

Epidural Triamcinolone and Adrenal Response to Hypoglycemic Stress in Dogs

Daniel W. Gorski, D.D.S., M.D.,* Tadikonda L. K. Rao, M.D.,† Silas N. Glisson, Ph.D.,‡
Mariadas Chinthagada, M.D.,§ Adel A. El-Etr, M.D.¶

The effect of an epidural steroid injection (triamcinolone) on plasma cortisol levels was studied in twelve beagle dogs following an insulin-induced hypoglycemic stress. The control group (n = 6) received epidural bupivacaine only. This group consistently increased their plasma cortisol values in response to the hypoglycemic stress induced by 0.6 units of insulin/kg administered intravenously. Dogs in the study group (n = 6) received epidural bupivacaine plus 2 mg/kg of triamcinolone. This group was unable to increase their plasma cortisol values in response to similar insulin-induced hypoglycemic stress for four weeks. Return to normal function occurred five weeks following epidural triamcinolone.

The authors hypothesize that the inability of the dogs to respond to hypoglycemic stress by increasing their plasma cortisol may interfere with homeostasis and decrease their tolerance to other types of stress up to 4 weeks following epidural triamcinolone administration. (Key words: Anesthetic techniques: epidural. Hormones: steroids, epidural. Pain: steroids, epidural.)

IATROGENIC SUPPRESSION of the hypothalamic-pituitary-adrenal (HPA) axis is a major problem in the care of patients following anesthesia and surgery.¹ A relatively uncomplicated operation in a patient with a suppressed HPA axis may be associated with problems in maintaining vascular tone and perfusion of vital organs. Chronic parenteral administration of steroids has been shown to result in the suppression of the HPA axis. However, the effect of administration of a single epidural injection of steroid on the HPA axis has not been investigated systematically. This study was undertaken to determine the effect of a uniform controlled stress on plasma cortisol levels in dogs that received epidural triamcinolone.

Materials and Methods

Twelve beagle dogs, weighing 15.2 (SE ± 1.4) kg were divided randomly into two groups. Group 1 served as the control group, and Group 2 served as the study

group. All dogs were brought to the laboratory and allowed to habituate to the surroundings for a one-hour period. A butterfly needle was then placed in a peripheral vein. Three milliliters of blood were withdrawn for measurement of serum cortisol and glucose values. Immediately following blood withdrawal, 0.6 u/kg crystalline insulin was administered intravenously which produced the hypoglycemic stress. After one hour, 3 ml of venous blood was withdrawn for the measurement of the poststress values of plasma cortisol and glucose. Following this, all dogs were returned to the animal quarters for resting. One week later, the dogs were returned to the laboratory and were anesthetized with a sleep dose of thiopental (15 mg/kg). While asleep, placement of a 17-gauge Touhy needle in the lumbar epidural space was accomplished using the loss of resistance technique. Dogs in the control group received 2 ml of 0.5% bupivacaine, while dogs in the study group received 2 ml of 0.5% bupivacaine mixed with triamcinolone (2 mg/kg). The dogs were allowed to recover from anesthesia and paresis of hind paws and were returned to the animal quarters. Three-milliliter samples of blood for plasma cortisol and glucose determinations were withdrawn, both before and one hour following insulin-induced hypoglycemic stress at the following time intervals: 24 h, 72 h, and weekly during weeks 1 and 5 after performance of the epidural block. All blood samples were analyzed for plasma glucose and cortisol values. Plasma cortisol was measured using a fluorometric method as described by Mattingly.² This method of measuring plasma cortisol has been shown repeatedly to be accurate, reproducible, and not influenced by blood levels of methylprednisone or triamcinolone, if present. Statistical analysis of the results was done using a Statistical Analysis System computing package. The data was subjected to one-way analysis of variance followed by a Duncan test and nonpaired Student's *t* test and Student's *t* test for paired values. All values are expressed as means ± SEM.

Results

Baseline values (those done in the awake state prior to performance of the epidural block) in Group 1 showed a significant increase ($P < 0.05$) in plasma cortisol from $6.40 \pm 1.02 \mu\text{g/dl}$ to $10.50 \pm 2.11 \mu\text{g/dl}$ after insulin-induced hypoglycemic stress. Twenty-four

* Clinical Instructor.

† Associate Professor.

‡ Associate Professor.

§ Clinical Assistant Professor.

¶ Professor and Chairman.

Received from the Department of Anesthesiology, Loyola University Medical Center and Stritch School of Medicine, Maywood, Illinois. Presented in part at the annual meeting of the American Society of Anesthesiologists, October 1981, New Orleans, Louisiana. Accepted for publication April 14, 1982.

Address reprint requests to Dr. Gorski: Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, Illinois 60153.

TABLE 1. Plasma Cortisol Values before and after Hypoglycemic Stress in Group I (n = 6) Dogs that Received Epidural Bupivacaine

Plasma Cortisol (µg/dl)															
Baseline		24 H		72 H		1 Wk		2 Wk		3 Wk		4 Wk		5 Wk	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
6.4 ± 1.0	10.5* ± 2.1	3.6 + 0.5	7.4* ± 1.2	4.1 ± 0.4	7.3* ± 0.9	4.2 ± 0.7	8.4* ± 1.4	5.5 ± 1.3	11.9* ± 1.0	4.9 + 0.8	12* ± 1.5	6.6 ± 0.5	12* ± 1.3	6.3 ± 0.6	11.3* ± 1.4

Values expressed as means ± SEM.

* P 0.05 compared with prestress level.

and seventy-two hours, as well as one to five weeks after performance of epidural block with bupivacaine alone, this group was consistently able to elevate their plasma cortisol levels after hypoglycemic stress (table 1). Comparison of preinsulin baseline cortisol values to the preinsulin values following epidural bupivacaine administration revealed a statistically significant decrease only at the 24-h value. Preinsulin cortisol values during the subsequent observation periods were not significantly different from the baseline value.

Table 2 shows the results of Group 2 dogs which received epidural bupivacaine and triamcinolone. Baseline studies while in the awake state prior to epidural placement of bupivacaine and triamcinolone revealed a significant increase ($P < 0.05$) in plasma cortisol from $5.14 \pm 0.78 \mu\text{g/dl}$ to $7.44 \pm 1.16 \mu\text{g/dl}$ following hypoglycemic stress. Following epidural triamcinolone administration, plasma cortisol values did not increase after hypoglycemic stress for a four-week period. Five weeks after placement of epidural triamcinolone, plasma cortisol values significantly increased from $4.81 \pm 0.67 \mu\text{g/dl}$ to $8.25 \pm 2.05 \mu\text{g/dl}$ following stress ($P < 0.05$). In this group of dogs, preinsulin cortisol values from 24 h through four weeks were decreased significantly compared with baseline preinsulin cortisol values ($P < 0.05$) with return towards the preinsulin baseline values only in the fifth week.

Measurement of blood glucose revealed similar values for both groups of dogs. Preinsulin glucose value was $88.4 \pm 1.2 \text{ mg/dl}$, and postinsulin value was $41.2 \pm 2.1 \text{ mg/dl}$, the difference being significant at less than 0.01 level. Comparison of the preinsulin values of the two groups demonstrated no significant difference.

Prior to epidural blockade, there was no statistically significant difference in the postinsulin cortisol values between the two groups. However, after epidural blockade, a statistically significant difference in plasma cortisol values was observed between the two groups at time periods of 24 h through four weeks. Five weeks after epidural triamcinolone, no difference in plasma cortisol values was observed between the two groups of dogs following insulin-induced hypoglycemic stress.

Discussion

Normal response to stress includes stimulation of the HPA axis resulting in a significant increase in plasma cortisol values.³ Modulation of this HPA axis is achieved by diurnal rhythm of ACTH and cortisol secretion, while "fine tuning" of the axis is achieved by feedback control and activation of the reserve capacity of the adrenal cortex at the times of stress.⁴ The stress response appears independent of the basic diurnal rhythm and feedback control mechanisms, and allows augmentation of steroidogenesis at any time of the day or night in response to a variety of stressful stimuli including acute illness, trauma, anesthesia and surgery. This response to stress depends on the integrity of the HPA axis. The integrity and ability of this axis response can be tested by determining the animal's capacity to increase plasma cortisol in response to a controlled stress.

In this investigation, the controlled uniform stress was the administration of 0.6 units/kg of insulin intravenously. This resulted in a comparable and significant reduction in the blood glucose values in both groups of dogs. The dogs that received epidural bupivacaine alone

TABLE 2. Plasma Cortisol Values before and after Hypoglycemic Stress in Group II (n = 6) Dogs that Received Epidural Bupivacaine and Triamcinolone

Plasma Cortisol (µg/dl)															
Baseline		24 H		72 H		1 Wk		2 Wk		3 Wk		4 Wk		5 Wk	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
5.1 ± 0.8	7.4* ± 1.2	2.3 ± 0.5	2.2 ± 0.7	2.2 ± 0.4	1.9 ± 0.4	2.7 ± 0.8	2.3 ± 0.5	1.5 ± 0.2	1.5 ± 0.3	2.5 ± 0.3	2.1 ± 0.7	2.5 ± 0.7	2.9 ± 0.1	4.8 ± 0.7	8.3* ± 2.0

Values expressed as means ± SEM.

* P 0.05 compared with prestress level.

showed a significant decrease in preinsulin plasma cortisol values at 24 h compared with baseline values, but during the further observation period there was no significant difference between the baseline preinsulin cortisol values and subsequent preinsulin values. The significant decrease in preinsulin cortisol value at 24 h may be secondary to the transient epidural blockade produced by bupivacaine as has been shown by Gordon *et al.*⁵ However, even at 24 h after epidural bupivacaine, following hypoglycemic stress, these dogs significantly increased their plasma cortisol values and this observation was found throughout the experimental period. However, the dogs who received epidural triamcinolone not only showed a significant decrease in preinsulin plasma cortisol values compared with baseline preinsulin, but also following the hypoglycemic stress, showed no change in the plasma cortisol values compared with the preinsulin values in periods 24 h through four weeks.

The dogs in Group 2 had significantly lower preinsulin values compared with the baseline preinsulin values. This and the inability of the experimental group dogs to increase their plasma cortisol values following hypoglycemic stress is due to the depression of the HPA axis following the systemic absorption of the steroid from the epidural space.

In humans, reports of systemic side effects of steroids following epidural administration support the hypothesis of systemic absorption of steroids from the epidural space.⁶ Sehgal *et al.* have shown no significant increase in the cerebrospinal fluid corticosteroid level following epidural injection of methylprednisolone acetate.⁷ They postulated that the steroid passes from the epidural space to plasma and caused suppression of endogenous steroid production by affecting the modulation of the HPA axis.

Triamcinolone was chosen over methylprednisolone in this investigation because of triamcinolone's ability to mix more completely with the vehicle. The potency and the anti-inflammatory activity of methylprednisolone and triamcinolone are equivalent when compared with hydrocortisone on a milligram per milligram basis.⁸ Baseline blood samples and all blood samples after epidural blockade were withdrawn at the same time of day to eliminate diurnal variation in plasma cortisol values.

Epidural injection of steroids has been advocated in the management of lumbar nerve root compression.^{9,10} Burn and Langdon studied 72 patients who had received epidural methylprednisolone for lumbosacral

syndrome, and observed decreases in cortisol values which were dose-dependent and lasted for a two-week period.¹¹ These patients were not subjected to a controlled stress during the period of HPA depression. Data examining the effect of a controlled stress on patients who had previously received exogenous epidural steroid are lacking.

This canine study clearly demonstrated that following a single epidural injection of 2 mg/kg of triamcinolone, the dogs exhibited significantly lower preinsulin plasma cortisol values when compared with the control group, and were unable to increase their plasma cortisol values in response to an insulin-induced hypoglycemic stress. The systemic effects of depressed cortisol values were not evaluated in this study. The degree and duration of cortisol depression following epidural administration of triamcinolone may be different in humans. However, depression of the HPA axis following a single dose of steroid administration and the inability of the dog to increase their plasma cortisol values following stress deserve consideration and further investigation. In the interim, exogenous steroid administration should be considered in periods of stress including the perioperative period for patients who received a single dose of epidural steroid in the recent past.

References

1. Goudsouzian NG, Karamanian A: Physiology for the Anesthesiologist. New York, Appelton-Century-Crofts, 1977, pp 333-334
2. Mattingly D: A simple fluorometric method for the estimation of free 11-hydroxycorticoids in human plasma. *J Clin Pathol* 15:374-379, 1962
3. Wilmore DW, Long JM, Mason AD, Pruitt BA: Stress in surgical patients as a neurophysiologic reflex response. *Surg Gynecol Obstet* 142:257-269, 1976
4. Skillman J: Hypothalamic-pituitary-adrenal axis in surgery, Intensive Care. Boston Little Brown and Company 1975, p 319
5. Gordon NH, Scott DB, Robb IWP: Modification of plasma corticosteroid concentrations during and after surgery by epidural blockade. *Br Med J* 1:581-582, 1973
6. Knight CL, Burnell JC: Systemic side-effects of extradural steroids. *Anaesthesia* 35:591-594, 1980
7. Sehgal AD, Tweed DC, Gardner WJ, Foote MK: Laboratory studies after intrathecal corticosteroids. *Arch Neurol* 9:64-68, 1963
8. Skillman JJ: Hypothalamic-pituitary-adrenal axis in surgery, Intensive Care. Boston, Little, Brown & Company, 1975, p 320
9. Dilke TF, Burry HC, Grahame R: Extradural Corticosteroid Injection in Management of Lumbar Nerve Root Compression. *Br Med J* 2:635-637, 1973
10. Winnie AP, Hartmann JT, Mylers HL, Ramamurthy S, Barangan V: Pain clinic II: Intrathecal and extradural corticosteroids for sciatica. *Anesth Analg (Cleve)* 51:990-1003, 1972
11. Burn JM, Langdon L: Duration of action of epidural methylprednisolone. *Arch Phys Med* 53:29-34, 1974