A Combination of Dexmedetomidine and Lidocaine Is a Cardiovascularly Safe Dental Local Anesthetic for Hypertensive Rats Treated With a Nonselective β -Adrenergic Antagonist

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Hypertensive patients receiving nonselective β -adrenergic antagonists are vulnerable to hypertension and bradycardia when injected with dental local anesthetic formulations containing epinephrine. Dexmedetomidine (DEX), an α_2 -adrenergic agonist, has been reported to prolong and enhance the local anesthetic effects of lidocaine. The cardiovascular effects of the DEX-lidocaine combination have not yet been investigated in the presence of nonselective β -adrenergic antagonists. Therefore, we assessed the cardiovascular effects of the DEX-lidocaine combination in spontaneously hypertensive rats (SHR) treated with a nonselective β -adrenergic antagonist (propranolol). We injected propranolol-treated rats with various concentrations of DEX alone, 100 $\mu\text{g/kg}$ epinephrine alone, or 5 $\mu\text{g/kg}$ DEX combined with 2% lidocaine and measured their blood pressure (BP) and heart rates (HR) to assess the cardiovascular effects. The BP of propranolol-treated SHR was significantly increased by treatment with 100 $\mu\text{g/kg}$ epinephrine alone. The BP and HR of propranolol-treated SHR were not significantly changed by treatment with low concentrations of DEX, but they were significantly decreased by treatment with a high concentration of DEX (50 $\mu\text{g/kg}$). Moreover, there was no significant difference in the BP and HR of propranolol-treated SHR after the injection of a combination of 5 $\mu\text{g/kg}$ DEX and 2% lidocaine. Thus, the DEX-lidocaine combination may be an acceptable addition to dental local anesthetic solutions from a cardiovascular standpoint for hypertensive patients receiving nonselective β -adrenergic antagonists.

Key Words: Dexmedetomidine, Lidocaine, Epinephrine; Nonselective β -adrenergic antagonist.

Dentists use vasoconstrictors such as epinephrine to prolong the duration of dental local anesthesia. However, vasoconstrictors occasionally produce adverse cardiovascular side effects such as hypertension and bradycardia, especially when administered to hypertensive patients. For those patients already taking nonselective β -adrenergic antagonists who were administered epinephrine, a large increase in blood pressure (BP) has previously been reported.^{1,2} This occurs because nonselective β -adrenergic antagonists causes epinephrine, which usually binds to both α - and β -adrenergic receptors, to act like a pure α -adrenergic agonist by binding only to α -adrenergic receptors, thus potentially

causing severe vasoconstriction with possible reflex bradycardia. Thus, the BP and heart rate (HR) of hypertensive patients receiving nonselective β -adrenergic antagonists may be negatively affected by the use of epinephrine that is present in dental local anesthetic formulations. On the other hand, epinephrine has less potential to cause cardiovascular changes in hypertensive patients taking cardioselective β -adrenergic antagonists.^{1,2} Therefore, safer and more effective dental local anesthetics are needed for hypertensive patients who are taking nonselective β -adrenergic antagonists.

Recent reports suggest that dexmedetomidine (DEX), an α_2 -adrenergic agonist, enhances the effect and prolongs the effective duration of local anesthesia.^{3–6} Further, as with all α_2 -adrenergic agonists, hypotension and bradycardia are the predominant side effects of DEX that are caused by its central sympatholytic effects.^{7–10} Therefore, we hypothesized that a combination of DEX and lidocaine might be a safer and more effective dental local anesthetic combination for hypertensive patients taking nonselective β -adrenergic antagonists. However,

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Figure 1. Measurement of the blood pressure (BP) and heart rate (HR) of rats using a sphygmomanometer. The rats were warmed to 37°C to 38°C using a cylinder thermostat and placed in a restrainer. The sphygmomanometer cuff was placed around the tail of each rat to measure the BP and HR.

the cardiovascular side effects of this combination have not yet been studied. Thus, we investigated whether the combination of DEX and lidocaine induces cardiovascular changes in a nonselective β -adrenergic antagonists treated hypertensive rat model.

MATERIALS AND METHODS

Animals

All experimental procedures and protocols used in the present study were approved by the Animal Care and Use Committee at The Nippon Dental University. All procedures were in accordance with the *Guide for the Care and Use of Laboratory Animals*. The experiments were performed using spontaneously hypertensive rats (SHR) weighing between 250 and 300 g ($n = 10$ for each experiment).

Reagents

Dexmedetomidine hydrochloride (DEX) was purchased from Sigma-Aldrich (St Louis, MO). Propranolol (Inderal) and 2% lidocaine were purchased from AstraZeneca (Osaka, Japan). Adrenaline (Bosmin) was purchased from Daiichi-Sankyo (Tokyo, Japan).

Measurement of Blood Pressure and Heart Rate

A computerized tail-cuff method (Softron Co Ltd, Tokyo, Japan) was used to measure the blood pressure (BP) and heart rate (HR) of rats,^{11–14} by placing a sphygmomanometer cuff around the tail of each rat (Figure 1). Propranolol was used as the nonselective β -

adrenergic antagonist in all experiments. All rats were injected intraperitoneally with propranolol (10 mg/kg) 15 minutes before the intraperitoneal injection of either 1 mL normal saline (NS), 1 mL of a solution of DEX (each of 3 individual injections at a concentration of 0.5, 5, or 50 μ g/kg) alone, 1 mL 100 μ g/kg epinephrine alone, or 1 mL 5 μ g/kg DEX combined with 1 mL of 2% lidocaine. The systolic BP (SBP), diastolic BP (DBP), and HR were measured and recorded every 5 minutes for 30 minutes (Figure 2).

Statistical Analyses

All SBP, DBP, and HR values were compared with baseline value. Data are represented as mean $\pm$

Figure 2. A schematic depicting the experimental schedule. Propranolol (10 mg/kg) was injected intraperitoneally 15 minutes prior to the experiments. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured by placing the sphygmomanometer cuff around the tail of each rat. The baseline values were recorded as control values 5 minutes prior to the experiments. The SBP, DBP, and HR were also monitored immediately after the injection of normal saline, dexmedetomidine (DEX; 0.5, 5, or 50 μ g/kg) alone, 100 μ g/kg epinephrine alone, or 5 μ g/kg DEX combined with 2% lidocaine and every 5 minutes thereafter for 30 minutes.

Figure 3. Cardiovascular effects of treatment with normal saline (NS; $n = 10$), dexmedetomidine (DEX; 0.5, 5, or 50 $\mu\text{g}/\text{kg}$; $n = 10$ for each experiment) alone, 100 $\mu\text{g}/\text{kg}$ epinephrine ($n = 10$) alone, or 5 $\mu\text{g}/\text{kg}$ DEX combined with 2% lidocaine ($n = 10$) on propranolol-treated hypertensive rats. White circles represent the NS group; black circles represent the 0.5 $\mu\text{g}/\text{kg}$ DEX (0.5D) group; black triangles represent the 5 $\mu\text{g}/\text{kg}$ DEX (5D) group; black squares represent the 50 $\mu\text{g}/\text{kg}$ DEX (50D) group; black diamonds represent the 100 $\mu\text{g}/\text{kg}$ epinephrine (Epi) group; white squares represent the 5 $\mu\text{g}/\text{kg}$ DEX combined with 2% lidocaine (SDL) group.

standard deviation. Statistical comparison of the BP and HR values at each time point among the various treatment groups was performed using repeated-measures analysis of variance and Tukey's post hoc test. p values < 0.05 were considered statistically significant.

RESULTS

As shown in Figure 3, we monitored the SBP, DBP, and HR of propranolol-treated SHR after the intraperitoneal injection of NS, DEX (0.5, 5, or 50 $\mu\text{g}/\text{kg}$), 100 $\mu\text{g}/\text{kg}$ epinephrine, or 5 $\mu\text{g}/\text{kg}$ DEX combined with 2% lidocaine ($n = 10$ for each experiment).

In the 100 $\mu\text{g}/\text{kg}$ epinephrine group, the SBP significantly increased at each time point. In contrast, the DEX (50 $\mu\text{g}/\text{kg}$) group showed a significant decrease in SBP from 15 to 30 minutes after injection. Also, there was a significant difference in DBP between the 100 $\mu\text{g}/\text{kg}$ epinephrine groups and DEX (50 $\mu\text{g}/\text{kg}$) groups at each time points. Moreover, there was a significant difference in HR between the NS and DEX (50 $\mu\text{g}/\text{kg}$) groups, DEX (0.5 $\mu\text{g}/\text{kg}$), and DEX (50 $\mu\text{g}/\text{kg}$), at 30 minutes after injection. Next, we monitored the SBP, DBP, and HR of the rats, which were

intraperitoneally injected with 5 $\mu\text{g}/\text{kg}$ DEX combined with 2% lidocaine. There was no significant difference in SBP, DBP, or HR among the NS, DEX (0.5 and 5 $\mu\text{g}/\text{kg}$), and 5 $\mu\text{g}/\text{kg}$ DEX combined with 2% lidocaine groups.

DISCUSSION

When we monitored the SBP, DBP, and HR of propranolol-treated SHR after various treatments (Figure 3), the 100 $\mu\text{g}/\text{kg}$ epinephrine-treated group showed a significant increase in SBP and DBP after epinephrine injection. These results were consistent with those of previous reports,^{1,2} which demonstrated that epinephrine when combined with a nonselective β -adrenergic antagonists markedly increases BP because of the unmasking of its α -adrenergic properties by nonselective β -adrenergic antagonists. While the injection of 0.5 or 5 $\mu\text{g}/\text{kg}$ DEX caused no significant difference in SBP, DBP, and HR, the injection of 50 $\mu\text{g}/\text{kg}$ DEX significantly decreased BP and HR. These results suggest that DEX does not produce hypotension at low concentrations, but at high concentrations, it produces hypotension and bradycardia in nonselective β -adrenergic antagonist-treated SHR. In addition,

in our study, transient hypertension from a high loading dose of DEX injection did not occur. In general, a high loading concentration of DEX causes transient hypertension from the stimulation of peripheral α_{2B} -adrenoceptors that mediate peripheral vasoconstriction. Moreover, low concentrations of DEX may show central sympatholytic effects associated with α_2 -adrenoceptor agonists.^{7–10} However, in our study, low doses of DEX did not decrease the BP or HR of nonselective β -adrenergic antagonist-treated SHR, which was in agreement with the report of Mizraket et al.¹⁵ Therefore, our results suggest that a low concentration of DEX could potentially be safely used for treating hypertensive patients receiving nonselective β -adrenergic antagonists without increased cardiovascular risks.

DEX has been reported to enhance the effect and prolong the effective duration of local anesthesia^{3–6} by 2 possible mechanisms. The first mechanism involves the α_2 -adrenoceptor-mediated analgesic effect. As α_2 -adrenoceptors are involved in pain regulation, α_2 -adrenoceptor agonists mediate antinociception.^{16–20} However, this is a central nervous system effect, which suggests that a sufficient time period from administration and an adequate amount of DEX would need to enter the central nervous system for this effect to take place. The second mechanism involves local peripheral vasoconstriction around the injection site, which is mediated by the α_{2B} -adrenergic receptor.^{7,21} While both mechanisms support the assertion that DEX exerts beneficial effects on local anesthesia efficacy, the second mechanism might imply negative side effects such as hypertension. This study helps to establish the cardiovascular safety profile of DEX with lidocaine in an animal model vulnerable to hypertension.

Further studies comparing DEX with lidocaine versus epinephrine (in standard doses) with lidocaine in this model will further clarify the safety profile of DEX versus epinephrine in this propranolol-treated hypertensive rat model.

CONCLUSION

In a hypertensive rat model treated with the nonselective β -adrenergic antagonist, propranolol, our results indicate that SBP, DBP, and HR were not changed by 5 μ g/kg DEX combined with 2% lidocaine. From our study, a combination of a low concentration of DEX and 2% lidocaine might be a safer and more effective dental local anesthetic solution for hypertensive patients taking nonselective β -adrenergic antagonists.

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REFERENCES

1. Tarnow J, Müller RK. Cardiovascular effect of low-dose epinephrine infusions in relation to the extent of preoperative beta-adrenoceptor blockade. *Anesthesiology*. 1991;74:1035–1043.
2. Houben H, Thien T, van't Laar A. Effect of low-dose epinephrine infusion on hemodynamics after selective and nonselective beta-blockade in hypertension. *Clin Pharmacol Ther*. 1982;31:685–690.
3. Brummett CM, Norat MA, Palmisano JM, Lydic R. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. *Anesthesiology*. 2008;109:502–511.
4. Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. *Anesth Analg*. 2008;107:96–101.
5. Brummett CM, Williams BA. Additives to local anesthetics for peripheral nerve blockade. *Int Anesthesiol Clin*. 2011;49:104–116.
6. Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. *Anesthesiology*. 2009;111:1111–1119.
7. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. *Ann Pharmacother*. 2007;41:245–252.
8. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology*. 1992;77:1134–1142.
9. Kallio A, Scheinin M, Koulou M, et al. Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. *Clin Pharmacol Ther*. 1989;46:33–42.
10. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med*. 2007;8:115–131.
11. Tomita N, Higaki J, Kaneda Y, et al. Hypertensive rats produced by in vivo introduction of the human renin gene. *Circ Res*. 1993;73:898–905.
12. Kim Y. Interaction between beta blockers and epinephrine on hemodynamics of spontaneously hypertensive rats. *Res Commun Chem Pathol Pharmacol*. 1993;80:3–19.
13. Siraskar B, Volki J, Ahmed MS, et al. Enhanced catecholamine release in mice expressing PKB/SGK-resistant GSK3. *Pflugers Arch*. 2011;462:811–819.
14. Tomita N, Yamasaki K, Osako MK, Komai N, Shimamoto T, Morishita R. Combination therapy based on the angiotensin receptor blocker olmesartan for vascular

protection in spontaneously hypertensive rats. *Mol Med Rep.* 2009;2:733–738.

15. Mizrak A, Gul R, Erkutlu I, Alptekin M, Oner U. Premedication with dexmedetomidine alone or together with 0.5% lidocaine for IVRA. *J Surg Res.* 2010;164:242–247.

16. Hunter JC, Fontana DJ, Hedley LR, et al. Assessment of the role of alpha2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. *Br J Pharmacol.* 1997;122:1339–1344.

17. Stone LS, MacMillan LB, Kitto KF, Limbird LE, Wilcox GL. The alpha2a adrenergic receptor subtype mediates spinal analgesia evoked by alpha2 agonists and is necessary for spinal adrenergic-opioid synergy. *J Neurosci.* 1997;17:7157–7165.

18. Fairbanks CA, Wilcox GL. Moxonidine, a selective alpha2-adrenergic and imidazoline receptor agonist, produces spinal antinociception in mice. *J Pharmacol Exp Ther.* 1999; 290:403–412.

19. Gaumann D, Forster A, Griessen M, Habre W, Poinso O, Della Santa D. Comparison between clonidine and epinephrine admixture to lidocaine in brachial plexus block. *Anesth Analg.* 1992;75:69–74.

20. Oda A, Iida H, Tanahashi S, Osawa Y, Yamaguchi S, Dohi S. Effects of alpha2-adrenoceptor agonists on tetrodotoxin-resistant Na⁺ channels in rat dorsal root ganglion neurons. *Eur J Anaesthesiol.* 2007;24:934–941.

21. Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care.* 2001;7:221–226.