

The Effect of Intravenously Administered 2-Chloroprocaine upon Uterine Artery Blood Flow Velocity in Gravid Guinea Pigs

David H. Chestnut, M.D.,* Carl P. Weiner, M.D.,† James E. Herrig, B.S.‡

The purpose of the present study was to assess the effect of intravenously administered 2-chloroprocaine upon uterine artery blood flow velocity (UBFV) in gravid guinea pigs. Ten experiments were performed in ten chronically instrumented animals between 0.7 and 0.9 of timed gestation. Each animal received four solutions of 2-chloroprocaine in random order: 1) 0.67 mg/kg; 2) 1.34 mg/kg; 3) 2.0 mg/kg; and 4) 1.34 mg/kg, with epinephrine 0.2 µg/kg. Six animals received a fifth solution, 0.2 ml of saline control. 2-Chloroprocaine 1.34 mg/kg significantly increased maternal mean arterial pressure (MMAP) at 30 s after injection, and 2-chloroprocaine 2.0 mg/kg significantly increased MMAP through 2 min. 2-Chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg, also significantly increased MMAP through 2 min. No other solution significantly altered MMAP. 2-Chloroprocaine 2.0 mg/kg significantly decreased UBFV at 30 s after injection. 2-Chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg, significantly decreased UBFV through 2 min. No other solution significantly altered UBFV. The authors conclude that iv administration of 2-chloroprocaine with epinephrine significantly decreased UBFV in pregnant guinea pigs. In contrast, only the largest dose (i.e., 2.0 mg/kg) of 2-chloroprocaine alone transiently decreased UBFV. These data suggest that, in doses up to 1.34 mg/kg, 2-chloroprocaine alone may not decrease uterine blood flow when used as a marker for intravenous injection in obstetric patients. (Key words: Local anesthetics: 2-chloroprocaine. Measurement techniques: Doppler flow probe. Sympathetic nervous system, catecholamines: epinephrine. Uterus: blood flow velocity.)

THE POTENTIAL for unintentional iv or subarachnoid injection of local anesthetic during induction of epidural anesthesia mandates the administration of a test dose before injection of a large therapeutic dose. Moore and Batra¹ first suggested that the epidural test dose should contain 15 µg of epinephrine. A subsequent increase in heart rate would indicate that iv injection had occurred, but an epinephrine-containing test dose may be neither sensitive nor specific for iv injection in laboring women²⁻⁵ and may decrease uterine blood flow and precipitate fetal distress.^{4,6,7} Grice *et al.*⁸ reported that iv injection of 100 mg of 2-chloroprocaine without epinephrine is 100% sensitive and 100% specific for production of symptoms of iv injection in male volunteers. The pur-

pose of this study was to assess the effect of intravenously administered 2-chloroprocaine upon uterine artery blood flow velocity (UBFV) in gravid guinea pigs.

Methods

Pulsed Doppler ultrasound was used to continuously monitor UBFV in chronically instrumented pregnant guinea pigs. The magnitude of change in the Doppler shift was measured, and all measurements are reported as percentage of baseline. We recently reported the validation of this model; the measured flow velocity was both directly proportional and linear to actual uterine artery blood flow ($R = 0.984$).⁹

The protocol was approved by the University of Iowa Animal Care Committee. We have previously described in detail the method of animal instrumentation.^{7,9-11} Briefly, mixed-breed guinea pigs of known mating were obtained from a commercial breeder at 0.6 of timed gestation (normal term gestation = 65 days) and allowed to acclimate to the laboratory environment for 2 days. With the use of sterile technique and general anesthesia (intramuscular xylazine 0.8 mg/kg and intraperitoneal ketamine 80 mg/kg, supplemented by local infiltration of 1.0% lidocaine), a ventral, midline neck incision was performed. Catheters (polyethylene 50, inside diameter = 0.58 mm, outside diameter = 0.96 mm) were inserted into the external jugular vein and carotid artery. The arterial catheter was advanced into the descending aorta below the origin of the renal arteries. Through a midline abdominal incision, a 5–10 mm segment of uterine artery was dissected free from the mesometrium with microsurgical techniques, and a miniaturized Doppler flow probe (20 MHz crystal, 0.75 mm in diameter, 100 mg in weight) was fixed to the underside of the vessel with a cyanoacrylic glue. Care was taken to confine the glue to the underside and prevent encasement of the artery. (Proper probe attachment does not result in maternal hypertension or fetal growth retardation, and UBFV increases progressively as expected during the remainder of the gestation.⁹) A probe shield was constructed *in situ* with the use of a medical grade silicone polymer. Probe wires and catheters were exteriorized *via* a stab wound in the nape of the neck. Catheter patency was maintained by a daily 1-ml bolus of heparin-saline solution (300 u/ml).

After surgery, each animal remained in a separate cage within a restricted area. Guinea pig chow, fresh vegetables,

* Associate Professor of Anesthesia and Obstetrics and Gynecology.

† Associate Professor of Obstetrics and Gynecology.

‡ Research Assistant.

Received from the Departments of Anesthesia and Obstetrics and Gynecology, University of Iowa College of Medicine, Iowa City, Iowa 52242. Accepted for publication September 19, 1988. Presented in part at the Annual Meeting of the Society for Gynecologic Investigation, Baltimore, Maryland, March 19, 1988, and at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 11, 1988.

Reprints will not be available.

TABLE 1. Baseline Maternal Hemodynamic Measurements

| | 2-CP 0.67 mg/kg (n = 10) | 2-CP 1.34 mg/kg (n = 10) | 2-CP 2.0 mg/kg (n = 10) | 2-CP 1.34 mg/kg, with EPI, 0.2 µg/kg (n = 10) | Saline Control (n = 6) |
|-------------|--------------------------------|--------------------------------|-------------------------------|---|---------------------------|
| MHR | 202 ± 9 | 204 ± 10 | 197 ± 14 | 192 ± 12 | 191 ± 11 |
| MMAP (mmHg) | 41 ± 3 | 43 ± 3 | 43 ± 3 | 38 ± 3 | 45 ± 4 |
| UBFV (kHz) | 2.21 ± 0.36 | 2.30 ± 0.38 | 2.28 ± 0.34 | 2.20 ± 0.33 | 2.48 ± 0.46 |

2-CP = 2-chloroprocaine; EPI = epinephrine; MHR = maternal heart rate; MMAP = maternal mean arterial pressure; UBFV = uterine

artery blood flow velocity, recorded as the mean velocity signal. All values are reported as mean ± SEM.

and water were supplied *ad libitum*. The room lights were cycled (12 h on, 12 h off). No experiments were undertaken until normal weight gain and activity had resumed and in no case before the eighth postoperative day. All experiments were performed with the animal in familiar surroundings, with unimpaired mobility and ready access to food.

Experiments were performed between 50 and 60 days gestation. The mean (±SD) animal weight on experiment days was 873 ± 99 g. Maternal heart rate (MHR), maternal mean arterial pressure (MMAP), and mean UBFV were recorded continuously on a biomedical strip chart recorder (Sensormedics R511A®, Sensormedics, Anaheim, California).

Ten experiments were performed in 10 chronically instrumented animals. Each animal received four solutions of 2-chloroprocaine each over 15 s intravenously, in random order, 30 min apart: 1) 2-chloroprocaine 0.67 mg/kg; 2) 2-chloroprocaine 1.34 mg/kg; 3) 2-chloroprocaine 2.0 mg/kg; and 4) 2-chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg. Six animals received a fifth solution, which was 0.2 ml of saline control. (When calculated on a milligram per kilogram basis, 1.34 mg/kg of 2-chloroprocaine and 0.2 µg/kg of epinephrine approximate the recommended test dosages of 2-chloroprocaine and epinephrine, when administered to a patient weighing 75 kg). Each solution was diluted with normal saline to a total volume of 0.2 ml.

Changes in MHR, MMAP, and UBFV during the 5 min after administration of a solution were compared with the preinjection baseline for that solution. Each measurement is expressed as the mean (±SEM) percent of the baseline for that solution. Statistical analysis was by repeated measures analysis of variance, followed by *t* tests for individual measurements. Bonferroni adjustment was used when appropriate. *P* < 0.05 was considered significant.

Results

The five treatment groups were similar with regard to baseline hemodynamic measurements (table 1).

2-Chloroprocaine with epinephrine significantly increased MHR at 30 s after injection (fig. 1A). Specifically, MHR was 105 ± 2% of baseline at 30 s. No other solution significantly altered MHR. 2-Chloroprocaine 1.34 mg/kg significantly increased MMAP at 30 s after injection (fig. 1B). Specifically, MMAP was 107 ± 2% of baseline at 30 s. 2-Chloroprocaine 2.0 mg/kg significantly increased MMAP through 2 min. Specifically, MMAP was 113 ± 3% of baseline at 30 s and remained 106 ± 3% of baseline at 2 min. 2-Chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg, significantly increased MMAP through 2 min. Specifically, MMAP was 127 ± 6% of baseline at 30 s and remained 107 ± 2% of baseline at 2 min. No other solution significantly altered MMAP. 2-Chloroprocaine 2.0 mg/kg significantly decreased UBFV at 30 s after injection (fig. 1C). Specifically, UBFV was 89 ± 5% of baseline at 30 s. 2-Chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg, significantly decreased UBFV through 2 min. Specifically, UBFV was 43 ± 6% of baseline at 30 s and remained 86 ± 6% of baseline at 2 min. No other solution significantly altered UBFV.

Discussion

In an earlier study using this model, we⁷ observed that bolus iv administration of epinephrine (0.2, 0.5, and 1.0 µg/kg) resulted in significant, dose-related reductions in UBFV. (We⁹ had earlier reported that changes in UBFV are directly proportional and linear to changes in actual uterine artery blood flow.) Others have observed similar, dose-related decreases in uterine blood flow after bolus and continuous iv infusion of epinephrine in gravid ewes.^{6,12,13} We⁷ and others^{4,6} have therefore criticized the epinephrine-containing test dose for its potential to precipitate fetal distress. Rebuttal of this criticism includes the following arguments. First, the decreases in UBFV and uterine blood flow after bolus iv epinephrine in pregnant guinea pigs and sheep were transient. Similar transient declines in perfusion occur during normal uterine contractions. Brar *et al.*¹⁴ recently observed transient reductions in uteroplacental perfusion during uterine contractions in healthy pregnant women. Second, the adverse

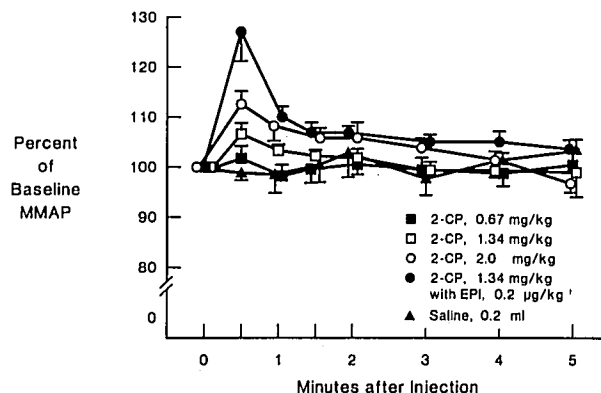
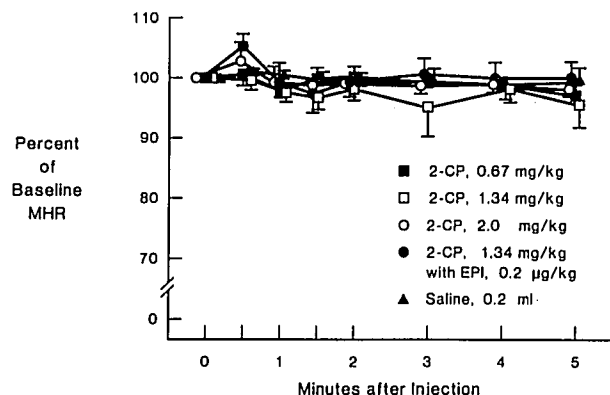
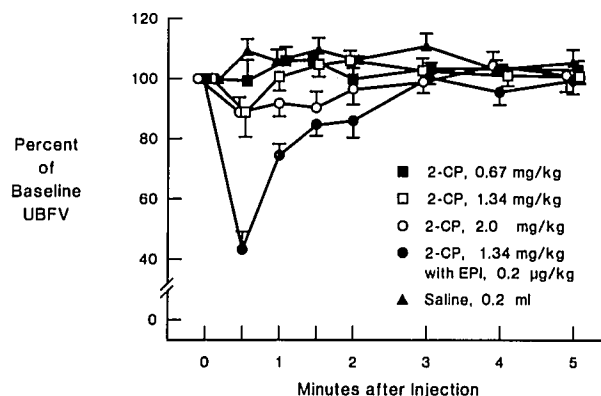


FIG. 1. A (upper, left). Responses over time of maternal heart rate (MHR). 2-Chloroprocaine (2-CP) with epinephrine (EPI) significantly increased MHR at 30 s. No other solution significantly altered MHR. B (upper, right). Responses over time of maternal mean arterial pressure (MMAP). 2-CP 1.34 mg/kg significantly increased MMAP at 30 s after injection, and 2-CP 2.0 mg/kg significantly increased MMAP through 2 min. 2-CP 1.34 mg/kg, with EPI 0.2 µg/kg, also significantly increased MMAP through 2 min. No other solution significantly altered MMAP. C (lower). Responses over time of uterine artery blood flow velocity (UBFV). 2-CP 2.0 mg/kg significantly decreased UBFV at 30 s after injection. 2-CP 1.34 mg/kg, with EPI 0.2 µg/kg, significantly decreased UBFV through 2 min after injection. No other solution significantly altered UBFV. Each value is expressed as the mean (\pm SEM)% of the preinjection baseline for that solution



consequences to mother and fetus of unrecognized iv injection of a large therapeutic dose of local anesthetic would likely be more severe. Third, there has been no published report of adverse neonatal outcome after iv injection of an epinephrine-containing test dose. Nonetheless, it would seem advantageous to administer a test dose that does not decrease uterine blood flow.

Wallis *et al.*¹⁵ observed that epidural administration of 2-chloroprocaine 90–120 mg, with epinephrine 60–80 µg, resulted in a transient 14% decrease in uterine blood flow in gravid ewes. However, epidural administration of 90–120 mg of 2-chloroprocaine alone did not alter uterine blood flow. To our knowledge, there are no published data on the effect of intravenously administered 2-chloroprocaine on uterine blood flow in pregnant patients or animals. Fishburne *et al.*¹⁶ noted dose-related decreases in uterine blood flow after intraarterial injection of bupivacaine, 2-chloroprocaine, and lidocaine in gravid ewes. We note two limitations to that study. First, the local anesthetic agents were injected directly into the uterine artery to mimic the “high, sustained uterine arterial concentrations” that occur after paracervical block. They noted that “the uterine arterial concentrations of anesthetic drugs that caused pronounced effects on UBF and myometrial tonus in this study are well above blood levels observed during epidural anesthesia. Even when an in-

travenous bolus injection complicates epidural anesthesia, the concentration of anesthetic drug is significantly diluted before the uterine vasculature is reached.”¹⁶ Second, the activity of plasma pseudocholinesterase in sheep is less than 10% of that in humans. In contrast, plasma pseudocholinesterase activity in guinea pigs is similar to that in humans.^{17,18} In the present study, intravenous administration of 0.67 and 1.34 mg/kg of 2-chloroprocaine alone did not significantly decrease UBFV, and intravenous administration of 2.0 mg/kg of 2-chloroprocaine transiently decreased UBFV $11 \pm 5\%$. Therefore, if given a sufficiently large dose, the guinea pig uterine artery does constrict after intravenous administration of 2-chloroprocaine.

The reliability of a 2-chloroprocaine test dose depends upon consistent recognition of subjective symptoms of iv injection. Grice *et al.*⁸ reported that iv injection of 100 mg of 2-chloroprocaine was 100% sensitive and 100% specific for production of symptoms of iv injection in male volunteers. The sensitivity and specificity of a 2-chloroprocaine test dose have yet to be established in pregnant women.

We conclude that iv administration of 2-chloroprocaine 1.34 mg/kg, with epinephrine 0.2 µg/kg, significantly decreased UBFV in gravid guinea pigs. In contrast, only the largest dose (*i.e.*, 2.0 mg/kg) of 2-chloroprocaine alone

transiently decreased UBFV. These data suggest that, in doses up to 1.34 mg/kg, 2-chloroprocaine alone may not decrease uterine blood flow when used as a marker for intravenous injection in obstetric patients.

References

1. Moore DC, Batra MS: The components of an effective test dose prior to epidural block. *ANESTHESIOLOGY* 55:693-696, 1981
2. Chestnut DH, Weiner CP: Monitoring maternal heart rate during epidural injection of a test dose containing epinephrine (letter). *ANESTHESIOLOGY* 64:839-840, 1986
3. Cartwright PD, McCarroll SM, Antzaka C: Maternal heart rate changes with a plain epidural test dose. *ANESTHESIOLOGY* 65:226-228, 1986
4. Leighton BL, Norris MC, Sosis M, Epstein R, Chayen B, Larijani GE: Limitations of epinephrine as a marker of intravascular injection in laboring women. *ANESTHESIOLOGY* 66:688-691, 1987
5. Chestnut DH, Owen CL, Brown CK, Vandewalker GE, Weiner CP: Does labor affect the variability of maternal heart rate during induction of epidural anesthesia? *ANESTHESIOLOGY* 68:622-625, 1988
6. Hood DD, Dewan DM, James FM: Maternal and fetal effects of epinephrine in gravid ewes. *ANESTHESIOLOGY* 64:610-613, 1986
7. Chestnut DH, Weiner CP, Martin JG, Herrig JE, Wang J: Effect of intravenous epinephrine upon uterine artery blood flow velocity in the pregnant guinea pig. *ANESTHESIOLOGY* 65:633-636, 1986
8. Grice SC, Eisenach JC, Dewan DM, Mandell G: Evaluation of 2-chloroprocaine as an effective intravenous test dose for epidural analgesia (abstract). *ANESTHESIOLOGY* 67:A627, 1987
9. Weiner CP, Herrig J, Wang J, Wang L, Farley D, Van Orden D, Chestnut D: Chronic measurement of uterine artery flow velocity in the gravid guinea pig using a Doppler probe. *J Reprod Fertil* 77:247-256, 1986
10. Chestnut DH, Weiner CP, Wang JP, Herrig JE, Martin JG: The effect of ephedrine upon uterine artery blood flow velocity in the pregnant guinea pig subjected to terbutaline infusion and acute hemorrhage. *ANESTHESIOLOGY* 66:508-512, 1987
11. Chestnut DH, Ostman LG, Weiner CP, Hdez MJ, Wang JP: The effect of vasopressor agents upon uterine artery blood flow velocity in the gravid guinea pig subjected to ritodrine infusion. *ANESTHESIOLOGY* 68:363-366, 1988
12. Greiss FC: The uterine vascular bed: Effect of adrenergic stimulation. *Obstet Gynecol* 21:295-301, 1963
13. Rosenfeld CR, Barton MD, Meschia G: Effects of epinephrine on distribution of blood flow in the pregnant ewe. *Am J Obstet Gynecol* 124:156-163, 1976
14. Brar HS, Platt LD, DeVore GR, Horenstein J, Medearis AL: Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. *Am J Obstet Gynecol* 158:952-956, 1988
15. Wallis KL, Shnider SM, Hicks JS, Spivey HT: Epidural anesthesia in the normotensive pregnant ewe: Effects on uterine blood flow and fetal acid-base status. *ANESTHESIOLOGY* 44:481-487, 1976
16. Fishburne JI, Greiss FC, Hopkinson R, Rhyne AL: Responses of the gravid uterine vasculature to arterial levels of local anesthetic agents. *Am J Obstet Gynecol* 133:753-761, 1979
17. Kruckenberg SM, Vestweber JGE: Whole blood cholinesterase activity of laboratory and domestic animals: Contribution of erythrocyte and serum enzymes. *VM SAC* 68:54-55, 1973
18. Morse CS: Interconversion of cholinesterase measurements by the Δ pH method of Michel and the DTNB method of Garry and Routh. *Clin Toxicol* 7:389-393, 1974