

Transplacental Passage and Hemodynamic Effects of Esmolol in the Gravid Ewe

Pontus L. Östman, M.D.,* David H. Chestnut, M.D.,† Jean E. Robillard, M.D.,‡
Carl P. Weiner, M.D.,§ Michael J. Hdez, B.A.¶

Using a chronic maternal-fetal sheep preparation, the authors determined the transplacental passage and the hemodynamic changes consequent to maternal administration of esmolol. Fifteen experiments were performed in six chronically instrumented pregnant ewes near term. Each animal received esmolol iv, $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, for 4 min and then $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 6 min. Maternal and fetal blood esmolol concentrations (mean \pm SEM) were 1.2 ± 0.28 and $0.1 \pm 0.03 \mu\text{g}/\text{ml}$, respectively, at the completion of the infusion, and $0.03 \pm 0.01 \mu\text{g}/\text{ml}$ in the mother and not detectable in the fetus 10 min after stopping the infusion. Despite the relatively low blood esmolol concentration in the fetus compared to the mother, the hemodynamic effects in the fetus were similar to those in the mother. The maximal decrease of maternal mean arterial pressure (MAP) and heart rate (HR) were 7 ± 2 and $14 \pm 3\%$ (mean \pm SEM), respectively ($P < .05$). The maximal decrease of fetal MAP and HR were 7 ± 2 and $12 \pm 3\%$, respectively ($P < .05$). No changes were seen in maternal or fetal acid-base variables, and intra-amniotic pressure was not affected. The authors conclude that esmolol has a rapid but relatively small transplacental passage, and it is eliminated rapidly from both maternal and fetal plasma. (Key words: Anesthesia: obstetric. Placental, transfer: esmolol. Pregnancy, hemodynamics: fetal; maternal. Sympathetic nervous system, β -adrenergic receptor antagonist: esmolol.)

ESMOLOL (methyl 3-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl}propionate hydrochloride) is a new water-soluble β -1-adrenoceptor antagonist with a rapid onset of action, a distribution half-life of 2 min, and an elimination half-life of approximately 9 min in non-pregnant patients.¹ Esmolol is rapidly and extensively metabolized in the blood by hydrolysis of the methyl ester resulting in an acid metabolite of esmolol and a clinically insignificant amount of methanol. An esterase in the red blood cell cytosol is responsible for the metabolism of esmolol.²

Rapid onset of action, short elimination half-life, and metabolic inactivation in the vascular compartment in-

dependent of hepatic or renal function make esmolol an attractive choice for the treatment of perioperative hypertension in obstetric patients. We hypothesized that, due to its low lipid solubility and rapid metabolism, a limited amount of esmolol would cross from the maternal to the fetal circulation. However, because of the relative immaturity of the adrenergic system in the fetus, β -adrenergic receptor sensitivity might be increased and a relatively low esmolol concentration could have a substantial effect. The purpose of the present study was to determine the transplacental passage and hemodynamic changes of esmolol in gravid ewes.

Materials and Methods

The protocol was approved by the University of Iowa Animal Care Committee. Fifteen esmolol and three control experiments were performed in six mixed-breed pregnant sheep weighing 66.7 ± 2.8 kg between 128 and 136 days gestation (term = 145–150 days). Sheep 1, 2, and 3 were used in two esmolol infusion experiments. Sheep 4, 5, and 6 were used in three esmolol and one control infusion experiments, respectively. All the ewes were close to term and it was not possible to do four experiments in each of them. Gestational ages were based on the induced ovulation technique.³ Esmolol experiments were done 24–48 h apart. The chronically instrumented animals were prepared as follows: using thiopental, halothane, N_2O , and O_2 anesthesia and sterile technique, the uterus was opened and catheters were inserted into the fetal femoral vein and artery, and the amniotic cavity. Additional catheters were inserted into either the maternal femoral artery and vein or the carotid artery and external jugular vein. After surgery, each animal was kept in a restricted area and fed a standard diet for at least 6 days prior to study. On the day of an experiment, the ewe was transferred into a small cart permitting it to stand in an upright position.

Each experiment was preceded by a control period of at least 1 h when baseline values for maternal and fetal mean arterial pressure (MAP), heart rate (HR), arterial blood gases, and intra-amniotic pressure were established. Intravenous esmolol hydrochloride (Breviblock®, DuPont Critical Care, McGraw Park, IL) infusion to the mother was started, $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 4 min and then $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 6 min. The dosage used was similar to that used in human studies to blunt the hemodynamic

* Fellow, Department of Anesthesia, University of Chicago.

† Assistant Professor of Anesthesia and Obstetrics and Gynecology, University of Iowa.

‡ Professor of Pediatrics, University of Iowa.

§ Associate Professor of Obstetrics and Gynecology, University of Iowa.

¶ Medical Student, University of Iowa.

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Address reprint requests to Dr. Östman: Department of Anesthesia and Critical Care, The University of Chicago, 5841 South Maryland Avenue, Box 428, Chicago, Illinois 60637.

response to endotracheal intubation.⁴ Control infusions consisted of the diluent used with esmolol. The volume (ml/kg) of the diluent-control was the same as in the esmolol group. Maternal and fetal arterial blood samples for blood gas and esmolol concentration determinations were taken before the infusion and at 10, 20, and 40 min after the esmolol infusion was started. During the experiment, maternal and fetal MAP, HR, and intra-amniotic pressure were continuously monitored and recorded on a Beckman® six-channel recorder (R6111). Arterial blood gas tensions were measured immediately after sampling using an Instrumentation Laboratory System 1303 pH Blood Gas Analyzer.

Arterial blood sampled for determination of esmolol concentration was processed immediately. The analysis of esmolol is based on the selective extraction of esmolol into methylene chloride under neutral conditions and back extraction of esmolol into an acidic buffer, which is analyzed using high-pressure liquid chromatography.¹ Heparinized blood was transferred into glass tubes containing sodium fluoride and was thoroughly mixed. One milliliter aliquots were taken immediately after mixing and extracted into methylene chloride (10 ml) containing internal marker (100 µl ACC-9038, Du Pont Critical Care). After centrifugation at 3000 rpm for 10 min, the remaining aqueous layer was discarded and the methylene chloride layer was collected and stored at -20° C until analysis at the analytical laboratories of Du Pont Critical Care. The acid metabolite of esmolol was not analyzed. The sensitivity of the assay was 0.050 µg · ml⁻¹. Esmolol concentration data for the first experiment were not available due to procedural error.

Esmolol concentrations and acid-base data are presented as absolute values (mean ± SEM). For the calculation of the fetal/maternal ratio at 10 min, a value of 0.025 µg/ml was assigned to those samples in which the esmolol concentration was below the level of detection. All hemodynamic data are presented as mean (±SEM) % of the baseline. Two factor analysis of variance followed by Bonferroni *t* test was used for statistical analysis of hemodynamic changes, intra-amniotic pressures, and arterial blood gas measurements.

Results

Ten, 20, and 40 min after initiation of the infusion, maternal esmolol concentrations were 1.2 ± 0.28 µg/ml, 0.03 ± 0.01 µg/ml, and not detectable, respectively (mean ± SEM, n = 14). Mean fetal esmolol concentrations were 0.1 ± 0.03 µg/ml at 10 min and not detectable thereafter (n = 14, table 1). When the esmolol concentration was below the sensitivity of the assay (0.05 µg/ml), the value 0.025 µg/ml was assigned to calculate the fetal/maternal ratio. The mean fetal-to-maternal ratio, calculated in this

TABLE 1. Esmolol Concentrations µg/ml (Mean ± SEM) in Maternal and Fetal Sheep after Beginning the Esmolol Infusion

Time (min)	Mother	Fetus
0	0	0
10	1.17 ± .28	0.10 ± .03
20	0.03 ± .01	0
40	0	0

fashion, was 0.13 ± 0.03 at 10 min (table 2). If those pairs where the fetal concentration of esmolol was below the sensitivity of the assay are excluded, the mean fetal-to-maternal ratio is 0.20 ± 0.04.

The maximal reduction in maternal MAP and HR was 7 ± 2% (*P* < .05) and 14 ± 3% (*P* < .05), respectively, at 10 min (figs. 1, 2). The maximal reduction in fetal MAP was 7 ± 2% (*P* < .05) at 40 min (fig. 1). The maximal reduction in fetal HR was 12 ± 3% (*P* < .05) at 10 min (fig. 2). Control animals showed no significant changes in any of the cardiovascular variables measured over the same time period. There were no significant changes over time in maternal or fetal arterial blood gases or intra-amniotic pressure. Furthermore, there were no significant changes in baseline maternal or fetal hemodynamic measurements, arterial blood gas tensions, or intra-amniotic pressure during successive experiments in any of the animals.

Discussion

β-adrenergic receptor blockade is one of a variety of treatment modalities available to attenuate adverse hemodynamic responses during surgery. However, the po-

TABLE 2. Esmolol Concentrations (µg/ml) and Fetal/maternal Ratio in Each Maternal and Fetal Sheep at the Completion of 10-Min Esmolol Infusion

Mother	Fetus	Fetus/Mother
0.67	0.08	0.13
2.97	<0.05	0.01
0.76	<0.05	0.03
2.36	<0.05	0.01
0.40	<0.05	0.06
0.50	<0.05	0.05
0.71	0.07	0.10
0.49	<0.05	0.05
0.75	0.08	0.11
0.48	0.12	0.26
0.57	0.20	0.36
0.40	0.15	0.37
3.53	0.44	0.12
1.86	0.24	0.13

When the esmolol concentration was below the sensitivity of the assay (0.05 µg/ml), the value 0.025 µg/ml was assigned to calculate the fetal/maternal ratio. The ratio is 0.13 (±.03). This is the mean of the individual fetal/maternal ratios, not a ratio of the mean concentrations.

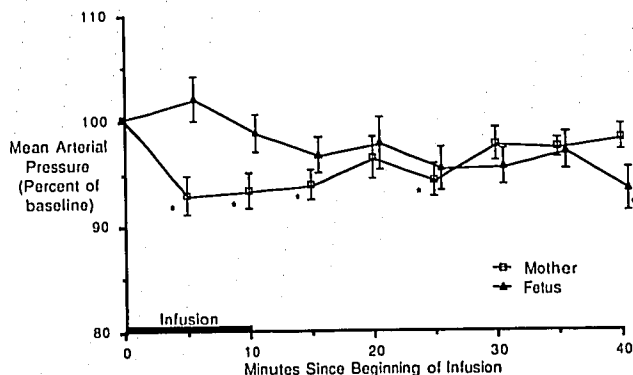


FIG. 1. Maternal and fetal mean arterial pressure during and after esmolol infusion in chronically instrumented gravid ewes. All values are expressed as mean (\pm SEM) % of baseline. The asterisk indicates $P < .05$ when compared to the baseline.

tential dangers of perioperative β -blockade are not negligible. Anesthetic agents, which have negative chronotropic and inotropic properties, can interact with the β -adrenergic blocking drugs and cause severe depression of cardiac contractility, which may not be rapidly reversible due to the long duration of action of the β -adrenergic blocking agents in current clinical practice.⁵ The pharmacokinetic profile of esmolol is remarkable for its high total body clearance and short elimination half-life.¹ Thus, esmolol should be more suitable for perioperative use than the longer acting β -blocking agents. This is particularly relevant in the obstetric patient in whom long-lasting β -adrenergic receptor blockade in the fetus may be detrimental.⁶ To our knowledge, there are no published data regarding placental transfer of esmolol hydrochloride.

This study shows that esmolol has a rapid transplacental passage and is rapidly eliminated from both the maternal and fetal sheep. The fetal arterial blood concentration of esmolol was approximately 13% of the maternal concen-

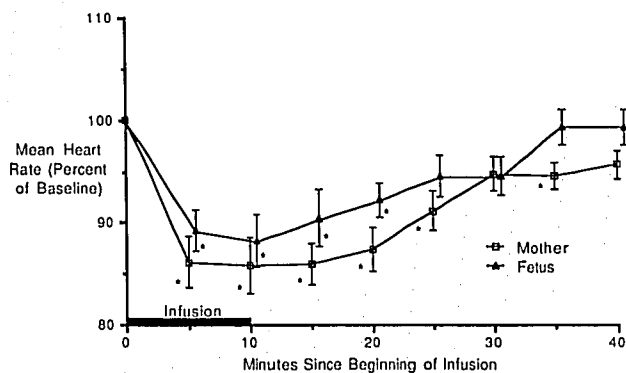


FIG. 2. Maternal and fetal heart rate during and after esmolol infusion in chronically instrumented gravid ewes. All values are expressed as mean (\pm SEM) % of baseline. The asterisk indicates $P < .05$ when compared to the baseline.

tration at the end of the 10-min infusion. At 20 min, only four mothers and no fetus had blood esmolol concentrations above the sensitivity of the assay. This differs from the placental transfer of other β -adrenergic receptor blocking drugs.^{7,8} In humans with pregnancy-induced hypertension, the umbilical cord plasma-to-maternal plasma concentration ratio for metoprolol was 0.9 and for propranolol 0.32.^{7,9} β -adrenergic receptor blockade in the fetus may decrease its tolerance to asphyxia, because the fetus relies on increased sympathetic activity to adapt itself during limited oxygen supply.⁶ Kjellmer *et al.* found that chronic maternal metoprolol therapy in the pregnant ewe caused impaired adaptive responses in fetuses exposed to moderately severe asphyxia.⁶

In this study, maternal and fetal mean HR decreased rapidly by 14 ± 3 and $12 \pm 3\%$, respectively, during the first 5 min of infusion, stayed at that decreased level for the remainder of the infusion period, and then gradually returned towards preinfusion baseline values (fig. 1). The changes in maternal MAP followed a similar time course as maternal HR, but were less marked. Fetal MAP showed no consistent changes during the first 20 min. At 40 min, the fetal MAP was $93 \pm 2\%$ of the preinfusion values. In 12 of the 15 experiments, fetal MAP was lower than baseline at 40 min. At this time, fetal plasma esmolol concentrations were below the level of detection, and fetal HR had returned to baseline. This may have represented residual β -adrenergic receptor blockade, although an earlier study in dogs showed that 20 min after the completion of esmolol infusion, the hemodynamic response to isoproterenol infusion had been fully reversed.¹⁰

There were no changes in maternal or fetal arterial blood gas tensions or in the intraamniotic pressure. This contrasts with an earlier study of pregnant ewes with another β -adrenergic receptor blocking agent. In that study, maternal propranolol infusion was accompanied by a reduction of fetal arterial blood pH, with the maximal reduction of fetal pH of 0.021 units (baseline pH was $7.380 \pm .005$, and at 60 min pH was $7.359 \pm .010$).¹¹ However, one may question the clinical significance of such a small pH change. Court *et al.* found no differences in cardiorespiratory measurements, regional blood flow, or peripheral resistance in fetal sheep following propranolol infusion.¹²

In this study of gravid ewes, we observed that esmolol had a rapid transplacental passage and was eliminated rapidly from both maternal and fetal plasma. Esmolol also caused small decreases in maternal HR and MAP without significantly altering maternal or fetal acid/base status or uterine activity. The changes in fetal HR were most likely caused by esmolol in the fetal circulation. However, changes in maternal cardiac output and/or uteroplacental perfusion may have contributed to such changes in the fetus. The dose used was similar to that used in standard

clinical practice.⁴ Others have noted that this dose blunts the hemodynamic response to laryngoscopy and intubation and causes only minor changes in baseline heart rate and blood pressure in humans. Further studies should evaluate fetal adrenergic receptor sensitivity, and long-term fetal hemodynamic sequelae to maternal esmolol administration, as well as the effects of esmolol on primate uterine tone.

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