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Nifedipine or Verapamil Counteracts Hypertension in Gravid Ewes

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Hypertension frequently complicates endotracheal intubation in the severely preeclamptic parturient. The calcium entry-blocking drugs nifedipine (N) and verapamil (V) are effective antihypertensive agents in nonpregnant patients. The authors studied the maternal and fetal hemodynamic effects of these drugs in chronically instrumented gravid ewes made hypertensive with an infusion of norepinephrine (NE). Initially NE was infused to increase maternal mean arterial pressure (MAP) by 20%. The NE infusion was continued and either N, 2 mg, or V, 10 mg, was administered intravenously. MAP decreased promptly to control values following both drugs. Maternal heart rate (MHR) decreased significantly following NE infusion. MHR returned to control values following V administration, and increased significantly above control following N administration. Uterine blood flow decreased 50–60% during NE infusion, and there was no further change following either N or V. Fetal hemodynamics were unchanged throughout the study. These results suggest that both N and V may be effective antihypertensive agents in the parturient. V did not produce maternal tachycardia and may be the preferable drug. (Key words: Anesthesia: obstetrics. Complications: preeclampsia. Pharmacology: nifedipine verapamil.)

ENDOTRACHEAL INTUBATION in parturients with severe preeclampsia often markedly increases maternal blood pressure (BP), which may cause pulmonary edema and subarachnoid hemorrhage.[1] Numerous drugs have been used to control this hypertension; however, none has proven ideal. The calcium entry-blocking drugs, nifedipine and verapamil, are effective antihypertensive agents in nonpregnant patients[2–4] and may be useful in the treatment of preeclampsia.[5] Any decrease in maternal BP is accompanied by a decrease in uterine perfusion pressure, which may diminish uterine blood flow (UBF) and, consequently, fetal blood supply. Placental function is often impaired in severe preeclamptics, and any decrease in blood supply to an already compromised fetus can be detrimental. We investigated the maternal and fetal hemodynamic response to nifedipine or verapamil, in ewes made hypertensive by infusion of norepinephrine (NE).

Methods

We studied eight gravid ewes, weighing 62.6 ± 3.5 kg (mean ± SEM), of 110–130 days gestation (term: 145 days). Following cannulation of a jugular vein, anesthesia was induced with pentobarbital (6 mg/kg) and maintained with halothane (1–2%) in oxygen by nasal insufflation. Through a midline abdominal incision, we exposed the uterus and extracted a fetal hind limb through a hysterotomy. Catheters were placed in a fetal tibial artery and a saphenous vein, and a pressure catheter was placed in the amniotic cavity, after which the uterine and abdominal incisions were closed. Through a groin incision, catheters were inserted in a maternal mammary artery and vein, and an electromagnetic flow probe was placed around a uterine artery. All catheters were tunneled subcutaneously and exteriorized through a flank incision. Finally, we placed a zero flow-occlusion loop[6] around the aorta. All animals rested at least 3 days before being studied.

On the day of the study, the sheep were placed in a quiet room with free access to food and water. Maternal mean arterial blood pressure (MAP), maternal heart rate (MHR), UBF, fetal mean arterial pressure (FAP), and fetal heart rate (FHR) were continuously monitored. Following a stable control period, an infusion of NE was begun in a dose sufficient to increase MAP by 20% (1.27 ± 0.19 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The NE infusion was continued at this dose throughout the study period. When all variables had again stabilized for 5–10 min, nifedipine (2 mg, n = 7) or verapamil (10 mg, n = 6) was administered by slow intravenous injection and all variables were monitored for 20 min. Maternal and fetal arterial blood gas analysis was performed during the control period, during NE hypertension, and 5 and 20 min following nifedipine or verapamil administration. At least 20 h elapsed between studies in a single animal.

Both drugs were given to five of the animals. The first two ewes studied received only nifedipine; the last ewe only verapamil. Although the order of administration was not formally randomized, three ewes received nifedipine first, while two received verapamil first. No ewe or fetus died within 12 h of any study.

All data are expressed as mean ± SEM. We used a

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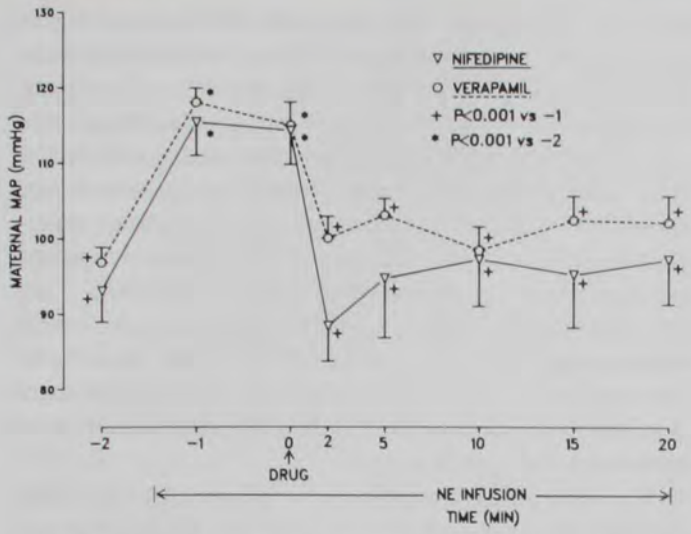

FIG. 1. Maternal blood pressure. −2 represents the baseline value. Norepinephrine (NE) infusion was begun and a stable 20% increase in MAP was achieved at point −1. Injection of either drug at time 0 returned MAP to control values at 2 min.

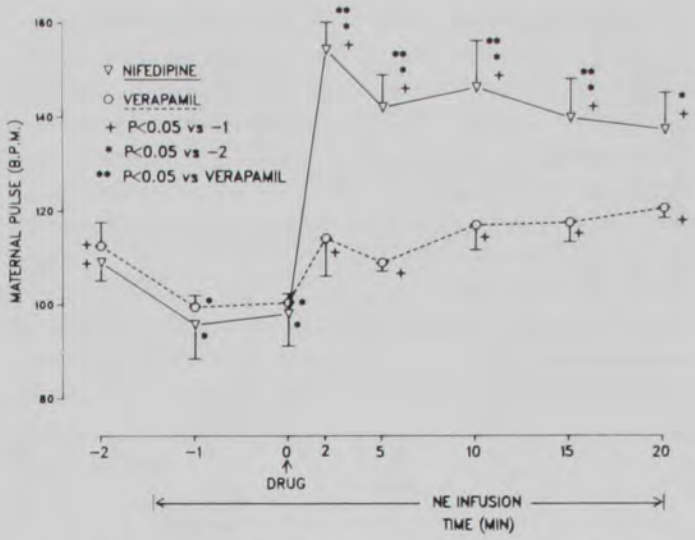

FIG. 2. Maternal heart rate (MHR). Time sequence as in figure 1. Norepinephrine (NE)-induced hypertension decreases MHR, following verapamil, MHR returns to baseline values, following nifedipine, a significant maternal tachycardia ensues.

multiple analysis of variance for repeated measures[7] to analyze our data and considered a $P < 0.05$ significant.

Results

All sheep tolerated the protocol, and there were no deaths within 12 h of any study. NE infusion at 77.3 ± 10.0 $\mu g \cdot min^{-1}$ (1.27 ± 0.19 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increased MAP 20% (fig. 1). MAP returned promptly (within 2 min) to control values following injection of either nifedipine or verapamil. (fig. 1) There were no further changes in MAP during the remainder of the experiment. MHR (fig. 2) decreased significantly ($P < 0.05$) during NE hypertension. Nifedipine was followed by a significant maternal tachycardia ($P < 0.05$ *vs.* control, $P < 0.05$ *vs.* verapamil), which persisted throughout the study period. In contrast, following verapamil administration, MHR returned only to control values. FHR and FAP were unchanged throughout the study. UBF (fig. 3) decreased 50–60% during NE hypertension and did not change further following either drug. Maternal arterial blood gases were unchanged throughout the protocol. However, fetal Pa_{O_2} and *p*H decreased significantly during NE hypertension. Fetal Pa_{O_2} improved slightly but significantly ($P < 0.05$) by 20 min following nifedipine or verapamil (fig. 4).

Discussion

Close control of maternal BP during laryngoscopy and intubation in the severely preeclamptic patient is recommended to prevent the significant morbidity that can occur.[1] An agent that rapidly decreases maternal BP without adversely affecting an already compromised fetus would be useful in this situation. An ideal drug would be potent, rapidly acting, controllable, and without significant maternal or fetal side effects. None of the currently used drugs fulfills all of these criteria.

Hydralazine is frequently used to treat the hypertension of preeclampsia. It has no deleterious effects on UBF or fetal acid–base status unless BP decreases excessively.[8] However, its slow onset and long duration of action make accurate, rapid changes in MAP difficult.

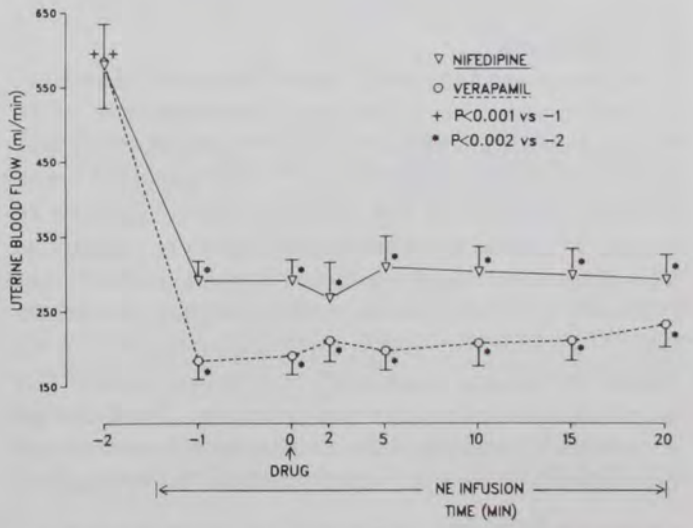

FIG. 3. Uterine blood flow (UBF). Time sequence as in figure 1. Norepinephrine (NE) reduces UBF. Neither drug causes any further change to UBF.

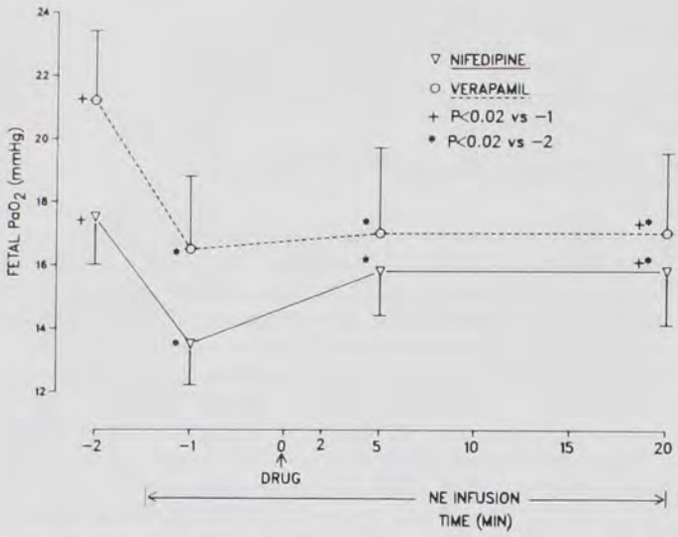

FIG. 4. Fetal Pa_{O_2}. Time sequence as in figure 1. Norepinephrine (NE) infusion decreases fetal Pa_{O_2}. Slight improvement occurs by 20 min after either drug.

Nitroglycerin also effectively controls BP during induction of general anesthesia in the severely preeclamptic patient.[9] It has a rapid onset and short duration of action and does not appear to adversely affect UBF.[10] However, it is primarily a venodilator and although effective in our hands, it may not be potent enough to control the maternal response to laryngoscopy and intubation in some preeclamptic patients.§

Nitroprusside is a very effective antihypertensive agent in the nonpregnant patient. Its use in the parturient has been limited by concerns about cyanide toxicity.[11] Considerable reflex maternal tachycardia also occurs.[12] Additionally, nitroprusside is extremely potent and may cause excessive hypotension even during careful titration. Significant rebound hypertension may occur when the drug is discontinued.[13]

Although used primarily in the treatment of tachyarrhythmias and coronary artery disease, calcium entry-blocking drugs are effective in the management of both acute and chronic hypertension.[14] The maternal hemodynamic responses in this study are similar to those reported by others in nonpregnant hypertensive patients. The onset of action of nifedipine is rapid (within 5 min) following both intravenous and sublingual administration,[15,2] and the decrease in MAP is accompanied by significant increases in heart rate[14] and cardiac output.[2] Our gravid ewes responded in a similar fashion. These changes are probably caused by a direct relaxant effect on peripheral arterioles and a reflex increase in sympathetic tone.[16,17] Verapamil also decreases BP in hypertensive humans, but in contrast to nifedipine, heart rate and cardiac output do not increase.[18] Its primary action is also as a vasodilator but its intrinsic negative inotropic and chronotropic properties inhibit reflex cardiac effects.[13,14] The stable heart rate in our animals is consistent with these findings. Thus, calcium entry-blocking drugs appear to be an alternative to the other antihypertensive agents used to control maternal response to intubation. They are more rapidly acting than hydralazine, more potent than nitroglycerin, and, unlike nitroprusside, do not produce toxic metabolites. In our animals, they did not cause excessive hypotension or rebound hypertension, which is consistent with previous work.[13]

We were concerned about the effects of these drugs on UBF. *In vitro* studies show that both nifedipine and verapamil inhibit NE-induced contractions of human arteries.[19] Murad *et al.* reported that verapamil decreases UBF 10–25% in normotensive gravid ewes and attributed this to an 11% decrease in MAP and reduced uterine perfusion pressure.[20] In nonpregnant rats, nifedipine increases UBF, but in estradiol-treated rats whose uterine arteries are maximally dilated, (a situation analogous to pregnancy), nifedipine does not affect UBF.[21] Nifedipine also appears to have no deleterious effects on UBF when given to normotensive pregnant ewes.[22] In this study, UBF did not change, despite a 20% decrease in uterine perfusion pressure following nifedipine or verapamil administration. We postulate that although nifedipine and verapamil did not completely correct the NE-induced uterine vasoconstriction, these drugs do have some direct vasodilating effect on the uterine artery, which compensates for the decrease in uterine perfusion pressure, and UBF is maintained but not improved.

There are few data available concerning the fetal effects of these drugs. Verapamil crosses the placenta.[23,24] Neither our work nor that of Murad *et al.*[23] indicates any effect on FAP, FHR, or fetal acid–base status. Verapamil has been used to treat maternal tachyarrhythmias without adversely affecting the fetus.[25] Similarly, nifedipine has been used as a tocolytic agent without apparent harmful fetal effects.[26] We have studied nifedipine in normotensive gravid ewes and saw no changes in FAP or fetal acid–base status.[22]

In the clinical setting, we would also be concerned with the effects of these drugs on uterine activity. Uterine contractility depends on calcium flux through cell membranes.[27] Calcium entry-blocking drugs inhibit calcium movement into and possibly within cells.[28,29] Nifedipine inhibits spontaneous uterine activity[30] and also contractions induced by oxytocin,[28] methylergonovine,[30] and prostaglandin F_{2a}.[31,32] Verapamil also inhibits spontaneous uterine activity, but less than nifedipine.[33] This

§ Longmire S, Jones M, Tessen J, Cotton D, Dorman K, Joyce T III: Hemodynamic effects of nitroglycerin in pregnancy induced hypertension. SOAP Abstract, May 10, 1985, p 17.

could increase blood loss at delivery. However, in a clinical study by Forman *et al.*,[30] nifedipine was given immediately postpartum and no increase in uterine size or bleeding was noted. Although our animals were not in labor, we saw no changes in amniotic fluid pressure during the experiment. Further clinical studies are needed in this area.

Preeclampsia is a systemic disease with generalized arteriolar vasospasm[34] and a hyperdynamic myocardial state.[35,36] Increases in both peripheral vascular resistance and cardiac output may contribute to the incrased BP. The antihypertensive agents, such as hydralazine, that are commonly used in the treatment of preeclampsia are primarily arteriolar dilators, and cardiac output normally increases both as a consequence of decreased afterload as well as increased heart rate. A more logical drug may be one with negative, chronotropic, inotropic, and vasodilator properties such as verapamil. Verapamil has been used in patients with both acute and chronic congestive heart failure, and its potent afterload-reducing effects compensated for any intrinsic cardiac depression and actually improved hemodynamics and cardiac function.[37,38]

An issue that may be raised in regard to this study is whether the hemodynamic responses seen were truly the effects of nifedipine or verapamil or the result of tachyphylaxis or maternal compensatory responses to the NE-induced hypertension. There are several points in favor of the initial response being a specific drug effect. First, there was no evidence of maternal tachyphylaxis or other compensatory response in the time between achieving a 20% increase in MAP and the administration of nifedipine and verapamil. Second, this stable hypertensive period was of variable duration and always terminated promptly with drug administration. Third, the hemodynamic changes that occurred with drug administration are consistent with those seen in other animal and human studies.[2–4,13–17,29,39] Fourth, also, while the BP response was similar with both drugs, the heart rate response was different. It is highly unlikely that a given animal would respond differently to NE infusion on two different days. Finally, when the NE infusion was stopped at the end of each study, UBF always returned to baseline within a few minutes (M.C.N., unpublished observations), suggesting that the persistent decrease in UBF was due to the continuing NE infusion and not nifedipine or verapamil. Therefore, the initial hemodynamic changes are most probably drug-specific effects. However, there are changes at 20 min that may represent tachyphylaxis or maternal compensation. There is a slight improvement in UBF at 20 min. (This is statistically significant in the verapamil group when analyzed separately.) A similar delayed improvement has been reported following nitroprusside in the same animal model.[12] Similarly, the slight increase in fetal Pa_{O_2} at 20 min may be due to compensatory changes.

In conclusion, the calcium entry-blocking drugs, nifedipine and verapamil, rapidly and effectively decrease maternal BP in the hypertensive gravid ewe without producing deleterious effects on UBF or fetal acid–base status. Although we realize the limitations of basing clinical judgements on animal studies, we believe that the use of both of these drugs during the induction of general anesthesia in the preeclamptic patient should be investigated further. Interestingly, Zaret[5] has suggested using nifedipine in the chronic treatment of preeclampsia and Walters and Redman[39] have reported use in this circumstance. However, verapamil, with its absence of maternal tachycardia, may be the preferable drug for control of maternal hypertension.

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