

Epidural Clonidine Analgesia in Obstetrics: Sheep Studies

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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 $178 \pm 30\%$ and $190 \pm 30\%$, respectively; mean \pm 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.

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-

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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 pH 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 \pm 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 \cdot 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 $C_{Max} \cdot$ 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 pH was lower before clonidine than before saline injection, clonidine injection did not affect fetal arterial pH (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 $52 \pm 0.3\%$ 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 sheep² 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 vasoconstriction²² and central depression of sympathetic nervous system activity²³), 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.

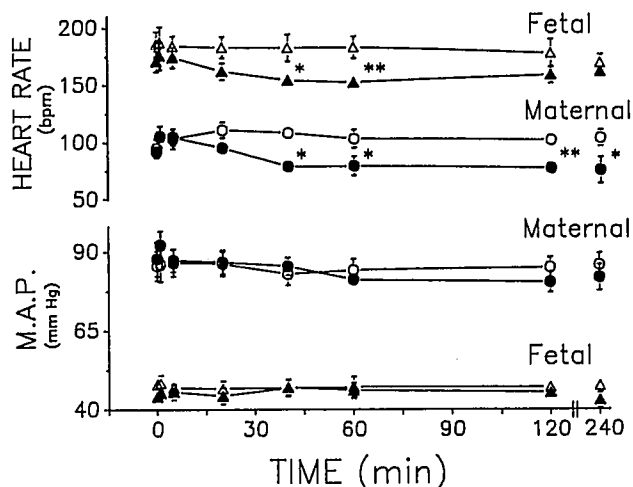


FIG. 1. Maternal (circles) and fetal (triangles) heart rate and MAP (mean arterial pressure) following maternal epidural injection of saline (○ △) or clonidine, 300 μg (● ▲). Each point represents the mean ± SEM of seven animals. * $P < .05$ versus saline. ** $P < .01$ versus saline.

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 myometrium²⁶ and human uterine arteries²⁷ 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 _{CO₂}					
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 _{O₂}					
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 pH					
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 _{CO₂}					
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 _{O₂}					
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-

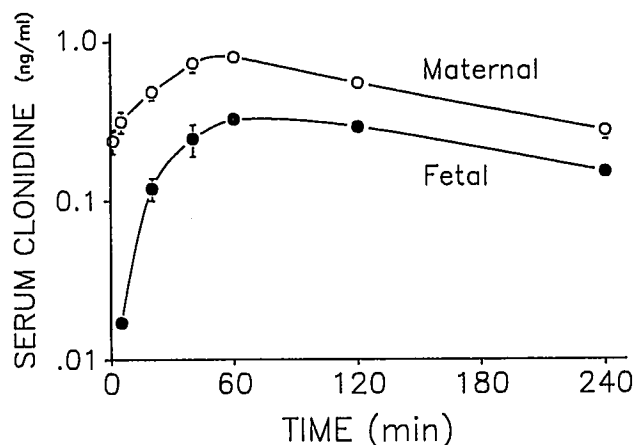


FIG. 2. Maternal (O) and fetal (●) serum clonidine following maternal epidural injection of clonidine, 300 µg. Each point represents the mean ± SEM of seven animals.

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 models³² but does not alter serum glucose in humans.

Clonidine decreases stress-induced ACTH release, and hence cortisol release,^{33,34} and inhibits the expected increase³⁵ 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 birth³⁶ are unknown.

Serum clonidine pharmacokinetics following epidural injection in sheep differ markedly from those of morphine in sheep³⁷ 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 morphine³⁷ 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 α₂-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 cats³⁹ or humans,⁴⁰ and epidural clonidine injection (100–

TABLE 4. Pharmacokinetic Parameters Following Epidural Injection

Parameter	Maternal	Fetal
t _{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.

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_{O₂} (unpublished observations).

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.

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