Anesthesiology
V 39, No 3, Sept 1973

Circulatory Effects of Peridural Block:

IV. Comparison of the Effects of Epinephrine and Phenylephrine

Michael Stanton-Hicks, M.B., B.S., F.F.A.R.C.S.,* Peter U. Berges, M.D.,*
John J. Bonica, M.D.†

The effects of lidocaine–epinephrine and those of lidocaine–phenylephrine on cardiovascular and respiratory variables following peridural block to a minimum level of T5 were compared in ten human volunteers. Epinephrine in a dose of 5 μg/ml was considered equipotent as a vasoconstrictor to 50 μg/ml of phenylephrine. In this concentration epinephrine was more effective in limiting vascular uptake of lidocaine from the peridural space, as determined by serial blood lidocaine levels. The beta-adrenergic response with epinephrine was marked, in contrast to the decrease in stroke volume, reduction in cardiac output and rise in central venous pressure seen with phenylephrine. This negative intotropic effect contrasts with previous reports which attribute the reduction in cardiac output to a reflex decrease in cardiac rate. Limb blood flow manifested the greatest differences: leg blood flow increased 219 per cent when epinephrine was used, versus 157 per cent with phenylephrine; arm blood flow increased 119 per cent after epinephrine, in contrast to a decrease during the entire period after phenylephrine. Key words: Peridural block; Circulatory effects; Vasoconstrictors; Lidocaine; Epinephrine; Phenylephrine.)

IN PREVIOUS STUDIES, our group has shown that epinephrine incorporated in the local anesthetic solution to prolong peridural block has systemic circulatory effects. In addition to producing local vasoconstriction of the peridural vessels, the drug apparently is absorbed into the circulation at a rate sufficient to produce beta-adrenergic stimulation, namely an increase in cardiac output and a decrease in total peripheral resistance. Mean arterial pressure falls. While the local effect is beneficial because slower absorption of the drug decreases the risk of systemic toxicity and increases duration, in some patients the beta-adrenergic effects of epinephrine may be undesirable. This report describes the results of a study done to determine whether phenylephrine substituted for epinephrine might retain the benefit of local vasoconstriction without producing cardiovascular changes.

* Assistant Professor.
† Professor and Chairman.
Received from the Department of Anesthesiology and the Anesthesia Research Center, University of Washington School of Medicine, Seattle, Washington 98195. Accepted for publication February 28, 1973. Presented at the Annual Meeting of Australasian Society of Clinical and Experimental Pharmacologists in Melbourne, November 26, 1971. Supported by U. S. Army Research and Development Command Contract No. DA-49-193-MD-2231.
Reprint requests should be addressed to Dr. Stanton-Hicks, Department of Anesthesiology, Mail Stop RN-10, University of Washington School of Medicine, Seattle, Washington 98195.

Methods

Ten healthy male volunteers, 21 to 42 years of age, were studied. Prior to the study each subject was examined and informed consent obtained. The method of study and the techniques of measurement were the same as those detailed in previous reports.[1, 2, 3] Each subject in the study served as his own control. After a 30-minute rest period, control measurements of mean arterial pressure (MAP), central venous pressures (CVP), heart rate (HR), blood lidocaine level, cardiac output (CO), blood gases, and arm and leg blood flows were made. Also, total peripheral resistance (TPR), stroke volume (SV), left ventricular stroke work (LVSW), and left ventricular minute work (LVMW) were calculated, and the electrocardiogram was monitored continuously throughout the study.

After control measurements, 18 to 22 ml of local anesthetic solution were injected at a rate of 0.5 ml/sec into a catheter placed in the lumbar peridural space. The solution consisted of 2 per cent lidocaine with either epinephrine, 1:200,000, or phenylephrine, 1:20,000, concentrations considered equipotent.[4] The dose was related to the height and age of the subject and was intended to produce analgesia to T5.[5] Levels of analgesia and hypalgesia were evalu-

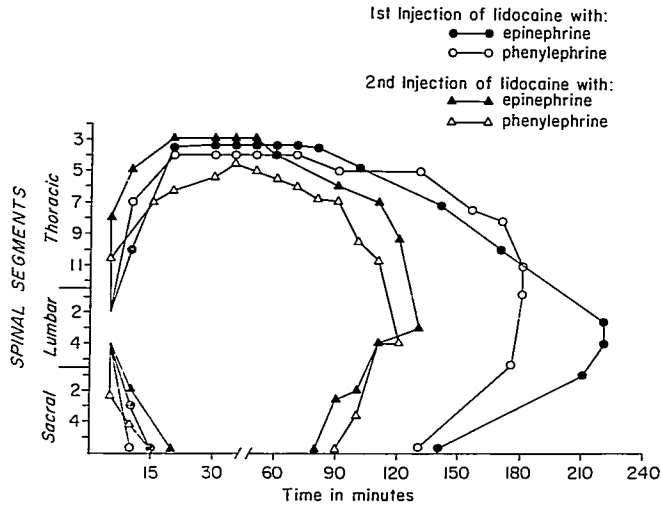


FIG. 1. Mean time-segment diagram of peridural block using lidocaine, 2 per cent, with epinephrine, 1:200,000, and lidocaine, 2 per cent phenylephrine, 1:20,000, during the first and second injections. For clarity, the areas shown indicate the extent of "hypalgesia" as defined by diminished sensibility to pain, while those indicating "analgesia" are omitted. The difference was consistently two dermatomes.

ated every five minutes by firm pin prick until the block disappeared. A decrease in the level of analgesia of two dermatomes was defined as the end of "therapeutic block," whereas the total disappearance of hypalgesia was considered the end of "residual block."[2] Both degrees of sensory blockade were recorded on a mean time-segment diagram.[6] Motor block was assessed by the method described by Bromage,[7] and when asymmetry in the quality of motor block existed, the average of the values for both legs was used. Following injection, serial measurements of the cardiorespiratory values were made at 5 and 15 minutes and every 30 minutes thereafter until analgesia of the skin had disappeared. When no residual block was evident, the subject was given a second 30-minute rest period and new control measurements were obtained. A second peridural injection containing the same amount of lidocaine but utilizing the other vasoconstrictor was performed. In successive subjects, the order of epinephrine and phenylephrine was reversed.

Circulatory measurements were converted to mean per cent changes from mean control values. Blood chemistry measurements were made for all subjects, the results being expressed as means of the absolute values. Analysis of the data was performed on an individual basis, *i.e.*, using each subject as his own control. Because the experimental design was such that in all cases the second injection might be influenced by the first, it was deemed necessary to do two analyses of the blood lidocaine levels, one eliminating drug and one eliminating order. The significance of these changes was determined by Student's t test for paired data.

Results

The doses of lidocaine ranged from 360 to 440 mg, with a mean for the group of 400 mg, which represented 4.4 to 5.4 mg/kg with a

mean of 4.9 mg/kg. After the first injection, analgesia to within one segment of T5 was achieved in eight subjects, but it extended to T2 in the other two. The two vasoconstrictors differed in their effects on duration of block, cardiovascular response, and blood levels of lidocaine.

Latency and Duration

The onset, or latency, of analgesia and the durations of therapeutic and residual block are shown in figure 1. The latencies, extents and durations of therapeutic block were similar with the two solutions. However, there was a significantly greater duration of residual block with lidocaine–epinephrine than with lidocaine–phenylephrine. There was also a significant difference between degrees of motor block, that following epinephrine being more intense. These differences bore no relationship to the orders in which the respective vasoconstrictors were used.

After the second injection there were differences between the latencies and extents of analgesia produced by the two vasoconstrictors. Analgesia to T5 was achieved in 10 minutes with lidocaine–epinephrine, but took 35 minutes with lidocaine–phenylephrine. Moreover, in all subjects in whom phenylephrine was used for the second injection, the uppermost level of analgesia was one or two dermatomes below the level reached with the first injection. This was not the case with epinephrine.

An attempt was made to quantify the sensory block by determining the mean areas of the time-segment diagram (see fig. 1). Using this technique, the areas encompassed by the lidocaine–phenylephrine in both the first and second injections are approximately 7 per cent less than those obtained with lidocaine–epinephrine in each case. This may imply that in the chosen dose of 50 μg/ml, phenylephrine is not equipotent to epinephrine, 5 μg/ml. Also, "tachyphylaxis," as expressed by the reduction in areas of the second injection, was approximately 6 per cent greater following previous phenylephrine.

Circulatory Effects

The circulatory effects and limb blood-flow changes, together with their standard errors, are summarized in figure 2. The beta-adrenergic response of the circulation to epinephrine is well demonstrated by the significant decreases in MAP and TPR and the concurrent increases in CO, CR, and SV, which were most pronounced during the first 30 minutes after injection.

Peridural injection with lidocaine–phenylephrine was associated with significant increases in CVP and TPR and a concomitant decrease in CO, with MAP remaining normal. The decrease in CO was primarily due to a significant decrease in SV. As with the lidocaine–epinephrine solution, the maximum changes occurred during the first 30 minutes.

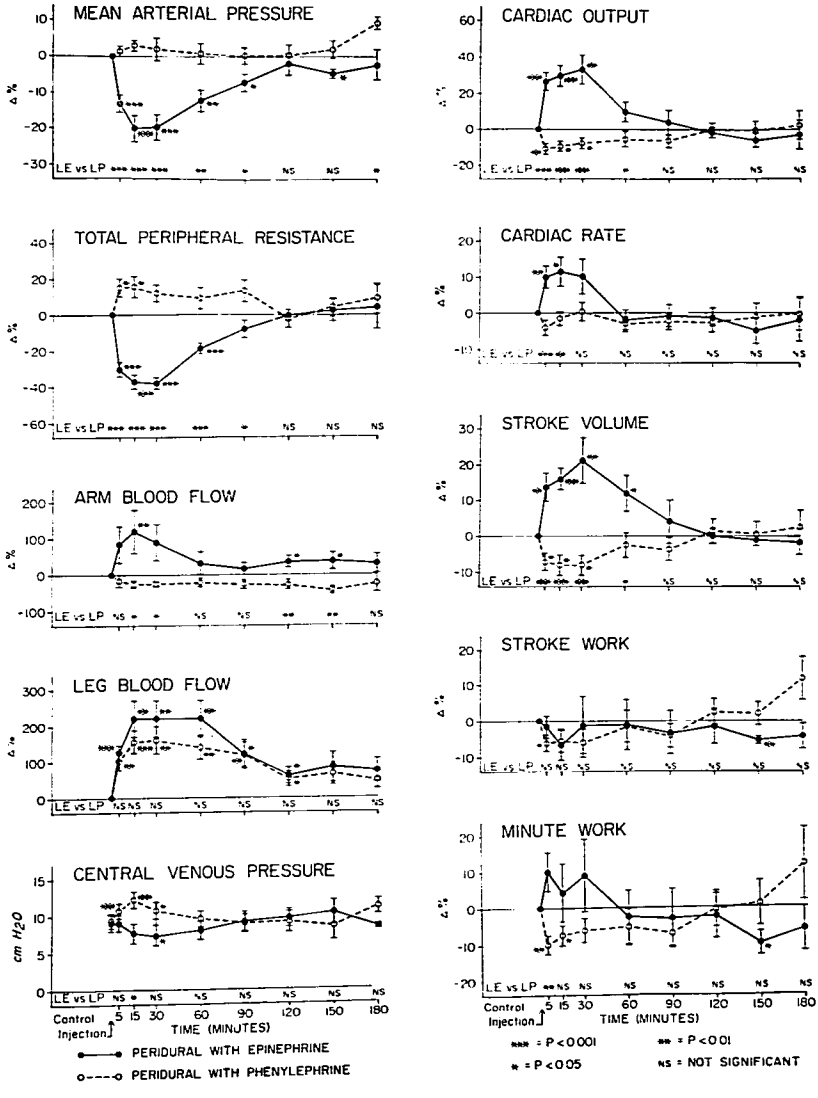
Limb blood flow data show very important differences between epinephrine and phenylephrine solutions. Leg blood flow was increased 219 per cent with epinephrine and 157 per cent with phenylephrine. Both of these changes from control values are statistically significant, but the difference between the effects of the two solutions was not. Within 15 minutes of injection, arm blood flow increased a maximum of 119 per cent with epinephrine but decreased 12 per cent with phenylephrine. The latter drug was associated with a subsequent progressive further reduction to a maximum of 44 per cent at 2½ hours, when the level of sympathetic blockade had receded to about the ninth thoracic segment.

The only alterations in acid–base balance and blood gases were seen with epinephrine, which caused *p*H to decrease from 7.392 to 7.365 and base excess from −2.0 to −3.0 at 60 minutes. Although statistically significant, these figures are of dubious importance. Like subjects in previous studies, some of the volunteers hyperventilated, but the mean Pa_{CO_2} for the entire group showed only a non-significant change.

Blood Lidocaine Level

The mean blood lidocaine levels obtained in the ten subjects are shown graphically, to-

Fig. 2. Circulatory responses to peridural analgesia. Each point represents the mean percentage change from control in all ten subjects. Statistical significances of these in respect to the mean control values are indicated alongside the graphed means, while significant differences between lidocaine, 2 per cent, with epinephrine, 1:200,000, and lidocaine, 2 per cent, with phenylephrine are shown at the bottom of each graph, thus: (LE) *vs.* (LP).



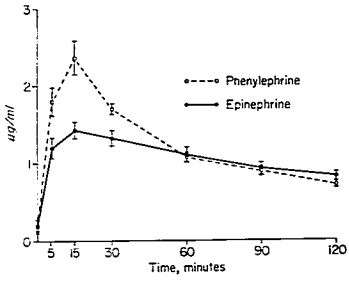


FIG. 3. Mean blood lidocaine levels, a comparison of the effects of epinephrine and phenylephrine on blood lidocaine levels, expressed as μg/ml. Each bar represents the standard error of the mean (SEM).

gether with their standard errors, in figure 3. Table 1 is included to show how the sequence of administration influenced the effect each vasoconstrictor had on blood lidocaine levels. Both phenylephrine and epinephrine differed significantly in their effects on blood lidocaine levels in the 5-, 15-, and 30-minute samples.

Discussion

This study confirms that the fall in MAP seen with high peridural block achieved with a local anesthetic solution containing epinephrine is the result of a combined effect of sympathetic blockade and the beta-adrenergic stimulating action of epinephrine on vascular beds.[2] These effects are emphasized by the changes in limb blood flow. Through its beta-adrenergic stimulating action, epinephrine enhances the vasodilating effect of sympathetic blockade, reported in an earlier paper,[3] and, what is more important, the compensatory vasoconstriction in the upper limb resulting from the hypotension usually seen with peridural block to T5 is markedly impaired.[1] In contrast, phenylephrine, which has only an alpha-adrenergic stimulating action, counteracts the vascular effects of sympathetic block and thus maintains normal blood pressure. Moreover, phenylephrine does not have the myocardial stimulating action of epinephrine. For these reasons, phenylephrine might be considered preferable to epinephrine for addition to local anesthetic solutions administered to the rare patient who has severe tachycardia from untreated hyperthyroidism. Also, phenylephrine would seem to be a better vasoconstrictor than epinephrine to add to local anesthetic solutions given to patients in whom beta-adrenergic stimulation of the cardiovascular system might be harmful. Phenylephrine as a vasoconstrictor in local anesthetic solutions might also be more suitable for patients receiving inhalation agents which sensitize the heart to epinephrine. Because it does not have a myometrial inhibiting effect characteristic of epinephrine,[5] phenylephrine may also be more desirable for peridural analgesia in labor and delivery by cesarian section. In a concentration of 1:20,000, the amounts needed for lumbar peridural analgesia are probably not sufficient to cause myometrial stimulation.

The observed effects of phenylephrine on cardiac output and central venous pressure are not in accord with data previously published. In the other three reports on the hemodynamic effects of phenylephrine in man, the decrease in cardiac output was due wholly to reflex slowing of the heart rate, and no-one has reported a negative inotropic effect. In contrast, each of our volunteers showed a direct negative inotropic effect, indicated by the decrease in stroke volume and increase in CVP. Our data do not provide an explanation for this discrepancy or for the mechanism of the negative inotropic action.

Epinephrine may also be preferable to phenylephrine for those patients whose circulation is severely compromised by acute hypovolemia. This suggestion is based on the present results and data from a previous study,[3] which indicated that the cardiac depression from absorbed lidocaine was aggravated in hypovolemic subjects. In these cases, the hypotension occurring with peridural block using lidocaine–epinephrine was only half to a third that seen with lidocaine alone. Although the first line of defense is blood-volume replacement, if for any reason a peridural block is used, then epinephrine should be added to the local anesthetic solution, not only to reduce its rate of absorption, but also to stimulate the myocardium.

There are no published data on the concentration of phenylephrine producing the same degree of vasoconstriction as the 1:200,000

concentration usually recommended for epinephrine. The concentration of 1:20,000 was chosen on the recommendation of Bonica, made two decades ago and based on older data on dental anesthesia solutions. The shorter duration of block and lower blood lidocaine levels suggest that phenylephrine in 1:20,000 concentration produces less local vasoconstriction of the peridural vessels than epinephrine 1:200,000. Clinically, the degree of motor block achieved with phenylephrine was less than that achieved with epinephrine. Apparently the systemic absorption of lidocaine was faster when given with phenylephrine than when combined with epinephrine. Consequently, less drug was available in the peridural space to diffuse to and into large motor fibers with high minimum anesthetic concentration (C_M).[9] Hence, less motor block and shorter sensory blockade resulted with lidocaine–phenylephrine than with lidocaine–epinephrine.

Our data show that following peridural injection lidocaine remains in the vascular compartment for many hours. When the second control measurements were made, an average of 5 hours after the first injection, the range of arterial blood levels of lidocaine was 0 to 0.59 μg/ml, with a mean of 0.33 μg/ml. There are no other data on blood levels after such long intervals of peridural injection, but on the basis of other experimental data, a significant amount of drug may have remained in neural tissue. Animal studies by Åkerman *et al.* showed that the amount of lidocaine in neural tissue was four to five times that in blood 5, 10, 30, 60, and 120 minutes after intramuscular injection.[10] Because the actual blood levels and the concentration-versus-time profiles of lidocaine after peridural injection are similar to those after intramuscular injection,[11] some lidocaine was probably present in neural tissue at the time of the second injection. On this basis, the amount remaining in neural tissue may have been greater than would have obtained had lidocaine without vasoconstrictor been injected. Moreover, the residual amount of lidocaine in the peridural space five hours after the first injection was greater following lidocaine–epinephrine than lidocaine–phenylephrine, suggesting that epinephrine was more efficient as a vasoconstrictor. Thus, the second injections were presumably against different residual

TABLE 1. Analysis of the Mean Blood Lidocaine Levels in Ten Subjects (μg/ml)

	Time, Minutes							
	5	15	30	60	90	120		
Drug effect after eliminating effect of order								
Epinephrine	1.141	1.386	1.281	1.082	0.806	0.778		
Phenylephrine	1.853	2.108	1.738	1.105	0.918	0.741		
SD	0.092	0.106	0.012	0.055	0.012	0.033		
Significance	$P < 0.001$	$P < 0.001$	*NS*	*NS*	*NS*	*NS*		
Order effect after eliminating drug effect								
1	1.248	1.442	1.326	0.942	0.746	0.656		
2	1.749	2.152	1.693	1.245	1.008	0.864		
SD	0.092	0.106	0.012	0.055	0.042	0.033		
Significance	$0.001 < P < 0.1$	$0.001 < P < 0.01$	$P < 0.001$	$0.001 < P < 0.1$	$0.001 < P < 0.01$	$0.001 < P < 0.01$		

levels of lidocaine remaining from the first block, a higher residual remaining after lidocaine–epinephrine than lidocaine–phenylephrine. Therefore, the injection of lidocaine–phenylephrine, after lidocaine–epinephrine, should have produced a more rapid, more intense, more prolonged block. Curiously, the opposite occurred, with lidocaine–epinephrine showing the greater effect, for reasons that are not readily apparent.

The authors wish to thank Mr. Charles E. Pearcy and Mrs. Carol D. Wilkerson for their technical assistance and Dr. E. A. Cornish for aid in the statistical analysis.

References

1. Bonica JJ, Berges PU, Morikawa K: Circulatory effects of peridural block. I: Effects of level of analgesia and dose of lidocaine. ANESTHESIOLOGY 33:619–626, 1970
2. Bonica JJ, Akamatsu TJ, Berges PU, et al: Circulatory effects of peridural block: II. Effects of epinephrine. ANESTHESIOLOGY 34: 514–522, 1971
3. Bonica JJ, Kennedy WF Jr, Akamatsu TJ, et al: Circulatory effects of peridural block: III. Effects of acute blood loss. ANESTHESIOLOGY 36:219–227, 1972
4. Bonica JJ: Management of Pain. Philadelphia, Lea and Febiger, 1953
5. Bromage PR: Physiology and pharmacology of epidural analgesia. ANESTHESIOLOGY 28: 592–622, 1967
6. Bromage PR, Burfoot MF, Crowell DE, et al: Quality of epidural blockade. I. Influence of physical factors. Br J Anaesth 36:342–352, 1964
7. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesth Scand suppl 16:55–69, 1965
8. Zuspan FP, Cibils LA, Pose SV: Myometrial and cardiovascular responses to alterations in plasma epinephrine and norepinephrine. Am J Obstet Gynecol 84:841–851, 1962
9. de Jong RH: Physiology and Pharmacology of Local Anesthesia. Springfield, Ill., Charles C Thomas, 1970
10. Åkerman B, Åstrom A, Ross S, et al: Studies on the absorption, distribution and metabolism of labelled prilocaine and lidocaine in some animal species. Acta Pharmacol Toxicol (Kbh) 24:389–409, 1966
11. Scott DB: Blood levels of lidocaine following various routes of administration. Lidocaine in the Treatment of Ventricular Arrhythmias: Proceedings at a Symposium, Edinburg, September 1970. Edited by DB Scott, DG Julian. Edinburgh and London, E. & S. Livingstone, 1971, pp 153–158

Infectious Diseases

CONTAMINATED WATER During a nine-month period in 1971, 40 patients in St. Thomas's Hospital, London, acquired infection with a previously undescribed organism, *Pseudomonas thomasii*. These patients belonged to several medical and surgical groups. The infections consisted principally of bacteremia and pulmonary or urinary-tract infections. Careful medical detective work uncovered the fact that the purified, distilled water manufactured by the hospital pharmacy and stored in tanks at 40 C was contaminated with this organism. This water was used throughout the hospital, including as a coolant for autoclaved fluids, for irrigation, and in the humidifiers of mechanical ventilators. Replacing the purified, distilled water with sterile water from a commercial source eliminated the acquired infections with this organism. (*Phillips, I., Eykyn, S., and Laker, M.: Outbreak of Hospital Infection Caused by Contaminated Autoclaved Fluids. Lancet 1: 1258, 1972.*) ABSTRACTER'S COMMENT: This report, coupled with our recent experience in the United States with contaminated commercially prepared intravenous fluid, must serve to remind us that constant vigilance is necessary.