 mg/kg.

* PFIR was examined using logistic regression but not found to be predictive either alone or in conjunction with ED or TFD.

† The odds ratio should be interpreted as the increased risk associated with each additional ECMO day and each milligram-per-kilogram increase in TFD.

‡ The odds ratio should be interpreted as the increased risk associated with having ED >5 or having a TFD >1.6 mg/kg.

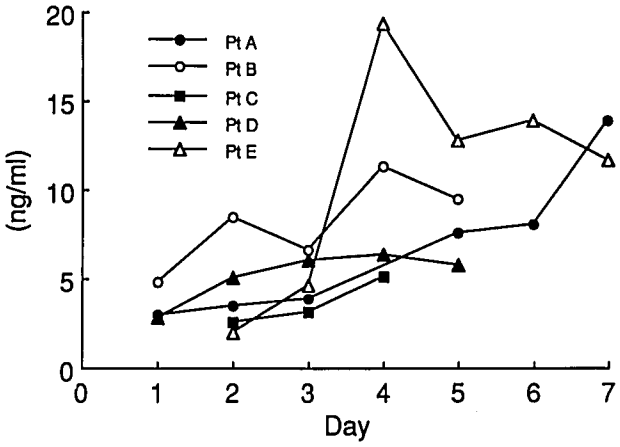

FIG. 4. Plasma fentanyl concentrations are plotted by ECMO day for five patients.

Fentanyl by continuous infusion, therefore, may have promoted the rapid development of tolerance in our patients.

Binding to the membrane oxygenator and extracorporeal circuit has been shown to reduce plasma fentanyl concentrations in patients undergoing extracorporeal circulation.[18,**] If binding of fentanyl to the ECMO circuit were the primary explanation for the large infusion rates observed, one would expect the infusion rates to decrease with time as the circuit became saturated. However, since both infusion rates and fentanyl concentrations rose steadily during ECMO therapy in the five patients for whom these data are available, the high fentanyl infusion rates were not entirely the result of sequestration by the extracorporeal circuit.

Dependence is an alteration in physiologic responses produced by repetitive drug administration and requiring continued use to avoid symptoms of withdrawal or abstinence. The abstinence syndrome after withdrawal of opioids has been well described in adults, children, and neonates. Withdrawal symptoms usually are associated with prolonged administration of opioids (days to weeks). However, acute opioid physical dependence has been demonstrated in animals within 3 days after a single dose of morphine.[19] In our study population, we noted NAS in 57% (21 of 37) despite a relatively brief duration of opioid exposure.

An abstinence syndrome has been described in infants after the abrupt discontinuation of benzodiazepines.[20] In our patients, however, benzodiazepines were maintained until the opioids were completely discontinued. The abstinence syndrome we observed occurred while the fen-

** Rosen DA, Rosen KR: A comparison of fentanyl uptake by three different membrane oxygenators. ANESTHESIOLOGY 65:A128, 1986

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tanyl dose was being decreased and before the benzodiazepine dosage was reduced.

It is likely that many of the symptoms of NAS in our patients were precipitated also by our attempts to facilitate enteral feeding by decreasing the opioid dose as rapidly as possible. Nutrition is essential to the therapy of respiratory insufficiency in any neonatal population[21] and particularly in the ECMO patient who may not tolerate enteral feeding for several weeks. The benefits of enteral feeding therefore must be weighed against the risks of NAS in selecting an optimal rate at which to decrease the opioid dosage.

We have identified a threshold for total opioid dose and duration of infusion that would identify those patients most likely to manifest NAS (figs. 2 and 3). Neonates with a total dose greater than 1.6 mg/kg or ECMO duration greater than 5 days appeared to have a significantly greater likelihood of developing NAS. However, these data must be validated by prospective evaluation in a large patient population.

Until very recently, newborns rarely received adequate analgesia or anesthesia during surgical procedures.[22] Recent trends in the practice of anesthesiology have greatly diminished this inhumane practice, but as is frequently the case with advances in medicine, this change has come at the price of unanticipated complications and side effects. We conclude that continuous administration of fentanyl for sedation is associated with the uniform development of tolerance and a significant incidence of dependence. Alternative approaches to sedation should be investigated.

References

1. Toomasian JM, Sneddecor SM, Cornell RG, Cilley RE, Bartlett RH: National experience with extracorporeal membrane oxygenation for newborn respiratory therapy. ASAIO Trans 34: 140–147, 1988
2. O'Rourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW, Parad RB, Epstein MF: Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective randomized study. Pediatrics 84:957–963, 1989
3. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA: Pulmonary and systemic hemodynamic responses to fentanyl in infants. Anesth Analg 64:483–486, 1985
4. Vacanti JP, Crone RK, Murphy JD, Smith SD, Black PR, Reid L, Hendren WH: The pulmonary hemodynamic response to perioperative anesthesia in the treatment of high-risk infants with congenital diaphragmatic hernia. J Pediatr Surg 19:672–679, 1984
5. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM: Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 64:1137–1142, 1985
6. Zelson C, Rubio E, Wasserman E: Neonatal narcotic addiction: 10-year observation. Pediatrics 48:178–189, 1971
7. Finnegan LP: Neonatal abstinence, Current Therapy in Neonatal and Perinatal Medicine. Edited by Nelson NM. St. Louis, CV Mosby, 1985, pp 262–272
8. Westphal LM, Cheng EY, White PF, Sladen RN, Rosenthal MH, Sung ML: Use of midazolam infusion for sedation following cardiac surgery. ANESTHESIOLOGY 67:257–262, 1987
9. Collins C, Koren G, Crean P, Klein J, Roy WL, MacLeod SM: Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. Anesth Analg 64:1078–1080, 1985
10. Eisenberg RM: Short-term tolerance to morphine: Effects of indomethacin. Life Sci 30:1399–1405, 1982
11. Yano I, Takemori AE: Inhibition by naloxone of tolerance and dependence in mice treated acutely and chronically with morphine. Res Commun Chem Pathol Pharmacol 16:721–734, 1977
12. Askitopoulou H, Whitwam JG, Al Khudhairi D, Chakrabarti M, Bower S, Hull CJ: Acute tolerance to fentanyl during anesthesia in dogs. ANESTHESIOLOGY 63:255–261, 1985
13. Cochin J, Mushlin BE: Effect of agonist–antagonist interaction on the development of tolerance and dependence. Ann NY Acad Sci 281:244–251, 1976
14. Dewey WL: Various factors which affect the rate of development of tolerance and physical dependence to abused drugs. NIDA Res Monogr 54:39–49, 1984
15. Hovav E, Weinstock M: Temporal factors influencing the development of acute tolerance to opiates. J Pharmacol Exp Ther 242:251–256, 1987
16. Cheney DL, Goldstein A: Tolerance to opioid narcotics: Time course and reversibility of physical dependence in mice. Nature 232:477–478, 1971
17. Cerletti C, Keinath SH, Reidenbery MM, Alder MW: Chronic morphine administration: Plasma levels and withdrawal syndrome in rats. Pharmacol Biochem Behav 4:323–327, 1976
18. Hynynen M: Binding of fentanyl and alfentanil to the extracorporeal circuit. Acta Anaesthesiol Scand 31:706–710, 1987
19. Grilly DM, Gowans GC: Acute morphine dependence: Effects observed in shock and light discrimination tasks. Psychopharmacology (Berlin) 88:500–504, 1986
20. Sury MR, Billingham I, Russell GN, Hopkins CS, Thornington R, Vivori E: Acute benzodiazepine withdrawal syndrome after midazolam infusions in children (letter). Crit Care Med 17:301–302, 1989
21. Monin P, Vert P: The management of bronchopulmonary dysplasia. Clin Perinatol 14:531–549, 1987
22. American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery: Neonatal anesthesia. Pediatrics 80:446, 1987

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