

## Intrathecal Clonidine in Obstetrics: Sheep Studies

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Clonidine may be administered intrathecally as an adjunct to local anesthetics or accidentally during attempted epidural analgesia. To examine clonidine's acute maternal and fetal effects, the authors injected clonidine (100, 300, 750, 1500  $\mu$ g cumulative dose at 15-min intervals) intrathecally in nine chronically prepared near-term ewes. Unlike intrathecal saline injection, which did not alter any parameters, clonidine altered maternal blood pressure in a biphasic manner (depression at lower doses and return to baseline after the highest dose). Clonidine produced a dose-dependent decrease in maternal and fetal heart rate. After the highest dose, 1500  $\mu$ g,  $P_{O_2}$  decreased in both ewe and fetus, accompanied by fetal hypertension and bradycardia. Clonidine increased maternal and fetal serum glucose, but not cortisol. Although clonidine-induced hypoxemia and hyperglycemia occur only in sheep, fetal bradycardia may limit the usefulness of clonidine in large doses ( $>10$   $\mu$ g/kg) in obstetrics. Lower doses, such as may be used to enhance spinal anesthesia, are well tolerated in sheep. (Key words: Anesthesia: obstetric. Anesthetic technique: spinal. Fetus: drug effects. Pain: drug therapy. Sympathetic nervous system,  $\alpha_2$ -adrenergic agonist: clonidine.)

INTRATHECALLY ADMINISTERED clonidine produces analgesia by activating  $\alpha_2$ -adrenoceptors in the *substantia gelatinosa* of the spinal cord.<sup>1</sup> Preclinical and early clinical experience suggest that intraspinally administered clonidine is safe and effectively relieves pain.<sup>2-11</sup>

Hypotension, the main side effect from intraspinal clonidine therapy, may be less likely to occur following epidural than intrathecal injection,<sup>12</sup> making epidural the preferred route of administration. However, unrecognized intrathecal placement of epidural catheters may result in accidental intrathecal injection of clonidine. In addition, clonidine may be intentionally injected intrathecally in combination with local anesthetics to improve and prolong the resulting spinal anesthesia.<sup>13,14</sup>

Despite advantages for the use of clonidine over other epidural agents in obstetrics,<sup>15</sup> possibility of accidental intrathecal injection with the epidural technique, and clonidine's demonstrated efficacy to enhance spinal anesthesia, there has been no investigation of intrathecally administered clonidine in pregnancy. Epidural clonidine injection in pregnant ewes decreases maternal and fetal heart rate without altering blood pressure or uterine per-

fusion.<sup>15</sup> However, the hemodynamic effect of clonidine may differ between epidural and intrathecal injection.<sup>12</sup> The purpose of this study is to examine the acute maternal and fetal hemodynamic, respiratory, and hormonal effects of intrathecally administered clonidine in pregnant ewes. In addition, we examine the reversibility of clonidine-induced effects with  $\alpha_2$ -adrenergic antagonists.

### Materials and Methods

#### ANIMAL PREPARATION

The Animal Care Committee approved the protocol. Nine near-term ( $132 \pm 2$  days gestation at time of study) ewes of mixed western breeds (42-57 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 tracheal intubation, anesthesia was maintained with halothane 0.5-1.5% in oxygen. The animal was placed in the prone position and a bilateral laminectomy was performed at L4-5 or L3-4 as described by Payne, *et al.*<sup>16</sup> Approximately 2-3 cm of spinal dura mater was exposed by gentle retraction of epidural fat. A single-port 20-G Portex<sup>®</sup> (Burrton Inc., Bethlehem, PA) catheter was inserted through a small nick in the dura, advanced 3 cm into the subarachnoid space, and the dural hole sealed with two 8-0 silk sutures. The epidural fat was replaced around the catheter, the catheter was secured, and the animal placed in the supine position. Polyvinyl catheters were then inserted into the descending fetal aorta and inferior vena cava *via* hindlimb vessels and into the amniotic sac. Following uterine closure, polyvinyl catheters were inserted into the maternal descending aorta and inferior vena cava *via* internal mammary vessels. Catheters were flushed daily with heparinized saline (1000 U/ml). Penicillin (900,000 U, im) and kanamycin (80 mg, intramniotically) 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 intrauterine catheter and maternal and fetal arterial catheters were connected to Gould<sup>®</sup> pressure transducers (Model P231D) for the continuous measurement of arterial pressure and heart rate, and intrauterine pressure using a Grass<sup>®</sup> 7-D polygraph recorder and a computer

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Received from the Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina. Accepted for publication November 15, 1989. Supported in part by Grant GM35523 from the National Institutes of Health. Presented in part at the Annual Meeting of the American Pain Society in Phoenix, Arizona, October 1989.

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on-line data acquisition system. Data were obtained on computer every minute throughout the study. Following 30 min of stable baseline measurements, clonidine dissolved in 0.9% saline was injected into the intrathecal catheter in a 1.5-ml volume followed by saline flush with one void volume (0.3 ml). In this dose-response study, clonidine was injected at 15-min intervals to achieve cumulative doses of 100, 300, 750, and 1500  $\mu\text{g}$ . This time interval and dose regimen was based on previous pharmacokinetic and pharmacodynamic studies in sheep performed in this laboratory.<sup>12</sup> Control experiments consisted of sequential injection of equal volumes of saline. For each animal, hemodynamic values obtained at 13, 14, and 15 min following each injection were averaged. Seven ewes received clonidine and saline in separate experiments that were separated by at least 48 h. Fifteen minutes following the last clonidine or saline injection, the  $\alpha_2$ -adrenergic antagonists idazoxan (1 mg/kg; four ewes) or DG-5128 (10 mg/kg; five ewes) were injected *via* the maternal venous catheter.

In addition to continuous maternal and fetal hemodynamic recording, maternal and fetal arterial blood samples were obtained before the first injection, just prior to each subsequent injection and 15 min following the antagonist injection and analyzed for arterial  $P_{\text{O}_2}$ ,  $P_{\text{CO}_2}$ , and  $p\text{H}$  using a Radiometer<sup>™</sup> BMD blood microanalysis system. Maternal and fetal arterial blood samples obtained before the first injection and 15 min following the last intrathecal injection were also analyzed for serum glucose using a Beckman<sup>™</sup> glucose analyzer system and for serum cortisol using a specific radioimmunoassay.<sup>17</sup>

#### STATISTICAL ANALYSIS

Data are presented as mean  $\pm$  SEM. Fetal blood pressure was corrected for changes in intrauterine pressure by subtraction of intrauterine pressure. Data following intrathecal injections were compared to baseline as a percent change and analyzed using a one-way analysis of variance for repeated measures followed by Newman-Keuls test. Data following intrathecal clonidine were compared to saline control using a multivariate analysis of variance for repeated measures followed by Tukey's multiple comparison test. Due to the large variability in baseline and final serum cortisol and glucose concentrations, these data were analyzed as changes from baseline values using a Wilcoxon two-sample test. Statistical difference between groups was considered to be present at  $P < 0.05$ .

#### 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., Rich-

mond, VA); halothane (Halocarbon Laboratories, Inc., Hackensack, NJ); heparin (LyphoMed, Inc., Rosemont, IL); procaine penicillin G (Pfizer, New York, NY). The following drugs were generous gifts: clonidine and kanamycin (LyphoMed, Inc., Rosemont, IL); DG-5128 (Daiichi Seiyaku Co., Ltd., Tokyo, Japan); and idazoxan (Reckitt and Colman, Kingston-upon-Hull, England).

#### Results

Intrathecal saline injection did not significantly affect any of the parameters measured. In contrast, clonidine altered maternal and fetal hemodynamic parameters in a manner that varied with dose. In the dose range 100–750  $\mu\text{g}$ , intrathecally administered clonidine decreased maternal blood pressure and heart rate, whereas following 1500  $\mu\text{g}$  only heart rate was decreased compared to baseline (fig. 1). Clonidine, 100–300  $\mu\text{g}$ , minimally altered

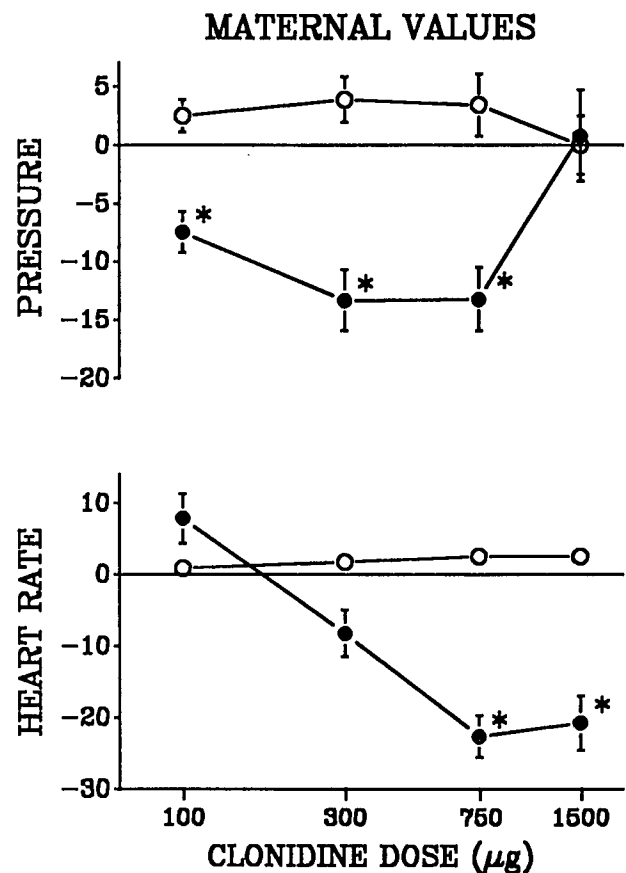


FIG. 1. Maternal effects of intrathecally administered clonidine (●) on blood pressure (upper panel) and heart rate (lower panel). For comparison, effects of sequential injections of saline (O) are also shown. Data expressed as percent change from baseline. Each point represents the mean  $\pm$  SEM of seven to nine animals.

\* $P < 0.05$  versus saline group and versus baseline.

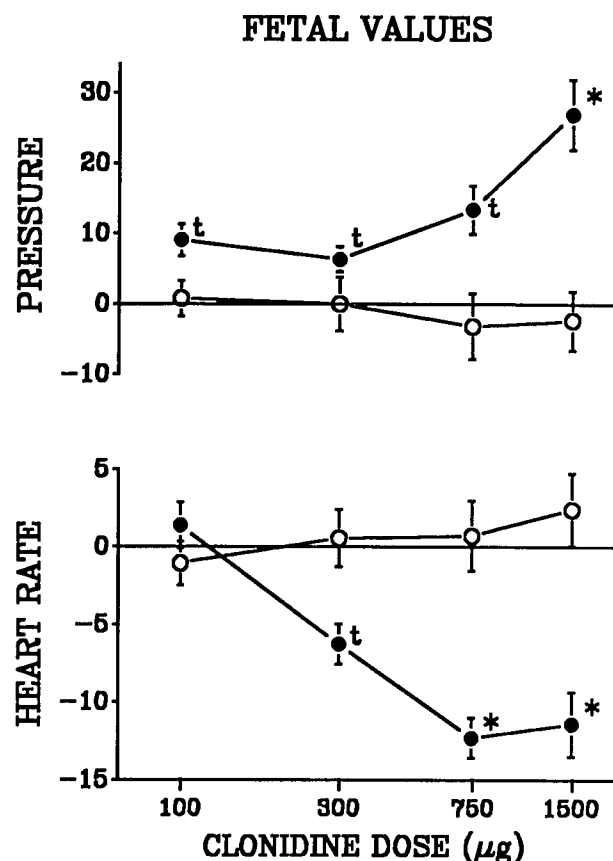


FIG. 2. Fetal effects of intrathecally administered clonidine (●) on blood pressure (upper panel) and heart rate (lower panel). For comparison, effects of sequential injections of saline (○) are also shown. Data expressed as percent change from baseline. Each point represents the mean  $\pm$  SEM of seven to nine animals.

\* $P < 0.05$  versus saline group and versus baseline.

† $P < 0.05$  versus baseline only.

fetal blood pressure and heart rate (no significant difference from saline control), whereas larger doses decreased fetal heart rate and increased fetal blood pressure (fig.

2). Arterial blood gas tensions were affected only following the 1500 µg dose, which caused both maternal and fetal hypoxemia (table 1). Clonidine increased maternal and fetal serum glucose but did not alter serum cortisol (table 2).

Idazoxan increased maternal blood pressure by  $19 \pm 5\%$  ( $P < 0.05$ ) in saline-treated controls without change in maternal heart rate or fetal blood pressure or heart rate. In animals following clonidine injection, idazoxan reversed maternal hypoxemia ( $P_{O_2}$   $55 \pm 4$  mmHg before and  $83 \pm 7$  mmHg after idazoxan;  $P < 0.05$ ) and increased maternal blood pressure by an insignificant amount ( $13 \pm 7\%$ ) without altering other parameters. In contrast, DG-5128 failed to reverse clonidine-induced hypoxemia ( $P_{O_2}$  was  $71 \pm 7$  mmHg before and  $71 \pm 3$  mmHg after DG-5128) and did not alter maternal or fetal hemodynamic parameters in saline- or clonidine-treated ewes.

### Discussion

These data are fundamental to the use of intraspinally administered clonidine for analgesia during pregnancy. In addition to providing safety information, these data, in combination with other animal and human studies, provide a rationale for the preferred dose and route of administration of clonidine.

### MATERNAL EFFECTS

Clonidine decreases blood pressure by actions in the brainstem<sup>18</sup> and spinal cord<sup>19</sup> to decrease sympathetic outflow. Cardiovascular changes of pregnancy<sup>20</sup> could alter the hemodynamic effects of intraspinally applied clonidine. However, these data and data from our earlier study<sup>12</sup> suggest a similar response in pregnant and nonpregnant ewes. Specifically, blood pressure decreases by a similar amount following intrathecal clonidine application and blood pressure decreases more following intrathecal than epidural administration in both pregnant and nonpregnant ewes.<sup>12,15</sup>

TABLE 1. Arterial Blood Gas Tensions Following Intrathecal Clonidine Injection

Parameter	Baseline	100 µg	300 µg	750 µg	1500 µg
Maternal					
pH	7.45 $\pm$ .01	7.47 $\pm$ 0.01	7.47 $\pm$ .01	7.47 $\pm$ .02	7.47 $\pm$ .02
P <sub>CO<sub>2</sub></sub>	34 $\pm$ 0.9	31 $\pm$ 1.1	33 $\pm$ 1.2	32 $\pm$ 1.6	32 $\pm$ 1.6
P <sub>O<sub>2</sub></sub>	103 $\pm$ 3	106 $\pm$ 5	105 $\pm$ 3	99 $\pm$ 4	71 $\pm$ 8*
Fetal					
pH	7.33 $\pm$ .01	7.34 $\pm$ .01	7.34 $\pm$ .01	7.33 $\pm$ .01	7.32 $\pm$ .01
P <sub>CO<sub>2</sub></sub>	48 $\pm$ 0.9	44 $\pm$ 1.1	43 $\pm$ 1.9	44 $\pm$ 1.6	48 $\pm$ 2.3
P <sub>O<sub>2</sub></sub>	17.3 $\pm$ 1.1	16.7 $\pm$ 1.2	16.4 $\pm$ 1.8	15.9 $\pm$ 1.5	12.9 $\pm$ 2.1*

Blood sampled 15 min following injection of each dose indicated. Data expressed as mean  $\pm$  SEM.

\*  $P < 0.05$  versus baseline.

TABLE 2. Effects of Intrathecal Saline and Clonidine on Glucose and Cortisol

Parameter	Treatment			
	Saline		Clonidine	
	Before	After	Before	After
Glucose (mg/dl)				
Maternal	54 ± 4	63 ± 6	55 ± 5	147 ± 15*
Fetal	15 ± 2	17 ± 1	17 ± 1	42 ± 5*
Cortisol (µg/ml)				
Maternal	18 ± 8	46 ± 15	19 ± 8	36 ± 12
Fetal	29 ± 9	40 ± 9	11 ± 3	20 ± 5

Data expressed as mean ± SEM.

\*  $P < 0.05$  versus Before value and versus Saline.

Clonidine increases blood pressure primarily by peripheral vasoconstriction,<sup>21</sup> such that the net effect on blood pressure is a balance between opposing central and peripheral actions. This results in a biphasic dose-response curve following intraspinal clonidine injection with depressor actions predominating at low doses and pressor at high doses in rats,<sup>22</sup> sheep, and humans<sup>11</sup> (fig. 3).

The appropriate dose of clonidine depends on its intended use. When used to enhance the effect of local anesthetics, small doses (2–3 µg/kg) are effective.<sup>13,14</sup> Since spinal local anesthetic injection by itself produces sympathetic blockade, the sympatholytic effect of low-dose clonidine is irrelevant, and addition of clonidine does not decrease blood pressure more than local anesthetic alone.<sup>13,14</sup> When clonidine is administered alone, however, only small (1 µg/kg) or large (10 µg/kg) doses avoid hypotension.<sup>11</sup> Unfortunately, such small doses may be ineffective<sup>11</sup> and such large doses may yield plasma concentrations adequate to produce uterine artery vasoconstriction and decreased uterine blood flow.<sup>23</sup>

Idazoxan is a lipophilic, highly specific  $\alpha_2$ -adrenergic antagonist<sup>24</sup> capable of blocking both central and peripheral  $\alpha_2$ -adrenoceptors following iv administration.<sup>25</sup> Systemically administered idazoxan reverses clonidine-induced hypoxemia in pregnant sheep but without decreasing blood pressure. This is consistent with blockade of the  $\alpha_2$ -adrenoceptor-mediated hypoxemia<sup>26</sup> and central depressor actions<sup>18</sup> of clonidine. Clonidine-induced peripheral vasoconstriction, however, is due to activation of both  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor activation,<sup>27</sup> and only combined blockade of both receptor subtypes abolishes clonidine's pressor effect. The effect of idazoxan on the depressor action of smaller doses of clonidine is currently being examined.

DG-5128 is a hydrophilic, highly specific  $\alpha_2$ -adrenergic antagonist,<sup>28</sup> and its effects following systemic administration are confined to the periphery.<sup>26,28</sup> We anticipated

that systemically administered DG-5128 would reverse clonidine-induced hypoxemia and partially reverse peripheral vasoconstriction, thereby unmasking clonidine's central vasodepressor action. However, in contrast to our results in nonpregnant sheep<sup>26</sup> the same dose of DG-5128 did not alter clonidine's effects in pregnant sheep. This discrepancy may be due in part to the 30–40% increase in plasma volume that occurs during pregnancy that could result in drug dilution and inadequate concentration at adrenergic receptors. Alternatively, DG-5128 may have been unable to competitively antagonize the peripheral effects of high plasma clonidine concentrations (estimated to be >5 ng/ml at the time of antagonist administration).

Clonidine decreases heart rate primarily by a central action.<sup>29</sup> The decrease in heart rate correlates with plasma clonidine concentration.<sup>15</sup> Since plasma clonidine concentrations are similar following epidural or intrathecal injection, this effect does not differ between these routes of administration.<sup>12</sup> Similarly to clonidine's effect on blood pressure, the present study and our earlier study collectively suggest that intrathecally administered clonidine decreases heart rate to a similar degree in nonpregnant and pregnant ewes.<sup>12</sup>

Clonidine injection produces hypoxemia and hyperglycemia in ewes.<sup>15,23,26</sup> These peripheral effects do not occur in mice,<sup>30</sup> dogs,<sup>31</sup> or humans.<sup>11</sup> However, the hemodynamic consequences of hypoxemia may complicate interpretation of hemodynamic measurements following large doses of  $\alpha_2$ -adrenergic agonists in sheep. Although clonidine may inhibit cortisol secretion,<sup>32</sup> this has not been observed after intraspinal clonidine injection in sheep<sup>15</sup> or humans.<sup>11</sup>

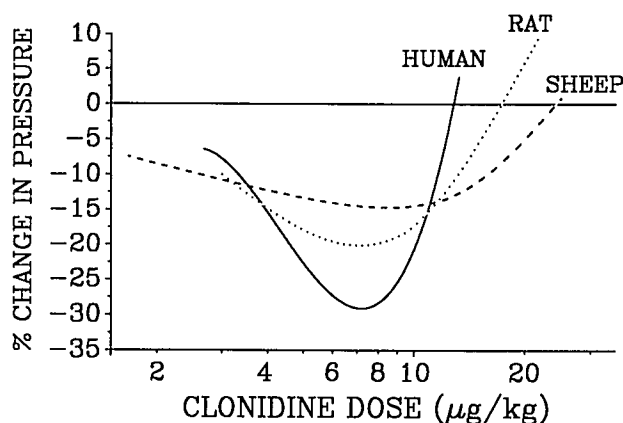


FIG. 3. Effect of intrathecal clonidine injection in rats (dotted line) and sheep (dashed line) and epidural clonidine injection in humans (solid line) on blood pressure. Data are expressed as percent change from baseline, and curves are monoexponential fits of raw data.

### FETAL EFFECTS

Based on clonidine's pharmacokinetics following intraspinal administration,<sup>12</sup> one would expect similar fetal effects from epidural or intrathecal injection. These results support this hypothesis: fetal blood pressure and heart rate are similar following maternal epidural<sup>15</sup> or intrathecal injection of clonidine 300  $\mu\text{g}$ . Clonidine in doses  $\leq 300 \mu\text{g}$  is well tolerated by the fetus, despite small reductions in maternal blood pressure. However, decreased fetal heart rate at doses greater than 100  $\mu\text{g}$  may complicate interpretation of fetal heart rate monitoring. Whether such small doses of clonidine also affect the fetus' ability to respond to hemodynamic or hypoxemic stress is currently unknown.

The fetal effects of large maternal doses of clonidine are likely due to a combination of direct actions on the fetus and alterations in maternal physiology.<sup>23</sup> Hypoxemia is likely due to decrease in maternal arterial  $\text{P}_{\text{O}_2}$ , because it does not occur following direct fetal infusion of clonidine in a dose that produces similar fetal plasma clonidine concentrations.<sup>23</sup> Fetal hypertension and bradycardia may occur in response to hypoxemia but are also observed following direct fetal clonidine infusion,<sup>‡</sup> suggesting a mixed etiology. Although clonidine in doses up to 900  $\mu\text{g}$  does not cause hypoxemia in humans, the fetal effects of such large doses, primarily bradycardia, would limit the usefulness of such therapy in the pregnant patient.

In summary, intrathecal injection of clonidine in low doses such as may be used to augment intrathecal or epidural anesthesia with other agents has minimal maternal or fetal hemodynamic effects. Larger doses ( $>300 \mu\text{g}$ ) such as would be required for effective analgesia alone decrease fetal heart rate and may decrease maternal blood pressure, depending on dose. These data support the safety of a low dose of clonidine for intrathecal or epidural analgesia during pregnancy.

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

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