Epinephrine and PLV-2: Cardiac Rhythm and Local Vasoconstrictor Effects

Ronald L. Katz, M.D.*

During the inhalation of cyclopropane in the cat, the intravenous injection of epinephrine produced cardiac arrhythmias. The intravenous injection of PLV-2 (2-phenylalanine-8-lysine vasopressin) under similar circumstances did not produce cardiac arrhythmias. In man, the intravenous injection of epinephrine during cyclopropane, trichlorethylene, halothane and fluroxene inhalation produced cardiac arrhythmias. The intravenous and subcutaneous injection of PLV-2 during cyclopropane, trichlorethylene and halothane inhalation did not produce cardiac arrhythmias. In a preliminary clinical trial, PLV-2 was found to be a safe and effective local vasoconstrictor.

THE USE of epinephrine during general anesthesia in man is safe, provided certain precautions are taken.[1, 2] Unfortunately, case reports [1] and personal communications of cardiac arrhythmias and cardiac arrests indicate that epinephrine has not always been used with proper care. These experiences have prompted the search for a local vasoconstrictor free of arrhythmic potential. Recently, 2-phenylanine-8-lysine vasopressin (PLV-2) was introduced for use as a systemic and local vasoconstrictor. The present study was therefore undertaken: (1) to compare the effects of epinephrine and PLV-2 on the cardiac rhythm during general anesthesia in the cat and in man; (2) to determine the effectiveness of PLV-2 as a local vasoconstrictor.

Methods

Cat. Fourteen cats weighing 2 to 4 kg. were studied. Each animal was placed in a clear plastic box, to which 10 per cent ether and 90 per cent oxygen were delivered from a Vernitrol anesthesia machine. When surgical anesthesia was established, the animal was removed from the box and a tracheostomy performed. The inhalation mixture was then changed to either 1 per cent halopropane and 99 per cent oxygen, or 25 per cent cyclopropane and 75 per cent oxygen. A nonrebreathing system (Sierra nonrebreathing value 28-560) and mechanical ventilation (Frumin-Lee respirator with pediatric bellows) were used. In some animals, halopropane or cyclopropane, rather than ether, was inhaled by the cat while in the plastic box. The results were not significantly different in these animals. The femoral artery and vein were cannulated. Femoral arterial pressure was measured with a Statham transducer. Lead 2 of the electrocardiogram and arterial pressure were recorded on a Grass polygraph at a paper speed of 2.5 or 25 mm./second. In order to check the adequacy of ventilation, arterial blood samples were drawn at appropriate intervals for analysis of *p*H and P_{CO_2} (Astrup AME-1). All injections were made into the femoral vein. A heating pad was used to maintain the rectal temperature within one degree centigrade of control.

Man. Fifty-nine patients given general anesthesia were studied. Most of the patients received atropine or scopolamine 0.4–0.8 mg., pentobarbital 100 mg. and/or meperidine 50–100 mg., 60–90 minutes prior to induction. Anesthesia was usually induced with 150–500 mg. of 2.5 per cent thiamylal and maintained, via a nonrebreathing system (Sierra nonrebreathing valve), with: (1) cyclopropane 20–30 per cent and oxygen; (2) halothane 1–2 per cent and oxygen; (3) trichlorethylene 0.5–1.0 per cent and oxygen; (4) fluroxene 4–7 per cent and oxygen; or (5) nitrous oxide 70 per cent and oxygen. All patients were intubated (following 60–100 mg. of succinylcholine) and artificially ventilated (manually) with a minute volume of 6–10 liters/minute (measured with a Wright ventilometer or Col-

* Department of Anesthesiology and Department of Pharmacology, Columbia University, and The Anesthesiology Service, The Presbyterian Hospital, New York, New York.

Supported in part by Grant GM-09069-02 from the National Institute of General Medical Sciences of the National Insittute of Health. Accepted for publication February 12, 1965.

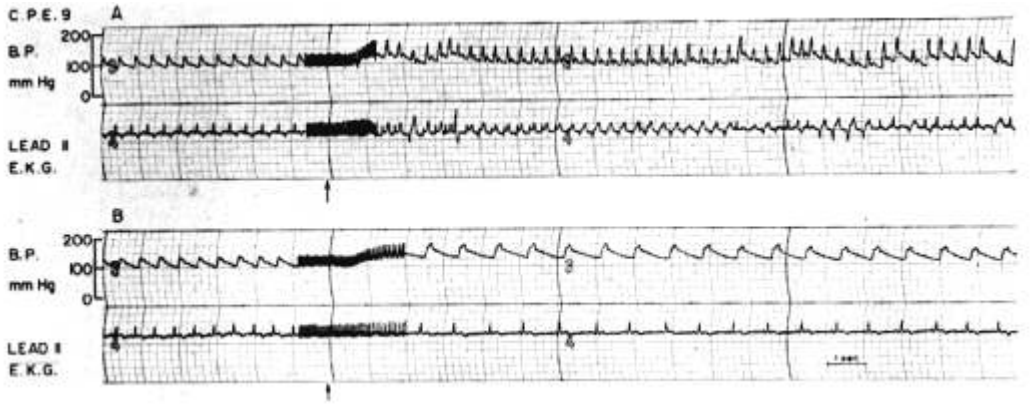

FIG. 1. Effects of epinephrine and PLV-2 on cardiac rhythm during cyclopropane inhalation. *Panel A:* At ↑ injection of 1 μg./kg. of epinephrine produced cardiac arrhythmias. *Panel B:* At ↑ injection of 2 U./kg. of PLV-2 did not produce arrhythmias.

lins Respirometer). During anesthesia analysis of arterialized samples of blood from the ear revealed that the *p*H was higher and P_{CO_2} lower than the control values obtained prior to the induction of anesthesia. Blood pressure was measured by auscultation. Lead 2 of the electrocardiogram was monitored on an ORM-1 cardioscope and recorded in some cases on a polygraph (Invengineering and Offner components).

Twenty-five surgical patients who received local anesthesia were also studied. The preoperative medication of these patients was similar to that given the patients who received general anesthesia. Blood pressure and lead 2 of the electrocardiogram were monitored as described above.

The following drugs were used: epinephrine (10 μg./ml.); PLV-2 (5 U./ml.); lidocaine 1 per cent; lidocaine 1 per cent with 1/100,000 epinephrine, lidocaine 1 per cent with 0.15 U. PLV-2/ml. Both epinephrine and PLV-2 were added to the lidocaine just prior to the time of injection.

Results

Cat. The intravenous injection of epinephrine during cyclopropane anesthesia produced transient (30–90 sec.) ventricular arrhythmias in 9 cats (fig. 1A). The smallest doses required to produce arrhythmias were 0.25 μg./kg. in 1 cat, 0.5 μg./kg. in 2, 1 μg./kg. in 5, and 2 μg./kg. in 1. The arrhythmic threshold dose of epinephrine produced a rise in systolic and diastolic pressure (15–25 per cent) in 7 of 9 cats. A fall in systolic and diastolic pressure (10–20 per cent) occurred in the cat whose arrhythmia threshold dose was 0.25 μg./kg. and in one of the cats whose threshold dose was 0.5 μg./kg. In these 9 cats, the intravenous injection of 1–2 U./kg. of PLV-2 never produced cardiac arrhythmias (fig. 1*B*). A rise in systolic and diastolic pressure of 15–25 per cent was usually produced.

In 5 other cats, ventricular arrhythmias were produced by the inhalation of 1 per cent halopropane and 99 per cent oxygen. The injection of 1 μg./kg. of epinephrine increased the frequency of ectopic activity in all 5 cats. The injection of 2 U./kg. of PLV-2 restored a normal sinus rhythm in 3 cats and decreased the frequency of ectopic activity in 2.

Man. The intravenous injection of epinephrine during cyclopropane anesthesia produced transient (30–90 seconds) ventricular arrhythmias in 5 patients. The doses required were 0.3 μg./kg. in 1 patient, 0.4 μg./kg. in 1, 0.5 μg./kg. in 2 and 0.8 μg./kg. in 1. In these 5 patients, nitrous oxide 70 per cent, oxygen 30 per cent, and intravenous meperidine were substituted and 1 μg./kg. of epinephrine injected 1 hour later. A normal sinus rhythm was maintained in these patients, as well as in 5 others who received 1 μg./kg. of epinephrine during anesthesia with 70 per cent nitrous oxide, 30 per cent oxygen, and intravenous meperidine. The intravenous injection of epinephrine during halothane anesthesia (3 patients), trichlorethylene (3 patients) and fluroxene (3 patients) also produced cardiac

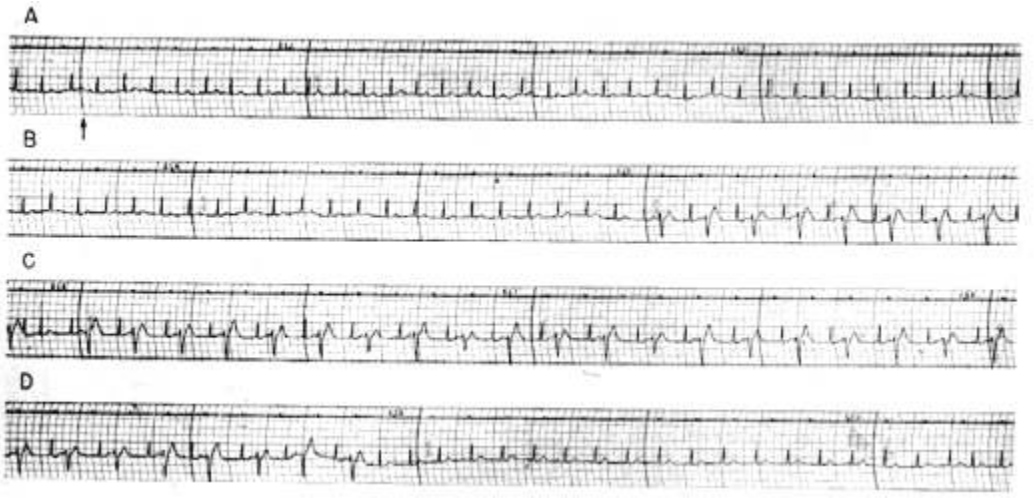

FIG. 2. Cardiac arrhythmias produced by injection of epinephrine during fluroxene inhalation. Injection of 0.8 μg./kg. of epinephrine at ↑ produced cardiac arrhythmias of 40 seconds duration.

arrhythmias of 30–90 seconds duration (fig. 2). The range of dose required was 0.3–1.0 μg./kg. The increase in blood pressure produced by 0.3–1 μg./kg. of epinephrine was 15–100 per cent.

Patients anesthetized with cyclopropane (7 patients), halothane (4 patients) or trichlorethylene (4 patients) received 3–5 U. (0.05–0.07 U.//kg.) of PLV-2 intravenously. A normal sinus rhythm was maintained in all 15 patients. The blood pressure increased 15–40 per cent. Circumoral pallor was noted in all 15 patients.

A clinical study of the local vasoconstrictor action of PLV-2 was carried out in 25 patients anesthetized with nitrous oxide-oxygen-trichlorethylene; cyclopropane-oxygen; diethyl ether-oxygen; fluroxene-oxygen; thiamylal-nitrous oxide-oxygen-meperidine. The surgeons were told that either 1 per cent lidocaine, 1 per cent lidocaine with 1/100,000 epinephrine or 1 per cent lidocaine with 0.15 U. of PLV-2/ml. might be used. However, each patient received 10 to 20 ml. of lidocaine-PLV-2 by intradermal and subcutaneous injection. The surgeons judged local hemostasis to be satisfactory in 23 of 25 patients. There were no changes in cardiac rhythm in any of the patients. Circumoral pallor was noted in 4 patients.

Twenty-five patients scheduled for plastic surgery with local anesthesia were also studied. Each patient had at least 3 lesions to be removed or repaired. The surgeon was given 20 ml. of three unknown solutions. One contained lidocaine 1 per cent, another lidocaine 1 per cent with 1/100,000 epinephrine, and the third lidocaine 1 per cent with 0.15 U. PLV-2/ml. The person who mixed the solutions was present but made no comment other than to record the opinion of the surgeon as to whether local hemostasis was satisfactory or unsatisfactory. The hemostasis with lidocaine 1 per cent was satisfactory in 4 patients and unsatisfactory in 21 patients. Lidocaine-epinephrine was satisfactory in 23 patients and unsatisfactory in 2 patients. Lidocaine-PLV-2 was satisfactory in 22 of 25 patients. After stating whether vasoconstriction was satisfactory or unsatisfactory, the surgeons were asked to compare the adequacy of hemostasis in each patient. Where a difference was believed to exist, epinephrine was rated as better than PLV-2 in 9 patients; while the reverse was noted in 3 patients. In one patient, lidocaine without epinephrine was rated superior to lidocaine-epinephrine.

There was a great deal of guessing by the surgeons who attempted to predict which of the three solutions they were using. Guessing was often successful because of differences in appearance of the injected areas. Pallor was noted in the area injected with PLV-2, while pallor and, in some patients, cyanosis were noted in the area injected with epineph-

rine. The onset of pallor was also more rapid in the area injected with epinephrine.

Discussion

In a series of papers from this department, the use of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man was studied.[1, 2, 3] We reviewed data from animal experiments from 1912 to the present which showed that the intravenous injection of epinephrine during the inhalation of cyclopropane or halogenated hydrocarbons may produce cardiac arrhythmia or death. It was also pointed out that there were many case reports of cardiac arrhythmia or death associated with the use of epinephrine during anesthesia with cyclopropane, trichlorethylene or halothane. Nevertheless, we demonstrated that epinephrine could be used safely during trichlorethylene or halothane anesthesia provided certain precautions concerning dose, route of administration, and prevention of acidosis were taken. Although arrhythmias were seen with cyclopropane and 1/60,000 epinephrine, we have used cyclopropane and 1/120,000 epinephrine and arrhythmias were rarely seen.

We previously found that the subcutaneous injection of as much as 1.4 μg./kg. every 5 minutes to a total dose of 7 μg./kg. did not produce cardiac arrhythmias during anesthesia with halogenated hydrocarbons.[1, 2] However, in the present study the single intravenous injection of as little as 0.3 μg./kg. of epinephrine could produce cardiac arrhythmias. A marked difference in the intravenous and intramuscular dose of epinephrine required to produce cardiac arrhythmia was also demonstrated by Hall and Norris[4] in dogs anesthetized with halothane. They found that the intramuscular dose of epinephrine required to produce arrhythmias was 159 times greater than the intravenous dose (approximately 1.7 μg./kg. intravenously and 262 μg./kg. intramuscularly).

The effects of intravenous epinephrine and norepinephrine in patients anesthetized with halothane and cyclopropane have been studied by Surks and Luger,[5] Price *et al.*,[6] and Andersen and Johansen.[7] Surks and Luger[5] infused norepinephrine (8–24 μg./minute) during cyclopropane anesthesia without producing cardiac arrhythmias. Price *et al.*[6] found that the intravenous infusion of epinephrine and/or norepinephrine at rates of 4–26 μg./minute produced arrhythmias in 6 of 8 subjects anesthetized with cyclopropane. Andersen and Johansen[7] reported that a continuous infusion of epinephrine at a rate of 4.4–13.2 μg./minute or norepinephrine at a rate of 5.5–13.2 μg./minute produced arrhythmias during halothane inhalation. In the present study, 0.3–1.0 μg./kg. of epinephrine in a single intravenous injection produced cardiac arrhythmias with halothane, cyclopropane, trichlorethylene, and fluroxene.

It should be pointed out that the problems associated with epinephrine are not entirely attributable to "sensitization" of the heart to catecholamines by cyclopropane or the halogenated hydrocarbons. Arrhythmias, as well as cardiac arrests, have been reported[8, 9] following the use of epinephrine during ether anesthesia. In addition, cardiac arrhythmias have been observed at the Presbyterian Hospital following the rapid (5–10 minutes) injection of 100–200 ml. of 1/100,000 epinephrine into the scalp during nitrous oxide anesthesia. Cardiac arrest also was seen in an unanesthetized patient following the intranasal injection of 6 to 8 mg. of epinephrine in the mistaken belief that lidocaine was being used.

It is the conviction of the author that epinephrine may safely be used during anesthesia, provided specific precautions are exercised and there is communication and understanding between the surgeon and anesthesiologist. However, since these conditions do not always prevail, the safety of epinephrine must be considered relative. It therefore seemed logical to explore the possibility of using an effective local vasoconstrictor agent which did not produce cardiac arrhythmias whether injected subcutaneously or intravenously.

In the present study, the intravenous injection of PLV-2 in cats anesthetized with cyclopropane did not produce cardiac arrhythmia. The intravenous and subcutaneous injection of PLV-2 in man during cyclopropane, trichloethylene, or halothane inhalation did not produce cardiac arrhythmias. Indeed, PLV-2 was found to have an antiarrhythmic action in the cat. The precise and objective clinical evaluation of the local vasoconstrictor action of PLV-2 was marred by the ability of the surgeons to distinguish among lidocaine, lido-

caine-epinephrine and lidocaine-PLV-2 on the basis of the appearance of the surgical field. In addition, evaluation of hemostasis is difficult because of variations in vascularity and the highly subjective nature of the evaluation. Despite these difficulties, PLV-2 was considered to be an effective local vasoconstrictor. In this and additional clinical studies in progress, the opinion of the surgeons has been either that PLV-2 is as good a local vasoconstrictor as epinephrine, or that PLV-2 is an effective vasoconstrictor not quite as good as epinephrine, but worth using because of the absence of cardiac arrhythmias.

PLV-2 has been used in Europe under the name Octapressin. It has been reported that PLV-2 is of value: (1) as a local vasoconstrictor during obstetrical, gynecological, and otorhinolaryngological surgery;[10, 11, 12] (2) as an intravenous vasopressor;[13] (3) in the treatment of esophageal varices (PLV-2 decreases portal venous pressure).[14] Shanks [15, 16] and Hügen [17] reported that the intravenous and subcutaneous use of PLV-2 with cyclopropane, halothane, or trichlorethylene did not produce cardiac arrhythmia. Klingenström and Westermark [18] compared the action of epinephrine (1/100,000) and PLV-2 (5 U./30 ml.) in prolonging the duration of action of lidocaine (0.5 per cent). The duration of action of lidocaine alone was 1 hour, lidocaine-epinephrine 3.5–4 hours and lidocaine-PLV-2 3.5–4 hours. They also observed that in the injected area epinephrine produced pallor and cyanosis, while PLV-2 produced only pallor. The tissue P_{O_2} in the area injected with epinephrine was lower than in the PLV-2 area. They suggested that tissue hypoxia produced by epinephrine might adversely affect wound healing and increase the possibility of postoperative hemorrhage and edema, and that PLV-2 might therefore be a better choice as a local vasoconstrictor.

The author is indebted to Dr. R. Bircher of Sandoz, Inc., for supplying PLV-2 and to Dr. E. M. Papper for critically reviewing the manuscript.

References

1. Matteo, R. S., Katz, R. L., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. 1. Trichlorethylene, ANESTHESIOLOGY 23: 360, 1962.
2. Katz, R. L., Matteo, R. S., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. 2. Halothane, ANESTHESIOLOGY 23: 597, 1962.
3. Matteo, R. S., Katz, R. L., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. 3. Cyclopropane, ANESTHESIOLOGY 24: 327, 1963.
4. Hall, K. D., and Norris, F. H., Jr.: Fluothane sensitization of dog heart to action of epinephrine, ANESTHESIOLOGY 19: 631, 1958.
5. Surks, S. S., and Luger, N. M.: Clinical use of Levo-arterenol during cyclopropane anesthesia, Surgery 35: 104, 1954.
6. Price, H. L., Lurie, A. A., Jones, R. E., Price, M. L., and Linde, H. W.: Cyclopropane Anesthesia. II. Epinephrine and norepinephrine in initiation of ventricular arrhythmias by carbon dioxide inhalation, ANESTHESIOLOGY 19: 619, 1958.
7. Andersen, N., and Johansen, S. H.: Incidence of catechol-amine-induced arrhythmias during halothane anesthesia, ANESTHESIOLOGY 24: 51, 1963.
8. Byrd, M. L.: Misuse of epinephrine during ether anesthesia: case report, ANESTHESIOLOGY 2: 654, 1941.
9. Guedel, A. E., and Knoefel, P. K.: Ventricular fibrillation in anesthesia, Amer. J. Surg. 34: 496, 1936.
10. Hochuli, E.: Klinische Erfahrungen mit del lokalen Anwendung von Octapressin in der Gynäkologie und in der Geburtshilfe, Schweiz. med. Wschr. 92: 654, 1962.
11. Bollobas, B.: Oto-rhino-laryngologische Erfahrungen mit Octapressin, Wien. med. Wschr. 113: 277, 1963.
12. de Grenus, E.: Die Kreislaufstabilisierung bei der Tonsillektomie in Lokalanesthesie (Ersatz des Adrenaline durch Octapressin), Pract. Otorhinolaryng. 25: 145, 1963.
13. Barbieri, G. C., and Roganti, M.: Contributo al trattamento farmacologico del collasso cardio-circolatorio in chirurgia generale ed urologica, Minerva Anest. 29: 434, 1963.
14. Tsakiris, A., Haemmerli, U. P., and Bühlmann, A.: Reduction of portal venous pressure in cirrhotic patients with bleeding from oesophageal varices, by administration of a vasopressin derivative, phenylalanine-2-lysine-8-vasopressin, Amer. J. Med. 36:825, 1964.
15. Shanks, C. A.: Intravenous Octapressin during halothane anesthesia: a pilot study, Brit. J. Anaesth. 35: 640, 1963.
16. Shanks, C. A.: The compatibility of Octapressin with cyclopropane, trichlorethylene and halothane, New Zeal. Med. J. 63: 156, 1964.
17. Hügen, W.: Die Vertraglichkeit von Octapressin mit verschiedenen Narkosen, Anaesthesist 11: 185, 1962.
18. Klingenström, P., and Westermark, L.: Local effects of adrenaline and phenylalanyl-lysyl-vasopressin in local anaesthesia, Acta Anaesth. Scand. 7: 131, 1963.