J Anesth (2003) 17:204–205
DOI 10.1007/s00540-003-0170-z

Journal of
Anesthesia

Short communications

Hemodynamic effects of felypressin and epinephrine on anesthetized rats

Glenan Singi, Nereida de Sousa Oliveira, Lourdes Dias Araujo, and Marianne Bastos Singi

Department of Biological Science, School of Pharmacy and Odontology of Alfenas, MG, Brazil

Key words Epinephrine plus felypressin combination · Local anesthetic · Vasoconstrictors

Vasoconstrictor substances are added to local anesthetics to increase the duration and intensity of the anesthesia, as well to decrease the salt toxic effects, because they reduce tissue perfusion and local metabolism, increasing the time of contact of the anesthetic with the nerve fiber [1]. The most commonly used vasoconstrictors in clinical practice are catecholamines (epinephrine and norepinephrine) [2]. The actions of catecholamines include increased arterial blood pressure, heart rate, coronary and cerebral blood flow, myocardial contraction, and oxygen consumption. Because of these effects, epinephrine can cause hypertension and tachydysrhythmias [3]. Attempting to find a vasoconstrictor without these side effects, Boisonnas and Guttman [4] synthesized felypressin from vasopressin or antidiuretic hormone (ADH). Gerke et al. [5], using a combination of felypressin and epinephrine in local anesthetic solutions, observed that felypressin potentiated the vasoconstriction provoked by epinephrine in the rabbit auricular artery. This potentiation would allow the use of a lower epinephrine concentration with local anesthetics, decreasing its risks to the cardiovascular system, due to the synergism between felypressin and epinephrine reported by Gerke et al. [5]. The purpose of this study was to verify the effects of the combination of these two vasoconstrictors on the arterial pressure and the electrocardiogram of anesthetized rats.

Address correspondence to: G. Singi, Rua Gabriel Monteiro da Silva, 714 Alfenas MG, Brazil CEP 37130-000.
Received: May 7, 2002 / Accepted: April 1, 2003

Rats ($n = 10$) were used. The animals were anesthetized with sodium pentobarbital ($30\,mg \cdot kg^{-1}$) intraperitoneally. After tracheotomy, cannulation of the jugular vein and the carotid artery was performed for injection of drugs and to record the mean arterial blood pressure (MAP), respectively. Preliminary studies were done to determine the doses. The injected doses were: 27.29μM of epinephrine, 4.80μM of felypressin, and a combination of 27.29μM of epinephrine plus 4.80μM of felypressin. The substances were prepared with serum. Epinephrine and felypressin were administered by i.v. injection of 0.2 ml, and the combination by i.v. injection of 0.4 ml, both followed by injection of 0.2 ml of serum to flush the residual. The interval between administrations was 15 min, and the rate of administration was 0.2 ml per 5 s. The hemodynamic variables stabilized, on average, 15 min after the end of the preparation. The sequence of application of the doses was drafted before each experiment. MAP was recorded with a transducer TBS 104A, coupled to a BIOPAC SYSTEM Model MP100 (Santa Barbara, CA, USA). An electrocardiograph ECG-4-FUNBEC (São Paulo, Brazil) was used to record the heart rate (HR). The electrocardiogram was evaluated in D2 derivation (with the negative electrode on the right front leg and the positive electrode on the left rear leg). The records were made before and 15 s after administration of the substances, at the time of the highest effect. The results were analyzed by ANOVA (Student-Newman-Keuls), with $P < 0.05$ indicating statistical significance.

The application of 27.29μM of epinephrine significantly ($P < 0.05$) increased the MAP by 148% (from 117.5 ± 4.7 mmHg in the control to 291.7 ± 40.0 mmHg at 15 s) (Table 1), and it did not change the HR significantly (Table 2). The application of 4.80μM of felypressin significantly increased ($P < 0.05$) the MAP by 37.0% (from 116.8 ± 4.9 mmHg in the control to 159.4 ± 20.6 mmHg at 15 s) (Table 1), but it did not change the HR (Table 2). The combination of epineph-

Table 1. Mean ± SEM mean arterial blood pressure (mmHg) in controls and 15 s after administration of 27.29 μM of epinephrine, 4.80 μM of felypressin, and a combination of 27.29 μM of epinephrine plus 4.80 μM of felypressin in anesthetized rats

Substance	Control	Effect at 15 s
Epinephrine	117.5 ± 4.7	291.7 ± 40.0[a,b]
Felypressin	116.8 ± 4.9	159.4 ± 20.6[a]
Combination	121.0 ± 4.5	181.6 ± 16.6[a]

[a] Significantly different from control ($P < 0.05$)
[b] Significantly different from felypressin and combination ($P < 0.05$)

Table 2. Mean ± SEM heart rate (beats·min^{-1}) in controls and 15 s after administration of 27.29 μM of epinephrine, 4.80 μM of felypressin, and a combination of 27.29 μM of epinephrine plus 4.80 μM of felypressin in anesthetized rats

Substance	Control	Effect at 15 s
Epinephrine	348.0 ± 10.6	356.0 ± 10.2
Felypressin	347.0 ± 8.4	351.0 ± 8.7
Combination	339.0 ± 8.9	362.4 ± 6.4[a]

[a] Significantly different from control ($P < 0.05$)

rine plus felypressin significantly ($P < 0.05$) increased the MAP by 50% (from 121.0 ± 4.5 mmHg in the control to 181.6 ± 16.6 mmHg at 15 s (Table 1), and it also significantly ($P < 0.05$) increased the HR from 339.0 ± 8.9 beats per minute in the control to 362.4 ± 6.4 beats per minute at 15 s (Table 2). The effects of epinephrine on the MAP were 83% greater than the effects of felypressin ($P < 0.05$) and were 60% greater than the effects of the combination ($P < 0.05$), with no significant difference between the values of HR. The elevation of the MAP with the use of the combination was 13% greater than that with the use of felypressin alone, but this increase was not significant and there was also no significant difference in the HR. After administration of epinephrine, felypressin, and the combination of epinephrine plus felypressin, the electrocardiogram did not change as compared with the control.

Our results are in accordance with those of several authors who demonstrated that the effects of felypressin on the cardiovascular system are much smaller than the effects of catecholamines [1,6,7]. Gerke et al. [5] reported potentiation of the vasoconstrictor effects of epinephrine by felypressin on the central artery of the rabbit's ear, but in the present study the opposite effect was found on the arterial blood pressure of rats: the combination reduced the vasoconstrictor effect of epinephrine, causing a smaller elevation of the MAP. According to Patel et al. [8], these effects probably occurred by inhibition of sympathetic ganglionic transmission by felypressin. The combination of epinephrine plus felypressin increased the HR 15 s after application, but the HR did not change when these substances were applied separately. It is possible that the epinephrine and the felypressin doses alone were not enough to induce a change in the HR.

From the data obtained in this study, it is difficult to explain the effects of the combination on the cardiovascular system, making it necessary to conduct new experiments, mainly at the level of the epinephrine (α) and felypressin (V_1) receptors.

According to these results, this combination of epinephrine plus felypressin, at doses to be determined for humans, may be used in local anesthetic solutions because it would attenuate the adverse effects of epinephrine.

References

1. Oliveira MAM, Tortamano N, Armonia PL, Rocha RG (1986) Estudo comparativo dos efeitos da lidocaína com noradrenalina e da prilocaína com felipressina sobre o sistema cardiovascular, em cães, em decorrência da variação da dose, via e tempo de administração (in Portuguese). Revista da Faculdade de Odontologia de São Paulo 24:75–92
2. Newcomb GM (1973) Contraindications to the use of catecholamine vasoconstrictors in dental local analgesics. New Zeal Dental J 69:25–30
3. Kochansky SW (1993) Use of vasoconstrictors anesthesia. Semin Periop Nursing 1:20–22
4. Boisonnas RA, Guttman ST (1960) Synthèse d'analogues de l'oxytocine et de la lysine-vasopressine contenant de la phénylalanine ou de la tyrosine en positions 2 et 3. Helvet Chim Acta 43:190–200
5. Gerke DC, Halloran TN, Frewin DB, Frost BR (1978) The use of mixtures of octapressin and adrenaline in local anaesthetic solutions to obtain more effective vasoconstriction. Aust Dental J 3:240–243
6. Hirota Y, Sugiyama K, Joh S, Kiyomitsu Y (1986) An echocardiographic study of patients with cardiovascular disease during dental treatment using local anesthesia. J Oral Maxillofac Surg 44:116–121
7. Singi G, Caram MM, Teixeira VE, Moreira LA (1996) Indicação do uso de felipressina (octapressin) como vasoconstritor nas anestesias locais (in Portuguese). Revista Brasileira de Medicina 7:597–604
8. Patel KP, Schmid PG (1988) Vasopressin inhibits sympathetic ganglionic transmission but potentiates sympathetic neuroeffector responses in hindlimb vasculature of rabbits. J Pharmacol Exp Ther 3:779–785