Cardiovascular Alterations After Injection of 2% Lidocaine With Norepinephrine 1:50,000 (Xylestesin) in Rats

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The purpose of the present study is to determine the cardiovascular effects produced by intravascular injection of 2% lidocaine with 20 µg/mL of norepinephrine on systolic, diastolic, and mean arterial pressures and heart rate of rats at the following times: control period, during the injection (first 15 seconds), during the first minute, and at the end of 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 minutes after drug administration. The study was performed on 13 male Wistar rats with weights between 200 grams and 220 grams that were awake during the recording of these parameters. The dose administered was proportional to 1 cartridge of local anesthetic (1.8 mL) in an average-size human, which is equivalent to 0.51 mg/kg of lidocaine hydrochloride and 0.51 µg/kg of norepinephrine hydrochloride. The average time of injection was 15.7 seconds. The results of this study showed significant increases in systolic, diastolic, and mean arterial pressure and a noticeable decrease in heart rate. The greatest variation occurred in the systolic blood pressure. The greatest alterations occurred during injection and within the first minute following administration of the anesthetic solution. We would anticipate these changes in the parameters analyzed to be clinically significant. Thus, dentists using 2% lidocaine with norepinephrine 20 µg/mL should be very careful to avoid intravascular injection.

Key Words: Intravascular injection; Lidocaine; Norepinephrine.

Local anesthetics are the most common drugs used by dentists in clinical practice. A reversible anesthetic effect and a wide margin of safety when administered in proper doses to obtain anesthesia are hallmarks of this drug class.

However, high blood concentrations obtained via intravascular injections or frank overdoses may produce significant toxic effects to the central nervous system and the cardiovascular system.^{1,2}

Other physiologic changes caused by the administra-

tion of local anesthetics may be due to the drug's direct and indirect effects on the heart and blood vessels.

We must also emphasize the role of vasoconstrictors, which are included in small concentrations in anesthetic solutions for the purpose of improving both the quality and the duration of anesthesia, as well as decreasing the systemic toxicity of the local anesthetic agent. In general, toxic effects caused by vasoconstrictors develop before the toxic effects produced by local anesthetics and, consequently, may constitute a limiting factor when considering the anesthetic solution dosage and volume in adults.^{3,4}

Individual susceptibility plays a significant role in determining the toxicity potential of a local anesthetic. Therefore, it is important to use appropriate anesthetic techniques to avoid intravascular injections.^{5,6} Adminis-

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tration speed is particularly important since a higher rate of injection of the local anesthetic solution leads to both a greater systemic blood level of the injected drug and greater potential toxic effects.⁵

Patients who are on antidepressants or beta-adrenergic blocking agents need a more careful preoperative evaluation of the maximum permissible dosages of local anesthetics and vasoconstrictors.^{7–9} In these patients, the use of phenylephrine is not recommended due to the higher risk of hypertension as a result of increased peripheral resistance. Felypressin is a nonadrenergic vasoconstrictor that would be recommended in these patients.¹⁰

These concerns become more relevant when we consider the possibility of accidental intravascular injection, especially when the local anesthetic is combined with adrenergic vasoconstrictors.^{5,11,12}

METHODS

This paper has been developed with the Physiology and Biophysics Department at the Institute of Biomedical Sciences of the University of São Paulo, Cardiovascular and Respiratory Section.

Thirteen (13) male Wistar rats with weights ranging from 200 grams to 220 grams were randomly selected at the Animal Center of the Institute of Biomedical Sciences, University of São Paulo.

The study was carried out according to the Ethical Standards for Animal Experiments, prepared by the COBEA (Brazilian School of Animal Experimentation), an agency affiliated with the International Council of Laboratory Animal Science (ICLAS), based on the International Standards for the Use of Animals in Research, which are established on the triad of sensibility, common sense, and good science. The animals went through a period of acclimatization, and were fed with Nutriara animal feed (Paulinia, São Paulo, Brazil).

The animals were sedated, then anesthetized in conformity with the veterinary protocol for general anesthesia. Ketamine hydrochloride, 30 mg/kg, was injected intraperitoneally for sedation. Ten minutes later, general anesthesia was performed with sulphuric ether through a mask made by Becker. Next, antisepsis was performed on the area to be operated, with 1% iodine povidone solution. The animals were then fixed to the surgery table by their paws, in a dorsal decubitus position, for the surgical procedures.

The surgical procedure included dissection and posterior cannulation of the carotid artery and jugular vein, in accordance with a standard technique from the laboratory of the Cardio-Circulatory Division of the Physi-

ology and Biophysics Department at the Institute of Biomedical Sciences, University of São Paulo.

We used polyethylene cannulas (PE 50), 8.5 cm long, previously tested and filled with heparin. With them we established the recordings of blood pressures. To aid the subsequent handling of cannulas, we used a 4-mm diameter trocar, through which they could be exteriorized. During recovery from anesthesia and throughout the experiment the rats were kept free in individual plastic cages. Recordings of the parameters that were studied, ie, systolic pressure, diastolic pressure, mean arterial pressure, and heart rate were obtained with a physiograph (Beckman Type RM Dynograph Recorder, Hato Rey, Puerto Rico).

To obtain the pulsatile pressure (systolic and diastolic arterial pressure), a 20-cm polyethylene cannula (P50), filled with 0.9% saline solution and a few drops of heparin, was connected to the carotid artery cannula. The mean arterial pressure was calculated from the systolic and diastolic pressures obtained from one of the channels of the Dynograph. The mean heart rate was obtained with a cardiometer coupler (Beckman Type 9875 B) and compared with pulsatile pressure, since each peak represents a cardiac cycle in a previously determined time interval. After the animal was adequately prepared and the Dynograph was calibrated, the equipment was set to record systolic, diastolic, and mean arterial pressures, as well as heart rate. A period of 15 minutes was used to stabilize the experiment (control period).

We then administered the test drug intravenously, through the trocar into the surgically exposed jugular vein, in dosages of 0.51 mg/kg lidocaine hydrochloride and 0.51 µg/kg norepinephrine hydrochloride. These doses were proportional to a 1.8 mL Xylestesin 2% (Cristália, Itapira, São Paulo, Brazil) cartridge administered to an adult person weighing 70 kg. The average time of injection was 15.7 seconds.

Graphs were then read: prior to drug injection (control period), during injection (first 15 seconds), during the first minute, and at the end of 1, 2, 3, 4, 5, 10, 15, 20, and 30 minutes from the beginning of the administration of the drug. These times were called T0 through T12, respectively. Blood pressure values (systolic, diastolic, and mean arterial) were determined using a scale ranging from 100 to 200 mm Hg, or 100 to 300 mm Hg, according to the animal's initial blood pressure in the control period.

To check the behavior of the data obtained in the evaluation of these parameters at different times, we used the analysis of variance (ANOVA) and the F test, 99% confidence level, expressing values as percentages. When alterations were significant, we used the Tukey

Figure 1. Averages for the systolic arterial pressure in mm Hg, after intravenous administration of 2% lidocaine hydrochloride (20 mg/mL) associated with norepinephrine hydrochloride (20 μ g/mL)—Xylestesin 2%, in a dose proportional to 1.8 mL.

test to determine the location of the significance. Decisions were made to a 0.01 significance level.

RESULTS

Figure 1 shows elevations in systolic blood pressure during the first 15 seconds of injection in T1 (9.51%), and during the first minute in T2 (25.16%). The ANOVA test showed that these alterations were statistically significant at 99% confidence level (Tukey test = 7.82). Following the first minute after intravascular administration of local anesthetic there was a tendency toward stabilizing that parameter, then returning to baseline values.

Figure 2 shows considerable diastolic blood pressure increases in T1 (23.47%), and beginning to stabilize in T2 (2.02%) during the first minute from the local anesthetic administration. The ANOVA test showed that this increase in T1 was statistically significant at 0.01 level (Tukey test = 8.21).

Figure 2. Averages of the diastolic arterial pressure in mm Hg, after intravenous administration of 2% lidocaine hydrochloride (20 mg/mL) associated with norepinephrine hydrochloride (20 μ g/mL)—Xylestesin 2%, in a dose proportional to 1.8 mL.

Figure 3. Averages of the mean arterial pressure measured in mm Hg, after intravenous administration of 2% lidocaine hydrochloride (20 mg/mL) associated with norepinephrine hydrochloride (20 μ g/mL)—Xylestesin 2%, in a dose proportional to 1.8 mL.

Figure 3 shows that the elevations in measured mean blood pressure started at T1 (8.71%), further increased at T2 (23.07%), and showed a tendency toward stabilization from that point on. These increases were statistically significant at 0.01 level (Tukey test = 7.88).

Figure 4 shows increases in calculated mean arterial pressure calculated in T1 (10.08%) and T2 (24.56%). The ANOVA showed that these increases were statistically significant at 0.01 level (Tukey test = 7.71).

The heart rate decreased in T1 with a variation of 2.15% as shown in Figure 5. This decrease was maximal in T2 with a 5.22% variation. The ANOVA test showed that these decreases were not statistically significant (0.01 level).

DISCUSSION

In general, when correctly selected and appropriately used in healthy patients, local anesthetics rarely cause

Figure 4. Averages of the mean arterial pressure calculated in mm Hg, after intravenous administration of 2% lidocaine hydrochloride (20 mg/mL) associated with norepinephrine hydrochloride (20 μ g/mL)—Xylestesin 2%, in a dose proportional to 1.8 mL.

Figure 5. Averages of heart rate, in cycles per minute, after intravenous administration of 2% lidocaine hydrochloride (20 mg/mL) associated with norepinephrine hydrochloride (20 µg/mL)—Xylestesin 2%, in a dose proportional to 1.8 mL.

problems. However, for patients with cardiovascular disorders there is some controversy.^{13–15} These patients may become extremely vulnerable especially when injected with drugs that affect the cardiovascular system.^{7,8,9,16}

It is important to consider that accidental intravascular injection or rapid administration of local anesthetic via infiltration may lead to significant blood pressure alterations and cardiac dysrhythmias.^{2,5}

Both laboratory¹⁷ and clinical research^{14,18,19} have evaluated changes occurring during dental procedures in the preoperative, intraoperative, and postoperative periods.^{1,15,16,19} We have observed in our experiments (Figure 1) that systolic blood pressure increased in T1 (138.3 mm Hg) and was maximal in T2 (158.38 mm Hg). These elevations represented an increase of 9.51% and 25.16%, respectively, and were statistically significant. The diastolic blood pressure increased in T1 (126.23 mm Hg), 23.47%. Following the first minute after intravascular administration of local anesthetic, there was a tendency toward stabilizing these parameters, then returning to baseline values.

The mean arterial pressure is a result of diastolic and systolic pressures, and it increased accordingly (Figure 3). The calculated mean arterial pressure followed the alterations of the measured arterial pressure, as was expected. This parameter was included in our study to verify the accuracy of the recording method used (Figure 4).

The heart rate decreased by 2.15% in T1 (353.7 beats per minute), as shown in Figure 5. This decrease was maximal in T2 (341.4 beats per minute) with an alteration of 5.22%. Cardiovascular alterations were likely caused by the alpha-adrenergic action of norepinephrine, that is, vasoconstriction. There was also a concomitant increase in peripheral vascular resistance. The heart rate decreased during injection with maximal reduction occurring during the first minute. This finding

was probably due to compensatory reflex mechanisms including the vagal reflex.^{12,15,18,20} This phenomenon is caused by receptors in great vessels, in the cardiac atrial walls, and in the vena cava and pulmonary veins. It results in a compensatory reflex that tries to maintain homeostasis by counterbalancing the increase in blood pressure.

Blood pressure elevations were observed by Oliveira et al¹⁷ when studying cardiovascular alterations due to intravenous injection of 2% lidocaine plus norepinephrine (20 µg/mL) in anesthetized dogs in doses of 1 and 3 cartridges containing 1.8 mL. In the first minute there were elevations in the blood pressure of 24.08% for the systolic, 18.52% for the diastolic, and 20.84% for the mean arterial pressure; and there was a 1.19% decrease in the heart rate with the 1.8 mL dose.

Our experimental findings, if applied to humans, may be a concern. This is especially true for patients with cardiac insufficiency or patients taking drugs that alter cardiovascular responses. We must emphasize the importance of studies that attempt to demonstrate the effect of sedative drugs on hemodynamic responses of the cardiocirculatory system.^{18,20} Their therapeutic action may block the receptors which are responsible for arteriolar vasoconstriction, which undoubtedly diminishes blood pressure responses.²¹

Additionally, during local anesthetic administration, intravascular injection may inadvertently occur. The stress of most dental procedures may trigger significant alterations in blood pressure and heart rate. These increases might incorrectly appear to be accidental intravascular injections. These cardiovascular changes are less of a concern when observed in normotensive patients who have normal physiologic adjustment mechanisms. However, this may not be acceptable in hypertensive patients or in those patients who present with unstable cardiovascular conditions, or where the changes may be greater such as in patients with diabetes, or patients taking tricyclic antidepressants, nonspecific beta-blockers, thyroid hormones, diuretics, or anorexic agents.^{20,22,23}

Finally, our results confirm those of Oliveira,¹⁷ the American Dental Association Council,³ and Faraco et al^{18,23} who recognize that accidental intravascular injection is the main cause of most toxic effects seen after administration of local anesthetics in dentistry and suggest the use of aspirating syringes for the safety of the patient.

CONCLUSION

When rats are administered lidocaine with norepinephrine intravenously in a dose equivalent to 1 cartridge in the average human:

1. Significant increases occur in the systolic, diastolic, and mean arterial pressures, with reflex bradycardia.
2. The greatest variation occurs in the systolic blood pressure.
3. The greatest alterations occur during injection and during the first minute following administration of the anesthetic solution.

The alterations of the parameters studied could be clinically significant in humans. Therefore, the anesthetic solution (2% lidocaine plus norepinephrine 20 µg/mL) should be used very carefully in dental practice, paying particular attention to avoiding accidental intravascular injection.

REFERENCES

1. Abraham-Inpijn LAL, Borgmeijer-Hoelen AB, Gortzak RAT. Changes in blood pressure, heart rate and electrocardiogram during dental treatment with use of local anesthesia. *J Am Dent Assoc.* 1981;116(4):531–536.
2. Yagiela JA. Local anesthetics. In: Yagiela JA, Neidle EA, Dowd FJ, eds. *Pharmacology and Therapeutics for Dentistry*. 4th ed. St Louis, Mo: Mosby; 1998:217–234.
3. American Dental Association Council on Scientific Affairs. *ADA Guide to Dental Therapeutics*. 2nd ed. Chicago, Ill: American Dental Association; 2000.
4. USP DI Updates On-line, United States Pharmacopeial Convention Inc. <http://library.dialog.com/bluesheets/html/bl0461.html#top> (accessed March 16, 2004).
5. Malamed SF. *Handbook of Local Anesthesia*. 5th ed. St Louis, Mo: Mosby; 2004:159–167.
6. Kiyomitsu Y, Sugiyama K, Joh S. The effects of catecholamines added to lidocaine on cardiac function. *Anesth Prog.* 1989;36:198–200.
7. Yagiela JA. Local anesthetics. *Anesth Prog.* 1991;38(4):128–141.
8. Mito RS, Yagiela JA. Hypertensive response to levonordefrin in patient receiving propranolol. report of case. *J Am Dent Assoc.* 1988;166(1):55–57.
9. Foster CA, Aston SJ. Propranolol and epinephrine interaction: a potential disaster. *Plast Reconstr Surg.* 1988;72(1):55–57.
10. Hargreaves KM, Neidle EA. Adrenergic drugs. In: Yagiela JA, Neidle EA, Dowd FJ, eds. *Pharmacology and Therapeutics for Dentistry*. 4th ed. St Louis, Mo: Mosby; 1988:85–99.
11. Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. *J Calif Dent Assoc.* 2006;34:971–976.
12. Van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog.* 1992;39(3):87–89.
13. Brand HS, Gortzak RA, Palmer-Buova CC, Abraham RE, Abraham-Inpijn L. Cardiovascular and neuroendocrine responses during acute stress induced by different types of dental treatment. *Int Dent J.* 1995;45(1):45–48.
14. Silvestre FJ, Verdú MJ, Sanchis JM, Grau D. Effects of vasoconstrictors in dentistry upon systolic and diastolic arterial pressure. *Med Oral.* 2001;6(1):57–63.
15. Fernieini EM, Bennett JD, Silverman DG, Halaszynski TM. Hemodynamic assessment of local anesthetic administration by laser Doppler flowmetry. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91(5):526–530.
16. Meechan JG, Parry G, Rattray DT, Thomason JM. Effects of dental local anaesthetics in cardiac transplant recipients. *Br Dent J.* 2002;192(3):161–163.
17. Oliveira MAM, Tortamano N, Armonia PL, Rocha, RG. Estudo comparativo dos efeitos da lidocaina com noradrenalina e da prilocaina com felipressina sobre o sistema cardiovascular, em cães, em decorrência da variação da dose, via e tempo de administração. *Rev Fac Odont São Paulo.* 1986;24(2):75–92.
18. Faraco FN, Armonia PL, Simone JL, Tortamano N. Assessment of cardiovascular parameters during dental procedures under effect of benzodiazepines: a double blind study. *Braz Dent J.* 2003;14(3):215–219.
19. Niwa H, Satoh Y, Matsuura H. Cardiovascular responses to epinephrine-containing local anesthetics for dental use: a comparison of hemodynamic responses to infiltration anesthesia and ergometer-stress testing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;90(2):171–181.
20. Shepherd SR, Sims TN, Jonhson BW, Hershman JA. Assessment of stress during periodontal surgery with intravenous sedation and with local anesthesia only. *J Periodontol.* 1988;59(3):147–154.
21. Charney DS, Mihic SJ, Harris A. Hipnóticos e sedativos. In: Goodman E, Gilman R, eds. *As Bases Farmacológicas da Terapêutica*. 10 ed. Rio de Janeiro, Brazil: McGraw-Hill; 2003:303–324.
22. Cioffi GA, Terezalmy GT, Chenow, Blake RG, Glah N. The hemodynamic and plasma catecholamine response to routine dental care. *J Am Dent Assoc.* 1985;111(1):67–70.
23. Faraco FN, Armonia PL, Sendyk WR. Análise da eficácia anestésica da lidocaina a 2% e a 3% em relação ao estresse do paciente odontológico. *Rev Bras Odontol.* 2004;61(1):8–11.