Anesthesiology
63:217–219, 1985

Placental Transfer of Ephedrine Does Not Affect Neonatal Outcome

SAMUEL C. HUGHES, M.D.,* MAJOR MICHAEL G. WARD, M.D.,† GERSHON LEVINSON, M.D.,‡
SOL M. SHNIDER, M.D.,§ RICHARD G. WRIGHT, M.D.,¶ LARRY D. GRUENKE, PH.D.,**
JOHN C. CRAIG, PH.D.††

Ephedrine is widely used to prevent and treat hypotension resulting from spinal or epidural anesthesia and analgesia in parturients. We previously demonstrated that the intramuscular or intravenous administration of ephedrine significantly increases fetal heart rate (FHR) and beat-to-beat variability.[1] We now investigate whether changes in FHR are due to placental transfer of the drug, and, if so, whether ephedrine has direct effects on the newborn.

MATERIALS AND METHODS

This study was approved by the Committee on Human Research; informed consent was obtained from all participants. We studied 40 patients undergoing elective or emergency cesarean section who were given lumbar epidural anesthesia with 3% chloroprocaine (n = 11), 0.5% bupivacaine (n = 16), or both 0.5% bupivacaine and 3% chloroprocaine (n = 13). Each patient was prehydrated with 1,000 ml of a balanced salt solution before the epidural block, and left uterine displacement was maintained. Twenty-one patients were given ephedrine 25–50 mg im to prevent hypotension; four of them were given an additional 10–20 mg of intravenous ephedrine to treat hypotension. The remaining 19 patients, the control group, received no ephedrine: blood pressure was kept stable with fluid therapy and left uterine displacement. In the control group, nine patients were given bupivacaine; five, chloroprocaine; and five, both anesthetics. Fetal heart rate was determined before administration of ephedrine. At delivery, Apgar scores were noted; and blood samples were obtained from the maternal artery and from a double-clamped umbilical-cord vein and artery for determination of ephedrine levels and acid–base status. At 5 and 30 min after birth, neonatal heart rate was recorded and blood pressure measured (Marion Scientific Corporation Infrasonde). The unpaired Student's t test was used to compare blood–gas data and neonatal heart rate.

Ephedrine levels were measured using selected ion recording and combined gas chromatography/mass spectrometry.[2] Ephedrine-N-methyl-d3 was synthesized for use as the internal standard. Plasma samples (typically 2 ml) were treated with 3 μg of the internal standard, made basic with 10% aqueous sodium hydroxide and extracted with benzene. For gas chromatography, extracts were purified by an acid–base process and evaporated and treated with derivatizing reagents to form the mixed N-trifluoroacetamide O-trimethylsilyl derivative of ephedrine. Selected ion records were obtained at m/e 227 (M^+ minus phenyl-CHO) for ephedrine and at m/e 230 for ephedrine-d3 using a 2-mm × 2-mm glass U-tube GC column packed with 1% OV-17 on Gas Chrom Q® (Applied Science). Ion current ratios were compared with standard curves obtained by analyzing blank plasma samples spiked with known amounts of ephedrine.

The presence of ephedrine in pooled fetal plasma samples was further confirmed by obtaining a complete mass spectrum of the ephedrine derivative gas chromatographic peak. Linear correlations between ephedrine concentrations in the maternal artery, umbilical vein, and umbilical artery were calculated by the method of least squares. Possible correlations with Apgar scores and acid–base status were also examined.

RESULTS

At birth, ephedrine concentrations ranged from 75 to 298 ng/g of plasma in maternal arterial blood and

* Assistant Clinical Professor of Anesthesia.
† Chief, Anesthesia and Operative Service, Fitzsimons Army Medical Center, Aurora, Colorado.
‡ Associate Professor of Anesthesia and Obstetrics, Gynecology and Reproductive Sciences.
§ Professor of Anesthesia and Obstetrics, Gynecology and Reproductive Sciences.
¶ Assistant Clinical Professor of Anesthesia, University of California, Davis, California.
** Assistant Research Chemist.
†† Professor of Chemistry and Pharmaceutical Chemistry.

Received from the Departments of Anesthesia and Obstetrics, Gynecology, Reproductive Sciences, and from the School of Pharmacy, University of California, San Francisco, California. Accepted for publication March 25, 1985. Supported in part by NIH Anesthesia Research Center Grant 1P01 GM15571-11 and the Anesthesia Research Foundation. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 1979.

Address reprint requests to Dr. Hughes: Department of Anesthesia, San Francisco General Hospital, Room 3S50, 1001 Potrero Avenue, San Francisco, California 94110.

Key words: Anesthesia: obstetric. Placenta. Pregnancy. Sympathetic nervous system: sympathomimetic agents, ephedrine.

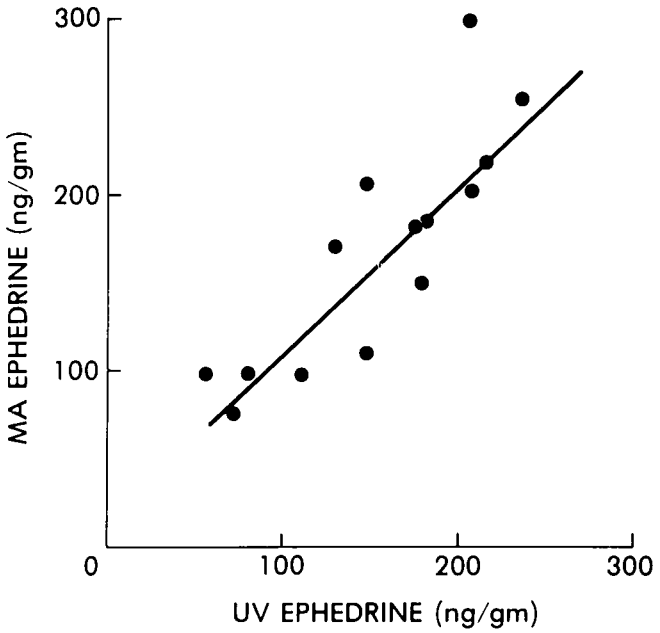

FIG. 1. The plot of ephedrine levels in maternal arterial blood (MA) against ephedrine levels in umbilical-cord venous blood (UV), in ng/g of plasma. The r value is 0.73. The equation for the regression line is: y = 30.9 + 0.73x.

from 56 to 236 ng/g in umbilical-cord venous blood. The level of ephedrine in fetal blood was directly related to the level in maternal blood (fig. 1). The ratio of the drug concentration in umbilical-cord venous blood to that in maternal arterial blood (UV/MA) was 0.71 and was not related to the time following ephedrine administration (range 38–98 min). We obtained enough umbilical-cord arterial blood to determine ephedrine levels in 11 of the 21 patients given ephedrine: the ratio of the drug concentration in umbilical-cord arterial blood

TABLE 1. Comparison of Neonates of Mothers Given Ephedrine (Ephedrine) with Neonates of Mothers not Given Ephedrine (Control)

	Control (n = 19)	Ephedrine (n = 21)
Apgar scores (no. of babies)		
<6 at 1 min	4	4
<8–10 at 5 min	1	0
Neonatal systolic blood pressure (mmHg)		
At 5 min	64 ± 2.0 (n = 13)	63 ± 2.4 (n = 9)
At 30 min	63 ± 1.5 (n = 15)	63 ± 1.8 (n = 7)
Neonatal heart rate (beats/min)		
At 5 min	156 ± 3.6 (n = 19)	159 ± 4.0 (n = 13)
At 30 min	147 ± 3.2 (n = 19)	165 ± 3.8* (n = 12)

Values are mean ± SEM.
* Significantly different ($P < 0.01$) when compared with the control group at the same time.

TABLE 2. Blood Gas Analyses for Neonates of Mothers Given Ephedrine (Ephedrine) *versus* Neonates of Mothers not Given Ephedrine (Controls)

	Controls (n = 19)	Ephedrine (n = 21)
Umbilical vein		
*p*H	7.34 ± 0.02	7.30 ± 0.02
P_{CO_2} (mmHg)	42.9 ± 1.6	45.4 ± 0.17
Base excess (mEq/l)	−3.0 ± 0.8	−4.2 ± 0.07
P_{O_2} (mmHg)	30.4 ± 1.4	32.6 ± 1.7
Umbilical artery		
*p*H	7.30 ± 0.02	7.20 ± 0.02*
P_{CO_2} (mmHg)	55.6 ± 1.9	60.9 ± 2.8
Base excess (mEq/l)	−3.4 ± 0.8	−4.8 ± 0.7
P_{O_2} (mmHg)	14.5 ± 1.1	14.7 ± 1.4

Values are mean ± SEM.
* $P < 0.005$ compared with control.

to that in umbilical-cord venous blood (UA/UV) was 0.83.

No relationship was found between ephedrine levels and Apgar scores at 1 or 5 min; all infants of mothers given ephedrine had Apgar scores of 8 or more at 5 min (table 1). At 5 and 30 min postpartum, infants of mothers given ephedrine had values for systolic blood pressure that did not differ significantly from values for the control group. At 30 min of age, infants of mothers given ephedrine had significantly faster heart rates than did control babies (165 *vs.* 147 beats/min) (table 1). No relationship was found between the neonatal ephedrine levels and umbilical-cord acid–base values (table 2).

DISCUSSION

Ephedrine is the vasopressor of choice for treating hypotension in parturients[3,4] after more conservative measures (left uterine displacement, rapid fluid infusion, or Trendelenburg positioning) have been taken to increase venous return and have not been successful in raising blood pressure. However, the use of vasopressor therapy in obstetrics carries special risks, including uterine vasoconstriction and hypertonus,[5] both of which may be deleterious to the fetus.

In animal studies, uterine vasoconstriction has occurred with the predominately alpha-adrenergic drugs, *e.g.*, methoxamine and phenylephrine.[6,7] On the other hand, ephedrine, a largely beta-adrenergic drug, returns uterine blood flow to near control values and restores maternal blood pressure.[8] Correction of maternal hypotension with this drug arrested fetal deterioration and returned blood–gas and base-excess values toward the normal range.[8] Multiple clinical studies have demonstrated the efficacy and safety of ephedrine. However, the increased FHR and beat-to-beat variability after administration of ephedrine led us to investigate its

placental transfer and possible direct effects on the newborn.

The central nervous system effects of ephedrine, similar to those of amphetamine but much milder, indicate that ephedrine crosses the blood–brain barrier and thus would be expected to cross the placenta.[9] However, Ralston *et al.*[10] reported that administration of ephedrine in the pregnant ewe did not significantly increase mean arterial blood pressure in the fetus.

In this study, we document the placental transfer of ephedrine, the fetal blood level of the drug at delivery being approximately 70% of the maternal level. The increase in FHR we observed previously occurred 40–50 min after intramuscular administration to the mother.[1] In this study, blood samples for determination of ephedrine levels were obtained 38–93 min after administration of ephedrine, encompassing the period of expected fetal effects. The presence of ephedrine in the fetal circulation seems to have no deleterious effects on fetal well-being or neonatal outcome, although the mean umbilical artery *p*H value in the ephedrine group was significantly lower than that in the control group. This is explained in part by several patients in the ephedrine group with obvious obstetric problems for whom it was felt that an epidural was otherwise appropriate. The minimal neonatal tachycardia that may result 30 min postpartum is not of clinical significance.

In a study of the efficacy and safety of prophylactic intramuscular administration of ephedrine,[11] fetal tachycardia did not occur, newborn heart rate did not change at 15 and 60 min postpartum, and there were no neurobehavioral effects. However, hypertension occurred in mothers given 50 mg of ephedrine prophylactically, a complication that did not occur in our study. In a recent review of 583 consecutive cesarean deliveries with epidural anesthesia, the routine prophylactic use of intramuscular ephedrine before epidural anesthesia did not seem to confer any advantage.[12] Ephedrine was still needed in many cases to treat hypotension, especially when local anesthetics having a more rapid onset were used.

This study documents that ephedrine crosses the placenta, an event that would explain changes in FHR. The minimal changes in newborn heart rate at 30 min are probably not clinically significant. We believe ephedrine is the vasopressor of choice for treating maternal hypotension associated with epidural anesthesia.

References

1. Wright RG, Shnider SM, Levinson G, Rolbin SH, Parer JT: The effect of maternal administration of ephedrine on fetal heart rate and variability. Am J Obstet Gynecol 57:734–738, 1981
2. Gruenke LD, Craig JC, Bier DM: An improved selection ion recording system for precise isotope ratio determination. Biomed Mass Spectrom 7:381–384, 1980
3. Shnider SM, Levinson G: Anesthesia for cesarean section, Anesthesia for Obstetrics. Baltimore, Williams and Wilkins, 1979, pp 254–275
4. James FM III, Greiss FC Jr, Kemp RA: An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. ANESTHESIOLOGY 33:25–34, 1970
5. Vasicka A, Hutchinson HT, Eng M, Allen CR: Spinal and epidural anesthesia, fetal and uterine response to acute hypo- and hypertension. Am J Obstet Gynecol 90:800–810, 1964
6. Shnider SM, deLorimier AA, Asling JH, Morishima HO: Vasopressors in obstetrics. II. Fetal hazards of methoxamine administration during obstetric spinal anesthesia. Am J Obstet Gynecol 108:680–686, 1970
7. Greiss FC Jr, Van Wilkes D: Effects of sympathomimetic drugs and angiotensin in the uterine vascular bed. Obstet Gynecol 23:925–930, 1964
8. Shnider SM, deLorimier AA, Holl JW, Chapler FK, Morishima HO: Vasopressors in obstetrics. I. Correction of fetal acidosis with ephedrine during spinal hypotension. Am J Obstet Gynecol 102:911–919, 1968
9. Gilman AG, Goodman LS, Gilman A: Goodman and Gilman's The Pharmacological Basis of Therapeutics, sixth edition. New York, Macmillan, 1980, pp 163–164
10. Ralston DH, Shnider SM, de Lorimier AA: Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. ANESTHESIOLOGY 40:354–370, 1974
11. Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgint S: Prophylactic intramuscular ephedrine before epidural anaesthesia for caesarean section: Efficacy and actions on the foetus and newborn. Can Anaesth Soc J 29:148–153, 1982
12. Brizgys RV, Shnider SM, Kotelko DM, Dailey PA, Levinson G: The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section (abstract). ANESTHESIOLOGY 57:A395, 1982