Anesthesiology
70:51–56, 1989

Epidural Clonidine Analgesia in Obstetrics: Sheep Studies

James C. Eisenach, M.D., Maria I. Castro, Ph.D.,* David M. Dewan, M.D.,† James C. Rose, Ph.D.‡*

Epidural clonidine administration produces analgesia by a non-opiate, spinal mechanism, and offers advantages over other epidural agents for labor analgesia. To examine clonidine's acute maternal and fetal effects, the authors injected clonidine, 300 μg, epidurally in seven chronically prepared, near term ewes. Unlike epidural saline injection, clonidine increased maternal and fetal serum glucose (by 178 ± 30% and 190 ± 30%, respectively; mean ± SEM, $P < .01$) 1 h following injection. Maternal and fetal serum cortisol and arterial blood gas tensions were unchanged following clonidine. Epidural clonidine injection produced minor decreases (10–15%) in heart rate in ewe and fetus, without altering maternal and fetal blood pressure, intra-uterine pressure, or uterine blood flow. Maternal and fetal serum clonidine concentrations peaked at 58 ± 8 and 73 ± 5 min following injection, respectively, and declined with similar half-lives. Heart rate correlated negatively with serum clonidine concentration in both ewe and fetus ($P < .05$). Apart from hyperglycemia, which does not occur in humans, these results in sheep suggest that epidurally administered clonidine does not adversely affect the fetus and may be evaluated as an analgesic in obstetrics. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Fetus: drug effects. Pain: drug therapy. Sympathetic nervous system, Alpha 2 adrenergic agonist: clonidine. Uterus: blood supply; drug effects.)

EPIDURAL CLONIDINE injection produces analgesia in animals by an α_2-adrenergic mechanism.[1,2] Preclinical safety assessment of epidural/intrathecal clonidine administration has been extensive: intraspinal clonidine administration does not produce neurotoxicity,[2,3] significant cardiovascular depression,[2,4,5] or decrease in spinal cord blood flow.[4,5] Initial clinical experience suggests that intraspinal clonidine administration effectively relieves pain.[6–8]

Epidurally administered clonidine may be ideally suited for obstetric use. Unlike epidurally administered local anesthetics, clonidine does not interfere with proprioception or produce motor blockade. Clonidine, unlike epidurally administered opiates, does not produce respiratory depression, nausea and vomiting, or pruritus.

Despite evidence of safety, efficacy, and suitability, there has been no investigation of epidural clonidine analgesia in pregnancy. Clonidine activates α_2-adrenergic receptors, with the potential to alter hemodynamic, respiratory, uterine, and hormonal regulation. In this study, we examine the acute uterine and maternal and fetal hemodynamic, respiratory, and hormonal effects of epidurally administered clonidine in pregnant ewes, and correlate these effects with maternal and fetal serum clonidine concentrations.

This article is accompanied by an editorial. Please see: Yaksh TL, Collins JG: Studies in animals should precede human use of spinally administered drugs. ANESTHESIOLOGY 70:4–6, 1989.

Materials and Methods

ANIMAL PREPARATION

The Animal Care Committee approved the protocol. Seven near term (116–131 days gestation) pregnant ewes of mixed western breeds (40–60 kg) were studied. Following a 48-h fast, animals were pretreated with atropine 0.03 mg/kg, iv, anesthesia was induced with 12–16 mg/kg ketamine HCl and sodium pentobarbital, 6–8 mg/kg, iv, and, following endotracheal intubation, anesthesia was maintained with halothane 0.5–1.5% in oxygen. Polyvinyl catheters were inserted into the descending fetal aorta and inferior vena cava *via* hindlimb vessels and into the amniotic sac. In one case, catheters were inserted in both twin fetuses. Following uterine closure, polyvinyl catheters were inserted into the maternal descending aorta and inferior vena cava *via* internal mammary vessels, and (in six of the ewes) a calibrated electromagnetic flow probe (Dienco™) was placed on the left uterine artery. The flow probe and catheters were tunneled subcutaneously, exiting the skin at the flank, and were maintained in a canvas pouch. A single distal port catheter (Portex™) was inserted 5 cm into the epidural space at the lumbo-sacral junction percutaneously using a #16 Hythe needle and loss of re-

* Assistant Professor of Anesthesia, Department of Anesthesia.
† Associate Professor of Anesthesia, Department of Anesthesia.
‡ Professor of Physiology and Obstetrics, Departments of Physiology and Pharmacology and Obstetrics and Gynecology.

Received from the Section of Obstetric Anesthesia, Department of Anesthesia, and Department of Physiology and Pharmacology, Wake Forest University, The Bowman Gray School of Medicine, Winston-Salem, North Carolina. Accepted for publication June 3, 1988. Supported in part by Grant GM35523 from the National Institutes of Health. Human studies supported in part by Grant FD-R-000171 from the Food and Drug Administration. Presented in part at the Annual Meeting of the American Society of Anesthesiologists in Atlanta, Georgia, October, 1987.

Address reprint requests to Dr. Eisenach: Department of Anesthesia, The Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

sistance technique. Catheters were flushed daily with heparinized saline (1000 U/ml). Penicillin (900,000 U, im) and kanamycin (80 mg, intra-amniotically) were administered daily until the third postoperative day. All animals were allowed a 4–6-day recovery period before any experimental procedure.

Experimental Protocol

On the day of the experiment, the ewe, standing in a portable metabolic cage, was placed in a quiet room. The maternal and fetal arterial catheters and intra-uterine catheter were connected to Gould™ pressure transducers (Model P23ID) for the measurement of maternal and fetal arterial blood pressure and heart rate, and intra-uterine pressure using a Grass™ Model 7D polygraph recorder. The flow probe was connected to a Dienco™ flow meter for the continuous recording of uterine blood flow. Following 30 min of stable baseline recordings, 10 ml saline or 10 ml saline containing 300 μg clonidine were injected epidurally over a 2-min period. Injections were given in random order and were separated by 24 h.

Measurements

In addition to continuous maternal and fetal hemodynamic recording, maternal and fetal arterial blood samples were obtained before and 5, 20, 40, 60, and 240 min following injection and analyzed for arterial P_{O_2}, P_{CO_2}, and *p*H using a Radiometer™ BMS blood microanalysis system and for serum clonidine using a specific radioimmunoassay with detection limit of 50 pg/ml.[9] Maternal and fetal arterial blood samples obtained before and 60 and 240 min following injection were also analyzed for serum glucose using a Beckman™ glucose analyzer system and for serum cortisol using a specific radioimmunoassay.[10]

Statistical Analysis

All data are expressed as the mean ± SEM. Fetal blood pressure was corrected for changes in intra-uterine pressure. Data following epidural injections were compared to baseline using a one-way analysis of variance for repeated measures followed by Newman-Keuls analysis. Data following epidural clonidine were compared to the saline control by a two-way analysis of variance for repeated measures followed by Tukey's multiple comparison test. Due to the large variation in baseline and/or stimulated serum cortisol and glucose concentrations, these data were analyzed as changes from baseline values using a Wilcoxon two-sample test. Correlation between heart rate and serum clonidine concentration was tested by first-order linear regression. Statistical difference between groups was considered to be present at $P < 0.05$.

Maternal and fetal serum clonidine *versus* time curves were analyzed according to a first-order absorption and one-compartment first-order elimination model using the PCNONLIN™ software. Fetal drug exposure index was calculated as the ratio of fetal to maternal area under the concentration · time curves.[11,12] The amount of drug in the fetal compartment at the time of peak concentration was calculated as $C_{Max} \cdot V_D$, where C_{Max} is the maximal calculated plasma concentration and V_D is the volume of distribution. Values for V_D were obtained from the iterative solution of plasma concentration *versus* time data for the appropriate pharmacokinetic model and values for C_{Max} were then calculated by standard methods. Fetal volume of distribution, estimated from pilot studies following infusion of clonidine, 20 μg, into a fetal vein, was 0.141 l/kg. A gestational age to weight table was used in estimating fetal weight. The amount of drug in maternal serum at the time of peak concentration was calculated as C_{Max} · Plasma Volume, and maternal plasma volume was estimated as 6% of body weight.[13]

Drugs

The following drugs were used in this study: atropine (Elkin-Sinn, Inc, Cherry Hill, NJ), ketamine HCl and sodium pentobarbital (Barber Veterinary Supply Co., Richmond, VA), and procaine penicillin G (Pfizer, New York, NY). The following drugs were generous gifts: clonidine HCl (Boehringer Ingleheim, Ltd., Ridgefield, CT) and kanamycin (LyphoMed, Inc., Rosemount, IL).

Results

Epidural saline injection did not significantly affect any of the parameters measured. In contrast, epidurally administered clonidine was followed by decreased maternal and fetal heart rate (fig. 1, upper panel) without altering arterial blood pressure (fig. 1, lower panel). Clonidine injection did not alter uterine blood flow or intra-uterine pressure (table 1) or maternal or fetal arterial blood gas tensions (table 2). Although fetal arterial *p*H was lower before clonidine than before saline injection, clonidine injection did not affect fetal arterial *p*H (table 2). Maternal and fetal serum glucose increased following clonidine, while serum cortisol did not change (table 3).

Maternal and fetal serum clonidine concentrations best fit a one compartment model, and elimination half-lives were similar in ewe and fetus (fig. 2; table 4). The fetal: maternal serum clonidine ratio during the elimination phase was 0.50 ± 0.04, and fetal drug exposure was 52 ± 0.3% of the maternal exposure. At the time of peak serum concentrations, 0.036% of the epidurally administered dose was in the fetal compartment, and 0.95% was in maternal serum. Although our data were clearly not obtained at steady state, there was a significant correlation

between maternal and fetal serum clonidine concentration and heart rate ($P < .05$).

Discussion

Preclinical assessment of epidural clonidine use for nonpregnant individuals is reasonably complete. However, prior to use during pregnancy, acute and chronic effects on fetal and uterine physiology should be examined.[14] Chronic oral clonidine administration, resulting in serum clonidine concentrations similar to those observed in this study, is tolerated well during pregnancy without adverse effects on mother, fetus, timing or course of labor, or neonate.[15–18] Effects of a broad dose range of clonidine administered epidurally and intravenously in nonpregnant sheep have been previously described.[2,19] In this study, we examined the acute effects of epidurally administered clonidine in a dose which produces maximal analgesia in sheep[2] and effective analgesia in humans.[7,8]

Orally administered clonidine is an effective anti-hypertensive, but epidurally administered clonidine minimally affects blood pressure in animals[2,4,5,20] (including the pregnant sheep in this study), and reduces blood pressure in a minority of patients.[8] Lack of hypotensive action following epidural injection in normotensive sheep may reflect clonidine's attenuated hypotensive efficacy in normotensive individuals.[21] Alternatively, since clonidine's net effect on blood pressure is a balance between opposing actions at different sites (peripheral vasoconstriction[22] and central depression of sympathetic nervous system activity[23]), differing peripheral *versus* central drug disposition may explain the difference in hemodynamic effects between oral and epidural administration.

Unlike epidural local anesthetic injection, systemic clonidine modulates,[15] but does not abolish, sympathetic responses. Therefore, one would expect that epidurally administered clonidine would interfere less with maintenance of blood pressure during aortocaval compression than local anesthetics, although we did not test this hypothesis in the current study.

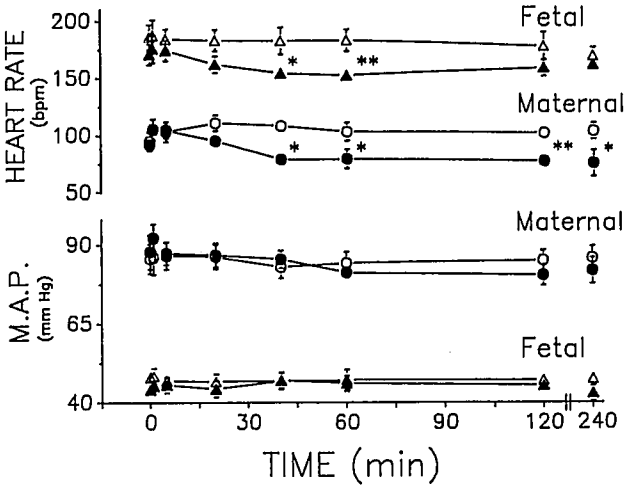

FIG. 1. Maternal (circles) and fetal (triangles) heart rate and MAP (mean arterial pressure) following maternal epidural injection of saline (○ △) or clonidine, 300 μg (● ▲). Each point represents the mean ± SEM of seven animals. $*P < .05$ *versus* saline. $**P < .01$ *versus* saline.

Clonidine decreases heart rate by direct cardiac, as well as central, mechanisms.[24] In pregnant sheep, fetal clonidine infusion decreases heart rate and heart rate variability by an α_2-adrenergic mechanism,[25] and maternal epidural clonidine administration produces adequate fetal serum clonidine concentrations to slow the fetal heart rate. These minor decreases in fetal and maternal heart rates, which do not alter blood pressure, appear inconsequential. However, whether these small effects would interfere with interpretation of fetal heart rate changes in labor, or limit the mother's and fetus' abilities to respond to hypoxemic or hypovolemic stress, is unknown.

Clonidine causes human myometrium[26] and human uterine arteries[27] to contract *in vitro*, primarily by activating α_2-adrenergic receptors. Although bolus iv injection of clonidine increases uterine tone and decreases uterine blood flow in pregnant sheep,[28] these effects are only observed at serum clonidine concentrations > 1.0

TABLE 1. Uterine Effects Following Epidural Injections*

Parameter	Baseline	1 Min	5 Min	20 Min	40 Min	1 h	2 h	4 h
Uterine blood flow								
Saline	364 ± 31	356 ± 31	345 ± 36	341 ± 42	351 ± 31	356 ± 33	370 ± 37	360 ± 26
Clonidine	357 ± 34	332 ± 47	290 ± 45	363 ± 41	360 ± 41	377 ± 42	361 ± 50	354 ± 41
Intra-uterine pressure								
Saline	8.2 ± 1.1	9.3 ± 1.1	7.7 ± 1.5	7.9 ± 1.1	8.4 ± 1.3	8.5 ± 1.2	9.0 ± 1.1	8.6 ± 0.8
Clonidine	8.3 ± 1.1	8.9 ± 0.9	9.6 ± 1.3	8.8 ± 1.6	9.7 ± 1.5	9.1 ± 2.0	8.1 ± 1.4	8.4 ± 0.7

Data expressed as mean ± SEM.
* Flow in ml/min; pressure in mmHg. No significant differences between groups by analysis of variance.

TABLE 2. Effects of Epidural Injections on Arterial Blood Gas Tensions

Parameter	Baseline	20 Min	1 h	2 h	4 h
Maternal pH					
Saline	7.49 ± .01	7.48 ± .02	7.49 ± .01	7.50 ± .01	7.49 ± .01
Clonidine	7.48 ± .01	7.51 ± .01	7.52 ± .01	7.52 ± .01	7.52 ± .01
Maternal P_{CO_2}					
Saline	31 ± 1.4	30 ± 1.8	31 ± 0.6	30 ± 1.6	31 ± 0.5
Clonidine	33 ± 1.6	33 ± 1.7	34 ± 2.0	33 ± 1.2	34 ± 2.3
Maternal P_{O_2}					
Saline	84 ± 3.5	85 ± 3.3	86 ± 3.0	86 ± 3.0	87 ± 3.6
Clonidine	89 ± 3.2	85 ± 3.5	82 ± 3.4	81 ± 3.9	87 ± 4.1
Fetal *p*H					
Saline	7.42 ± .01	7.42 ± .01	7.42 ± .01	7.43 ± .02	7.41 ± .01
Clonidine	7.39 ± .02*	7.38 ± .02*	7.37 ± .02*	7.35 ± .02*	7.38 ± .02
Fetal P_{CO_2}					
Saline	41 ± 2.0	39 ± 2.0	41 ± 1.6	42 ± 2.7	42 ± 1.7
Clonidine	43 ± 2.2	45 ± 2.1	46 ± 2.6	45 ± 3.1	44 ± 2.8
Fetal P_{O_2}					
Saline	18 ± 1.8	19 ± 1.5	18 ± 1.4	19 ± 1.6	18 ± 1.7
Clonidine	20 ± 1.7	19 ± 1.6	18 ± 1.5	18 ± 1.5	18 ± 1.7

Data expressed as mean ± SEM. Blood gas tensions in mmHg.
* Saline and clonidine groups differ ($P < .05$) by two-way analysis of variance. No significant difference from baseline following clonidine injection by one-way analysis of variance.

ng/ml (not obtained in this study following epidural injection), and which may be secondary to the stress of hypoxemia rather than a direct effect (see below). In humans, orally administered clonidine does not increase the incidence of premature labor,[15] nor does intravenously administered clonidine increase the frequency of uterine contractions.[18]

TABLE 3. Hormonal Effects of Epidural Injections

Parameter	Time		
	Baseline	1 h	4 h
Maternal glucose			
Saline	72 ± 3	64 ± 5	69 ± 3
Clonidine	64 ± 4	180 ± 23*†	119 ± 10†
Fetal glucose			
Saline	28 ± 5	35 ± 4	38 ± 6
Clonidine	27 ± 4	79 ± 14*†	60 ± 12
Maternal cortisol			
Saline	20 ± 6.4	22 ± 10	14 ± 5.4
Clonidine	14 ± 5.4	7.4 ± 2.3	8.0 ± 3.4
Fetal cortisol			
Saline	10 ± 2.9	18 ± 6.6	15 ± 4.9
Clonidine	8.5 ± 5.4	13 ± 5.0	14 ± 4.4

Data expressed as mean ± SEM. Glucose in mg/dl; cortisol in μg/ml.
* $P < .01$ *versus* saline by two-way analysis of variance.
† $P < .05$ *versus* baseline by one-way analysis of variance.

Clonidine increases serum glucose by inhibiting insulin release.[29] In sheep, epidural clonidine injection produces maternal and fetal hyperglycemia, which may reduce umbilical blood flow and fetal oxygenation *in utero*[30] and produce rebound neonatal hypoglycemia. However, there is no evidence that clonidine produces clinically significant hyperglycemia in humans: neonatal serum glucose concentrations are normal during chronic oral clonidine use in pregnancy,[16] and systemically administered clonidine does not increase fasting serum glucose and decreases ex-

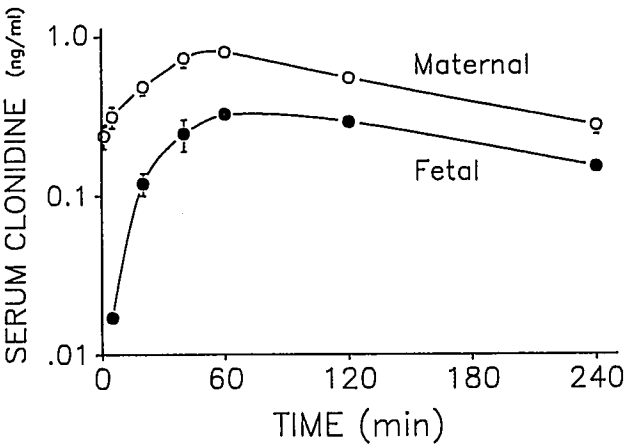

FIG. 2. Maternal (○) and fetal (●) serum clonidine following maternal epidural injection of clonidine, 300 μg. Each point represents the mean ± SEM of seven animals.

ercise-induced hyperglycemia in volunteers.[31] In preliminary studies in nonpregnant humans, epidural injection of clonidine (100–300 μg) did not change serum glucose (86 ± 6 mg/dl before and 95 ± 9 mg/dl 1 h after clonidine injection; N = 5). It may be noted for comparison that intrathecally applied morphine produces hypoglycemia in certain animal models[32] but does not alter serum glucose in humans.

Clonidine decreases stress-induced ACTH release, and hence cortisol release,[33,34] and inhibits the expected increase[35] in maternal and fetal cortisol in sheep exposed to hypoxemia.[28] Although we did not observe a significant decrease in serum cortisol following epidurally administered clonidine, variability in serum cortisol reduced the certainty that a drug-induced decrease may nonetheless have occurred, and clonidine's effect on the hormonal stress response was not examined. The risks of inhibiting the normal rise in maternal and fetal cortisol at birth[36] are unknown.

Serum clonidine pharmacokinetics following epidural injection in sheep differ markedly from those of morphine in sheep[37] and humans.[38] The fetal:maternal serum concentration ratio following redistribution is greater for clonidine (0.50 ± 0.04) than for morphine (0.22 ± 0.02) following epidural injection in sheep. This suggests more rapid and complete placental transfer of clonidine than morphine, although other explanations are possible.[11,12] Despite greater lipid solubility, epidurally administered clonidine is absorbed more slowly into the systemic circulation than morphine (peak maternal serum concentrations occur at 58 ± 8 min following clonidine *versus* 15–30 min following morphine).[37] This may be due to clonidine absorption in, and slow release from, epidural fat. Slowed absorption may limit fetal toxicity by decreasing peak maternal and fetal serum concentrations. As expected from these pharmacokinetic differences, peak serum drug concentrations following epidural injection are 46% lower with clonidine than morphine[37] in sheep, after correcting for dose.

Finally, preclinical assessment of a drug for epidural use in pregnancy should include effects when injected iv, as accidental iv cannulation and injection of epidural catheters may occur. In sheep, iv clonidine injection produces dose-dependent hypoxemia, mediated by a peripheral α_2-adrenergic receptor, and not due to respiratory or cardiovascular depression.[19] In pregnant sheep, iv injection of clonidine (300 μg) produces maternal and (secondarily) fetal hypoxemia, accompanied by increased uterine tone and decreased uterine blood flow.[28] Although the mechanism of clonidine-induced hypoxemia in sheep is unknown, it is suggested to be due to platelet aggregation and pulmonary microembolism.[19] However, iv clonidine injection does not produce hypoxemia in cats[39] or humans,[40] and epidural clonidine injection (100–300 μg) does not alter arterial oxygen saturation in humans (unpublished observations). Preliminary studies suggest that clonidine produces an unusual form of activation of sheep, but not human, platelets, which may account for the species difference in effect on arterial P_{O_2} (unpublished observations).

TABLE 4. Pharmacokinetic Parameters Following Epidural Injection

Parameter	Maternal	Fetal
$t_{\frac{1}{2}}$ Elimination (min)	100 ± 11	112 ± 10
C_{Max} (ng/ml)	0.79 ± .04	0.34 ± .04
T_{Max} (min)	58 ± 8	73 ± 5

Data expressed as mean ± SEM. C_{Max} = maximal serum concentration calculated from nonlinear kinetics; T_{Max} = time of maximal serum concentration calculated from nonlinear kinetics.

In summary, epidural injection of clonidine produces minor reductions in maternal and fetal heart rate, as well as maternal and fetal hyperglycemia, without affecting other hemodynamic, uterine, or hormonal parameters. Clonidine appears to be a promising new agent for epidural analgesia in obstetrics. However, clinical studies of epidural clonidine analgesia in normal pregnancy await a wider clinical experience and evaluation of the effects of accidental iv and spinal injection, while use of epidurally administered clonidine in complicated pregnancies awaits evaluation of effects of this hemodynamically active drug on the stressed fetus.

The authors wish to thank Tony Yaksh, Ph.D., for assistance in experimental design and Mr. William Brooks and Ms. Barbara Tucker for technical assistance.

References

1. Yaksh TL: Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 22:845–858, 1985
2. Eisenach JC, Dewan DM, Rose JC, Angelo JM: Epidural clonidine produces antinociception, but not hypotension, in sheep. ANESTHESIOLOGY 66:496–501, 1987
3. Gordh T Jr, Post C, Olsson Y: Evaluation of the toxicity of subarachnoid clonidine, guanfacine, and a substance P-antagonist on rat spinal cord and nerve roots: Light and electron microscopic observations after chronic intrathecal administration. Anesth Analg 65:1303–1311, 1986
4. Eisenach JC, Grice SC: Epidural clonidine does not decrease blood pressure or spinal cord blood flow in awake sheep. ANESTHESIOLOGY 68:335–340, 1988
5. Gordh T Jr, Feuk U, Norlen K: Effect of epidural clonidine on spinal cord blood flow and regional and central hemodynamics in pigs. Anesth Analg 65:1312–1318, 1986
6. Coombs DW, Saunders RL, LaChance D, Savage S, Ragnarsson TS, Jensen LE: Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. ANESTHESIOLOGY 62:357–363, 1985
7. Glynn CJ, Teddy PJ, Jamous MA, Moore RA, Lloyd JW: Role of spinal noradrenergic system in transmission of pain in patients with spinal cord injury. Lancet ii:1249–1250, 1986

8. Kalia PK, Madan R, Batra RK, Latha V, Vardham V, Gode GR: Clinical study on epidural clonidine for postoperative analgesia. Indian J Med Res 83:550–552, 1986
9. Arndts D, Stahle H, Forster H-J: Development of a RIA for clonidine and its comparison with the reference methods. J Pharmacol Methods 6:295–307, 1981
10. Rose JC, Morris M, Meis PJ: Hemorrhage in newborn lambs: Effects on arterial blood pressure, ACTH, cortisol and vasopressin. Am J Physiol 240:E585–E590, 1981
11. Szeto HH: Pharmacokinetics in the ovine maternal-fetal unit. Ann Rev Pharmacol Toxicol 22:221–243, 1982
12. Kanto J: Obstetric analgesia: Clinical pharmacokinetic considerations. Clin Pharmacokinet 11:283–298, 1986
13. Krauer B, Krauer F, Hytten FE: Drug disposition and pharmacokinetics in the maternal-placental-fetal unit. Pharmacol Ther 10:301–328, 1980
14. Yaksh TL, Wilson PR, Kaiko RF, Inturrisi CE: Analgesia produced by a spinal action of morphine and effects upon parturition in the rat. ANESTHESIOLOGY 51:386–392, 1979
15. Horvath JS, Phippard A, Korda A, Henderson-Smart DJ, Child A, Tiller DJ: Clonidine hydrochloride-A safe and effective antihypertensive agent in pregnancy. Obstet Gynecol 66:634–638, 1985
16. Hartikainen-Sorri A-L, Heikkinen JE, Koivisto M: Pharmacokinetics of clonidine during pregnancy and nursing. Obstet Gynecol 69:598–600, 1987
17. Tuimala R, Punnonene R, Jouppila E: Clonidine in the treatment of hypertension during pregnancy. Ann Chir Gynaecol 74:47–50, 1985
18. Johnston CI, Aickin DR: The control of high blood pressure during labour with clonidine ("Catapres"). Med J Aust 2:132–135, 1971
19. Eisenach JC: Intravenous clonidine produces hypoxemia by a peripheral alpha2-adrenergic mechanism. J Pharmacol Exp Ther 244:247–252, 1988
20. Ghignone M, Calvillo O, Quintin L, Caple S, Kozody R: Haemodynamic effects of clonidine injected epidurally in halothane-anesthetized dogs. Can J Anaesth 34:46–50, 1987
21. Wing LMH, Reid JL, Davies DS, Neill EAM, Tippett P, Dollery CT: Pharmacokinetic and concentration-effect relationships of clonidine in essential hypertension. Eur J Clin Pharmacol 12: 463–469, 1977
22. Langer SZ, Hicks PE: Alpha-adrenoreceptor subtypes in blood vessels: Physiology and pharmacology. J Cardiovasc Pharmacol 6(Suppl 4):S547–S558, 1984
23. van Zweiten PA, Thoolen MJMC, Timmermans PBMWM: The hypotensive activity and side effects of methyldopa, clonidine, and guanfacine. Hypertension 6(Suppl 11):28–33, 1984
24. van Zweiten PA, Timmermans PBMWM: Pharmacology and characterization of central alpha-adrenoceptors involved in the effect of centrally acting antihypertensive drugs. Chest 83(Suppl):340–343, 1983
25. Bamford OS, Dawes GS, Denny R, Ward RA: Effects of the α2-adrenergic agonist clonidine and its antagonist idazoxan on the fetal lamb. J Physiol (Lond) 381:29–37, 1986
26. Berg G, Andersson GG, Ryden G: α-Adrenergic receptors in human myometrium during pregnancy. Am J Obstet Gynecol 154: 601–606, 1986
27. Ribeiro CAF, Macedo TA: Pharmacological characterization of the postsynaptic α-adrenoceptors in human uterine artery. J Pharm Pharmacol 38:600–605, 1986
28. Eisenach JC, Rose JC, Dewan DM, Grice SC: Intravenous clonidine produces fetal hypoxemia (abstract). ANESTHESIOLOGY 67: A449, 1987
29. Metz SA, Halter JB, Robertson RP: Induction of defective insulin secretion and impaired glucose tolerance by clonidine. Selective stimulation of metabolic alpha-adrenergic pathways. Diabetes 27:554–562, 1978
30. Crandell SS, Fisher DJ, Morriss FH Jr: Effects of ovine maternal hyperglycemia on fetal regional blood flows and metabolism. Am J Physiol E454–E460, 1985
31. Joffe BI, Haitas B, Edelstein D, Panz V, Lamprey JM, Baker SG, Seftel HC: Clonidine and the hormonal responses to graded exercise in healthy subjects. Horm Res 23:136–141, 1986
32. Lux F, Brase DA, Dewey WL: Differential effects of subcutaneous and intrathecal morphine administration on blood glucose in mice: Comparison with intracerbroventricular administration. J Pharmacol Exp Ther 245:187–194, 1988
33. Ganong WF, Kramer N, Salmon J, Reid IA, Lovinger R, Scapagnini U, Boryczka AT, Shackelford R: Pharmacological evidence for inhibition of ACTH secretion by a central adrenergic system in the dog. Neuroscience 1:167–174, 1976
34. Masala A, Satta G, Alagna S, Anania V, Frassetto GA, Rovasio PP, Semiani A: Effect of clonidine on stress-induced cortisol release in man during surgery. Pharmacol Res Commun 17: 293–298, 1985
35. Bocking AD, McMillen IC, Harding R, Thorburn GD: Effect of reduced uterine blood flow on fetal and maternal cortisol. J Dev Physiol 8:237–245, 1986
36. Bacigalupo G, Langner K, Schmidt S, Saling E: Plasma immunoreactive beta-endorphin, ACTH and cortisol concentrations in mothers and their neonates immediately after delivery—Their relationship to the duration of labor. J Perinat Med 15: 4552, 1987
37. Craft JB, Bolan JC, Coaldrake LA, Mondino M, Mazel P, Gilman RM, Shokes LK, Woolf WA: The maternal and fetal cardiovascular effects of epidural morphine in the sheep model. Am J Obstet Gynecol 142:835–839, 1982
38. Youngstrom PC, Cowan RI, Sutheimer C, Eastwood DW, Yu JCM: Pain relief and plasma concentrations from epidural and intramuscular morphine in post-cesarean patients. ANESTHESIOLOGY 57:404–409, 1982
39. Kanawati IS, Yaksh TL, Anderson RE, Marsh RW: Effects of clonidine on cerebral blood flow and the response to arterial CO2. J Cereb Blood Flow Metab 6:358–365, 1986
40. Zochowski RJ, Lada W: Intravenous clonidine treatment in acute myocardial infarction (with comparison to a nitroglycerin-treated and control group). J Cardiovasc Pharmacol 8(Suppl. 3):S41–S45, 1986