Anesthesiology
71:426–430, 1989

The Effect of Fentanyl Anesthesia and Intrathecal Naloxone on Neurologic Outcome Following Spinal Cord Injury in the Rat

Daniel J. Cole, M.D., John C. Drummond, M.D.,† Harvey M. Shapiro, M.D.,‡ Roxanne E. Hertzog,§ Floyd S. Brauer, M.D.¶*

Whereas opiate receptor agonists have resulted in spinal cord damage; opiate receptor antagonists have demonstrated protection against spinal cord injury. Because opioids are used in clinical anesthesia, the effect of an opiate antagonist was evaluated on neurologic outcome in a rat model of spinal cord injury occurring during opioid anesthesia. One day prior to spinal cord injury, a catheter was inserted into the spinal subarachnoid space with the tip at T8. On the day of spinal cord injury a balloon tipped catheter was inserted in the epidural space with the tip at the thoracolumbar junction. Spinal cord injury was produced by balloon inflation during one of the following states: 1) group 1 (A/S), injury was produced in awake rats and saline was administered in the subarachnoid space immediately following injury; 2) group 2 (F/S), injury was produced during a fentanyl/nitrous oxide (N_2O) anesthetic, and subarachnoid saline administered; and 3) group 3 (F/Nx), injury was produced during a fentanyl/N_2O anesthetic, and subarachnoid naloxone (1 mg/kg) was administered immediately following injury. Dose–response curves describing the relationship between the duration of balloon inflation and the percentage of animals with a persistent neurologic deficit were constructed and compared for differences by use of a group *t* test. The duration of balloon inflation required to produce a neurologic deficit was greater in both the F/S and F/Nx groups than in the A/S group ($P < 0.05$). There was no difference between the F/S and F/Nx groups. In summary, in rats receiving a fentanyl/N_2O anesthetic, neurologic outcome was improved compared with the awake state. The administration of naloxone in the subarachnoid space adjacent to injury did not further improve neurologic outcome. These results do not support the supposition that opioid anesthesia produces an adverse effect upon neurologic outcome following a compressive spinal cord injury. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl. Antagonists, opiate: naloxone. Spinal cord: injury.)

ANESTHESIOLOGISTS are called upon to manage patients at risk for spinal cord injury. These injuries may occur either by extension of an antecedent injury or as a result of a primary intraoperative injury. One factor that may influence the extent of injury and is meaningful to anesthetic management concerns the effect of opioids on spinal cord injury.[1–7]

Opiate receptor antagonists (of which naloxone has been the most extensively studied) have repeatedly produced beneficial effects on spinal cord injury.[1–7] In addition, dynorphin, an endogenous kappa opiate, results in paraplegia when administered in the spinal canal.[8,9] The above findings have led to a concern that opioid anesthesia may produce a harmful effect upon intraoperative spinal cord injury. We addressed this possibility in a previous study and found that a fentanyl-based anesthetic did not result in a detrimental effect on neurologic outcome.[10] However, because spinal cord injury is mediated by multiple factors,[7,11–16] it is possible that fentanyl produces both favorable and detrimental effects upon specific pathophysiologic components of spinal cord injury. If this were true, it may be postulated that despite an overall favorable effect by fentanyl/N_2O on spinal cord injury (possibly through improved perfusion pressure and autoregulation), there may be a deleterious influence of fentanyl/N_2O on the pathophysiologic process (possibly a decrease in postinjury spinal cord blood flow). If this deleterious component were reversed by opiate antagonism, an even more favorable neurologic outcome may result in the course of spinal cord injury occurring during fentanyl/N_2O anesthesia. The present study evaluated the hypothesis that any detrimental effect of opioid anesthesia upon spinal cord injury might be prevented by local opiate receptor antagonism.

Methods

Approval was obtained from the Institutional Animal Research Committee. Male, Sprague-Dawley rats (n = 77) of similar weights (300–350 g) were surgically prepared as follows:

Day 1 Preparation

Each rat was anesthetized with N_2O (65%) and isoflurane (1.0–1.5%) *via* a face mask. A PE-10 catheter was inserted into the spinal subarachnoid space *via* the atlantooccipital membrane.[17] The tip of the catheter was positioned at T8 (verified at necropsy). The incision was infiltrated with 0.25% bupivacaine. Each rat was allowed a 24-h anesthetic recovery period with systematic neu-

* Assistant Professor of Anesthesiology, Loma Linda University.

† Staff Anesthesiologist, Veteran's Administration Medical Center, San Diego, California; Associate Professor of Clinical Anesthesiology, University of California at San Diego.

‡ Professor and Chairman, Department of Anesthesiology; Professor of Neurosurgery, University of California at San Diego.

§ Medical Student, Loma Linda University.

¶ Professor and Chairman, Department of Anesthesiology, Loma Linda University.

Received from the Departments of Anesthesiology, Loma Linda University, Loma Linda, California, the Veteran's Administration Medical Center, San Diego, California, and the University of California at San Diego, La Jolla, California. Accepted for publication April 11, 1989.

Address reprint requests to Dr. Cole: Department of Anesthesiology, Loma Linda University, Loma Linda, California 92354.

rologic exams (alertness of the rat, the motor and sensory function of the extremities, and the gait).

Day 2 Preparation

Following verification of normal neurologic function a tail artery catheter was inserted during N_2O/isoflurane anesthesia *via* a face mask. A midline laminectomy was performed at L3–4, and a 2-Fr Fogarty® balloon tipped catheter was secured in the epidural space, with the tip at the thoracolumbar junction. The incisions were closed and infiltrated with 0.25% bupivacaine. The preparatory period was 30–45 min. A 120-min anesthetic recovery period was allowed, and normal neurologic function was verified prior to production of the spinal cord injury by epidural balloon inflation.

Spinal Cord Insult

Physiologic parameters (pH,Pa_{CO_2}, Pa_{O_2}, mean arterial pressure, serum glucose, and hematocrit) were monitored before, during, and immediately following spinal cord insult. Temperature was monitored rectally and servocontrolled at 37° C with a heat lamp. Awake animals were kept in an oxygen enriched atmosphere($FI_{O_2} \approx 35$–40%). Anesthetized animals received an FI_{O_2} of 35%. Each rat was randomized to one of the following anesthetic treatments during spinal cord injury:

Group 1 (awake [n = 22]). Each rat was awake and unrestrained during spinal cord insult.

Group 2 (fentanyl–N_2O [n = 22]). A fentanyl (57 μg/kg subcutaneously)/N_2O (65%) anesthetic was administered during spinal cord insult.

Group 3 (fentanyl–N_2O [n = 22]). An identical fentanyl/N_2O anesthetic was delivered as in group 2.

The fentanyl/N_2O dose was roughly equivalent to 1.3 MAC.[18,19] In the fentanyl groups, animals were placed in a 2.5-l plexiglass box and anesthetic induction was begun with 65% N_2O/35% O_2. A sedative anesthetic plane was achieved with N_2O (≈1 min), and the fentanyl dose was injected. A 5-min period was allowed and each rat in the fentanyl groups was orotracheally intubated and their lungs mechanically ventilated with a Harvard® rodent ventilator. An additional 10-min period of fentanyl equilibration was allowed (total of 15 min) before spinal cord injury.

When anesthetic equilibrium was achieved (or after an equivalent period in awake animals), the epidural balloon was inflated with a constant volume of air (0.1 ml), and inflation maintained over varying times of 0, 6, 12, 24, or 42 min. In animals at the lower inflation times (0, 6, 12, and 24 min) an additional simulated period of balloon inflation was allowed to maintain a constant 42-min period for this portion of the study. Immediately following spinal cord insult the epidural and arterial catheters were quickly removed (<10 min) during a N_2O (65%)/isoflurane (1%) anesthetic. The N_2O/isoflurane anesthetic was administered to all three groups for less than 10 min (by face mask to the awake group and *via* the endotracheal tube in the two fentanyl anesthetized groups). At the conclusion of arterial and epidural catheter removal (10 min following the spinal cord insult) either naloxone (1 mg/kg) or preservative free saline was administered in the spinal subarachnoid space as follows:

Group 1 (awake/saline [n = 22]). Each rat in the awake group received 30 μl of preservative-free saline (37° C) *via* the spinal subarachnoid catheter.

Group 2 (Fentanyl–N_2O/saline [n = 22]. Each rat in this fentanyl–N_2O anesthetized group received 30 μl of preservative-free saline (37° C) *via* the spinal subarachnoid catheter.

Group 3 (Fentanyl–N_2O/naloxone [n = 22]). Each rat in this fentanyl–N_2O anesthetized group received naloxone powder (1 mg/kg [Du Pont Pharmaceuticals, Inc.]) reconstituted in 30 μl of pH buffered, preservative-free saline (37° C) *via* the spinal subarachnoid catheter.

Each rat was awake, with spontaneous ventilation 5 min following discontinuation of the N_2O/isoflurane anesthetic. Each rat was examined for the presence or absence of hindlimb paralysis by an investigator blinded to treatment. The exam was performed at a similar time each day for seven postinsult days. Hindlimb paralysis was defined as the lack of spontaneous or purposeful movement of either hindlimb. A flicker of movement did not qualify as movement. A rat exhibiting a purposeful response to paw pinch without spontaneous movement was not graded as paralyzed.

During the recovery period nursing care was given as follows:

1. Each rat was kept in a thermally controlled rodent intensive care cage for 72 h. Subsequently, one standard rodent cage was allotted to each rat (also in a thermally controlled environment).
2. Bladders were voided twice daily using a Credé maneuver, and intramuscular gentamicin (1 $mg \cdot kg^{-1} \cdot day^{-1}$) was administered.
3. Each rat was bathed and weighed daily.
4. Subcutaneous fluids (0.9% NaCl) were administered depending upon the presence and magnitude of weight loss.
5. Each rat had *ad libitum* access to water and Tekland® rat chow.

Statistical analysis was performed on the physiologic data using an analysis of variance.[20] The relationship between the duration of balloon inflation and the number of animals with a neurologic deficit on recovery day 7 was determined by constructing dose–response curves with a logistic function of: $P = D^s/(D^s + D_{50}^s)$. P is the probability of a neurologic deficit, D the duration of

TABLE 1. Physiologic Data (mean ± SD)

	Awake/S	Fentanyl/S	Fentanyl/Nx
Weight (g)	322 ± 16	314 ± 12	324 ± 17
Mean arterial pressure (mmHg)	113 ± 17	110 ± 14	109 ± 10
Pa_{CO_2} (mmHg)	40 ± 3	38 ± 3	38 ± 3
Pa_{O_2} (mmHg)	120 ± 26	113 ± 17	116 ± 21
*p*H (units)	7.41 ± 0.03	7.41 ± 0.02	7.42 ± 0.03
Hematocrit (%)	43 ± 2	42 ± 2	43 ± 3
Serum glucose (mg/dl)	128 ± 14	139 ± 24	144 ± 31

S represents the groups that received subarachnoid saline following spinal cord injury. Nx represents the group that received subarachnoid naloxone (1 mg/kg) following spinal cord injury.

compression (min), D_{50} is an estimated parameter that is the time that has a 50% probability of a hindlimb deficit occurring, and s is a parameter that is the slope of the logistic curve.[21,22] The group curves were compared for slope and D_{50} by examining the 95% confidence bounds of the parameter estimates. This logistic regression is a statistical tool to evaluate quantal biologic responses, which has been described by Waud[22]; it has been applied in this study to characterize the effect of a treatment upon the relationship between the duration of balloon inflation and the presence or absence of hindlimb paralysis.[21] A P value of less than 0.05 was considered significant.

Results

A total of 77 rats were entered into the study; 11 were excluded. Three were omitted because of a neurologic deficit following insertion of the subarachnoid catheter. One was excluded because of a neurologic deficit following insertion of the epidural catheter. Seven rats died in the postinsult period. Two of the rats that died were in the awake/saline group, two in the fentanyl/saline group, and three in the fentanyl/naloxone group. All of the deaths in the postinsult period occurred in paralyzed animals.

There were no between groups differences in the physiologic data (weight, *p*H, Pa_{CO_2}, Pa_{O_2}, hematocrit, serum glucose, mean arterial pressure, and temperature [see table 1]).

The neurologic results are presented as dose–response curves in figure 1. The duration of balloon inflation is plotted against the percentage of animals with a persistent neurologic deficit (hindlimb paralysis). There was a significant decrease in the incidence of hindlimb paralysis in the fentanyl/saline and fentanyl/naloxone groups compared with that in the awake/saline group (right shift in the dose–response curve). There was no difference between the fentanyl/saline and fentanyl/naloxone group. When the neurologic results are examined as a duration of balloon inflation required to produce a deficit in 50% of animals (ET_{50s}, tables 2 and 3), identical differences are observed.

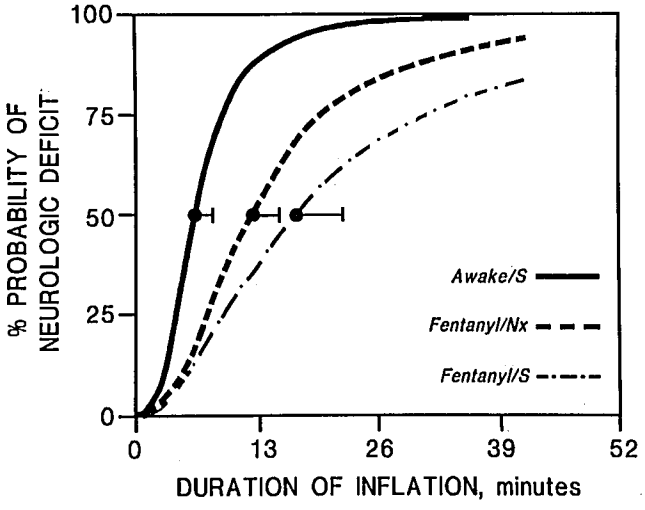

FIG. 1. Postinsult day 7 dose–response curves demonstrating the percentage of rats with a neurologic deficit (hindlimb paraplegia) as a result of the duration of lumbar epidural balloon inflation. The fentanyl group and the fentanyl–naloxone group demonstrated a decrease in the incidence of sustained neurologic deficits compared with the awake group ($P < 0.05$). There was no difference in the incidence of hindlimb paralysis between the fentanyl and fentanyl-naloxone group. Standard error of the D_{50} parameter estimate is indicated as ● —— |.

Discussion

The present study indicates that an opioid-based anesthetic administered during spinal cord injury does not result in a detrimental effect upon neurologic outcome. Intrathecal naloxone (1 mg/kg), administered immediately following a spinal cord insult produced during fentanyl anesthesia, did not influence neurologic outcome.

In the present study, spinal cord injury may have been affected by physiologic factors.[13–16] However, because no between groups differences were present, these factors should not have affected the relative position of the dose–response curves. It should be noted that the physiologic data were monitored only through the immediate post-injury period, and differences may have existed later in the postinsult period (although none were observed in pilot evaluations of this spinal cord injury model).

A potential mechanism explaining why the awake animals had a poorer neurologic outcome than anesthetized animals is the state of stress. In comparing the awake state with the anesthetized state, a prediction may have been made that catecholamine levels would have been higher in awake animals. Because increased catecholamine levels can produce deleterious effects upon spinal cord injury,[15,16] this issue should be addressed when explaining the observed decrease in spinal cord injury during fentanyl/N_2O anesthesia. However, based upon serum glucose as an indicator of stress,[23] it is unlikely that significant differences were present. Prior to spinal cord injury each animal spent 120 min in a quiescent environment. The only maneuver necessary to produce injury was inflation of the epidural balloon without otherwise disturbing the animal. In a previous study,[10] the awake control group also had the lowest serum glucose level. Accordingly, it is plausible that in this model of spinal cord injury, catecholamine levels are not elevated in awake animals (although this has yet to be verified).

One concern was the removal of the arterial and epidural catheters. Because noxious stimuli were present during removal, anesthesia was required. This would not have been a methodologic problem had all groups been anesthetized. However, one group was awake during the spinal cord injury. Consequently, a standardized anesthetic regimen of 60% N_2O and 1% isoflurane was administered to all study groups during catheter removal (<10 min). An additional concern involved potential spinal cord toxicity by naloxone. In pilot studies we did not observe histologic evidence of spinal cord toxicity by a 1 mg/kg intrathecal dose of naloxone.

The objectives of the present study were to determine both the effect of opioid anesthesia on spinal cord injury and that of naloxone on spinal cord injury during opioid anesthesia. The intrathecal route of naloxone administration was chosen to maintain the fentanyl/N_2O anesthetic state. Studies that have shown a positive effect of naloxone on spinal cord injury have been restricted to the systemic route of administration, and have employed relatively large doses (2–10 mg/kg). Accordingly, one intent of the present study was to administer the largest naloxone dose (1 mg/kg) that did not result in either behavioral (arousal, agitation, *etc.*) or physiologic perturbations (increase in heart rate, blood pressure, and respiratory rate).

A second intent of the study was to design the dose of naloxone to antagonize spinal cord opiate receptors in parallel to the pharmacokinetic binding profile of fentanyl. In this manner, any deleterious effect fentanyl anesthesia might have on spinal cord injury *via* opiate receptors would be competitively blocked. In the rat, naloxone and fentanyl have comparative CNS partition coefficients and CNS elimination half-lives (60 min for naloxone and 45 min for fentanyl[24,25]). Accordingly, the observation that neurologic outcome was not different between the fentanyl/naloxone and fentanyl/saline groups does not support the contention that a fentanyl anesthetic produces a deleterious effect on neurologic outcome *via* direct opioid receptor mechanisms. However, if the dose, duration, or timing of the naloxone dose had been specifically designed to influence spinal cord injury, a beneficial affect of naloxone may have been observed.

TABLE 2. Epidural Balloon Inflation Time (mean ± SE) Required to Produce a Neurologic Deficit in 50% of Animals (D_{50}) and the Slope (±SE) of the Balloon Inflation Time *versus* Percentage of Rats with a Persistent Neurologic Deficit

Group	D_{50} (min)	95% Confidence Bound (min)	Slope	95% Confidence Bound
Awake/S	6.2 ± 1.7	2.7–9.7	2.8 ± 1.6	−0.5–6.1
Fentanyl/S	16.9 ± 5.2*	6.1–27.7	1.8 ± 0.9	−0.1–3.7
Fentanyl/Nx	12.3 ± 3.1*	5.8–18.8	2.3 ± 1.0	0.2–4.4

* Significant difference between the awake group compared with both fentanyl groups ($P < 0.05$).

Another consideration is the elimination of potential beneficial systemic effects of naloxone by the intrathecal route of administration; this appears unlikely.[5,26] In addition, if naloxone were to affect spinal cord injury *via* mechanisms in CNS regions above the injury, it is plausible that the local intrathecal delivery of naloxone may have resulted in different naloxone concentrations in these regions compared with the systemic delivery of naloxone.

Do the results of the present study contradict previous findings that opioid receptor antagonism produces a beneficial effect upon postinjury spinal cord blood flow and neurologic outcome? We believe they do not. The present observations may be attributable to a neglible interaction of fentanyl at spinal cord kappa receptors. A proposed mechanism explaining the interaction between opioid receptor agonists, such as dynorphin, opioid receptor antagonists, and spinal cord injury has been developed by Faden *et al.*[4–6,27–30] Following spinal cord injury there is a proliferation and up-regulation of spinal opioid recep-

TABLE 3. The Number of Animals at Each Epidural Balloon Inflation Time That were Normal (not paralyzed) and Abnormal (hindlimb paralysis)

Inflation Time	Awake/S (n = 22)		Fentanyl/S (n = 22)		Fentanly/Nx (n = 22)	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
0 min	3	0	3	0	3	0
6 min	3	3	5	1	5	1
12 min	1	5	4	2	3	3
24 min	0	4	2	2	1	3
42 min	0	3	0	3	0	3

tors of the kappa subtype. A release of endogenous opiates also occurs, which acts at the up-regulated opioid receptors and results in a decrease in spinal cord blood flow and a worse neurologic outcome. If opioid receptor antagonists mediate spinal cord injury *via* kappa opioid receptors, it is plausible that the lack of a beneficial effect of naloxone upon spinal cord injury may have been due to an insufficient action of fentanyl at kappa receptors. If the anesthetic dose of fentanyl did not significantly interact at kappa receptors, the pathologic milieu necessary to demonstrate a naloxone reversible component of injury secondary to the opioid anesthetic would not have been present.

The clinical correlate of the present model may be the patient susceptible to an intraoperative insult from an unstable spine and impingement of bone or ligamentous elements on the spinal cord. This study provides no data to support the restriction of anesthetic doses of opioids during spinal cord injury in such a patient group. The precise mechanisms whereby spinal cord protection was afforded by opioid-based anesthesia and not by naloxone, and their anesthetic interactions, may be multiple, complex, and require additional study.

The authors thank Laura Breen and John Hough for technical assistance and Jackie Breyer in the preparation of the manuscript. The authors also acknowledge the supply of naloxone powder from Du Pont Pharmaceuticals, Inc.

References

1. Faden AI, Jacobs TP, Mougey E: Endorphins in experimental spinal injury. Therapeutic effect of naloxone. Ann Neurol 10: 326–332, 1981
2. Flamm ES, Young W, Demopoulos HB, DeCrescito V, Tomasula JJ: Experimental spinal cord injury: Treatment with naloxone. Neurosurgery 10:227–231, 1982
3. Young W, Flamm ES, Demopoulos HB, Tomasula JJ, DeCrescito V: Effect of naloxone on posttraumatic ischemia in experimental spinal contusion. J Neurosurg 55:208–219, 1981
4. Faden AI, Jacobs TP, Smith MT, Zivin JA: Naloxone in experimental spinal cord ischemia: Dose–response studies. Eur J Pharmacol 103:115–120, 1984
5. Faden AI, Sacksen I, Noble LJ: Opiate–receptor antagonist nalmefene improves neurological recovery after traumatic spinal cord injury in rats trough a central mechanism. J Pharmacol Exp Ther 245:742–748, 1988
6. Faden AI, Takemori AE, Portoghese PS: Kappa-selective antagonist norbinaltorphimine improves outcome after traumatic spinal cord injury in rats. Cent Nerv Syst Trauma 4:217–237, 1987
7. Hamilton AJ, Black PM, Carr DB: Contrasting actions of naloxone in experimental spinal cord trauma and cerebral ischemia: A review. Neurosurgery 17:845–849, 1985
8. Herman BH, Goldstein A: Antinociception and paralysis induced by intrathecal dynorphin A1. J Pharmacol Exp Ther 232:27–32, 1985
9. Faden AI, Jacobs P: Dynorphin-related peptides cause motor dysfunction in the rat through a non-opiate action. Br J Pharmacol 81:271–276, 1984
10. Cole DJ, Shapiro HM, Drummond JC, Zivin JA: Halothane, fentanyl/nitrous oxide, and spinal lidocaine protect against spinal cord injury in the rat. ANESTHESIOLOGY 70:967–972, 1989
11. Osterholm JL: The pathophysiological response to spinal cord injury. The current status of related research. J Neurosurg 40: 5–53, 1974
12. Young W, Koreh I, Yen V, Lindsay A: Effect of sympathectomy on extracellular potassium activity and blood flow in experimental spinal cord contusion. Brain Res 253:115–125, 1982
13. Drummond JC, Moore SS: The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. ANESTHESIOLOGY 70:64–70, 1988
14. Gilbert J: Critical care management of the patient with acute spinal cord injury, Critical Care Clinics—July 1987, Acute Spinal Cord Injury. Edited by Albin M. Philadelphia, WB Saunders, 1987, pp 549–568
15. Osterholm JL, Mathews GJ: Altered norepinephrine metabolism following experimental spinal cord injury. Part 1: Relationship to hemorrhagic necrosis and post-wounding neurological deficits. J Neurosurg 36:386–394, 1972
16. Osterholm JL, Mathews GJ: Altered norepinephrine metabolism following experimental spinal cord injury. Part 2: Protection against traumatic spinal cord hemorrhage necrosis by norepinephrine synthesis blockade with alpha methyl tyrosine. J Neurosurg 36:395–401, 1972
17. Yaksh TL, Rudy TA: Chronic catheterization of the spinal subarachnoid space. Physiol Behav 17:1031–1036, 1976
18. Shinga K, Eger EI II, Johnson BH, Lurz FW, Hickey RF: MAC values of thiopental and fentanyl in rats. Anesth Analg 62:151–157, 1983
19. Difazio CA, Brown RE, Ball CG, Heckel CG, Kennedy SS: Additive effects of anesthetics and theories of anesthesia. ANESTHESIOLOGY 36:57–63, 1972
20. BMDP Statistical Software 1981; Program P7D. Edited by Dixon WJ. Los Angeles, University of California, 1981, p 105
21. Zivin JA, DeGirolami U, Hurwitz EL: Spectrum of neurological deficits in experimental CNS ischemia. Arch Neurol 39:408–412, 1982
22. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 183:577–607, 1972
23. Bialik RJ, Smythe JW, Roberts DC: Alpha 2-adrenergic receptors mediate the increase in blood glucose levels induced by epinephrine and brief footshock stress. Prog Neuropsychopharmacol Biol Psychiatry 12:307–310, 1988
24. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S: Pharmacokinetics of naloxone in rats and in man. ANESTHESIOLOGY 44:398–401, 1976
25. Hug CC Jr, Murphy MR: Tissue redistribution of fentanyl and termination of its effects in rats. ANESTHESIOLOGY 55:369–375, 1981
26. Holaday JR, Faden AI: Naloxone acts at central opiate receptors to reverse hypotension, hypothermia and hypoventilation in spinal shock. Brain Res 189:295–299, 1980
27. Krumins SA, Faden AI: Traumatic injury alters opiate receptor binding in rat spinal cord. Ann Neurol 19:498–501, 1986
28. Faden AI: Neuropeptides and central nervous system injury. Clinical implications. Arch Neurol 43:501–504, 1986
29. Faden AI, Knoblach S, Mays C, Jacobs TP: Motor dysfunction after spinal cord injury is mediated by opiate receptors. Peptides 6:390–397, 1985
30. Faden AI, Molineaux CJ, Rosenberger JG, Jacobs TP, Cox BM: Endogenous opioid immunoreactivity in rat spinal cord following traumatic injury. Ann Neurol 17:386–390, 1985