Hemodynamic Impact of Drug Interactions With Epinephrine and Antipsychotics Under General Anesthesia With Propofol

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Objective: Antipsychotic drugs exhibit α-1 adrenergic receptor-blocking activity. When epinephrine and antipsychotic drugs are administered in combination, β-2 adrenergic effects are thought to predominate and induce hypotension. This study aimed to assess hemodynamic parameters in patients regularly taking antipsychotics who were administered epinephrine-containing lidocaine under general anesthesia in a dental setting.
Methods: Thirty patients taking typical and/or atypical antipsychotics and scheduled for dental procedures under general anesthesia were enrolled. Five minutes after tracheal intubation, baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and percutaneous oxygen saturation (SpO_2) measurements were taken. The SBP, DBP, HR, and SpO_2 measurements were repeated 2, 4, 6, 8, and 10 minutes after the injection of 1.8 mL of 2% lidocaine (36 mg) with 1:80,000 epinephrine (22.5 mcg) via buccal infiltration.
Results: Differences between the baseline measurements and those of each time point were analyzed using Dunnett test, and no statistically significant changes were observed.
Conclusions: Our findings demonstrate that the use of epinephrine at a clinically relevant dose of 22.5 mcg for dental treatment under general anesthesia is unlikely to affect the hemodynamic parameters of patients taking antipsychotic medications.

Key Words: Epinephrine; Typical antipsychotics; Atypical antipsychotics; Drug interaction; Local anesthesia; General anesthesia; Hypotension.

Successful local anesthesia is essential to virtually all dental procedures. Many local anesthetics used today are combined with a vasoconstrictor (eg, epinephrine), which provides several advantages including increased anesthetic duration, decreased local anesthetic systemic toxicity, surgical site hemostasis, and enhanced neural blockade.[1–4] Because typical (first-generation) and atypical (second-generation) antipsychotic drugs have an α-1 adrenergic receptor blocking action,[5] it is thought that β-2 adrenergic receptor activity predominates when combined with epinephrine, causing dilation of peripheral blood vessels in skeletal muscle and inducing hypotension. Therefore, epinephrine-containing local anesthetics should be carefully administered in patients concurrently taking antipsychotics, such as those with schizophrenia, autism, intellectual disability, and dementia.

The Japanese Dental Society of Anesthesiology conducted a retrospective survey on the administration of epinephrine-containing lidocaine for dental patients taking antipsychotic medications at dental school hospitals and hospitals with both dentistry and psychiatry departments. The survey suggested that hypotension arising from the concomitant use of antipsychotics and epinephrine-containing lidocaine may be rare.[6] However, no prospective study has assessed the effects of the interaction between epinephrine-containing lidocaine used for dentistry and antipsychotics on hemody-

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namic parameters. In addition, general anesthesia is often necessary when providing dental care for patients regularly taking antipsychotic drugs, as they may exhibit uncooperative behavior and/or poor compliance. Because many general anesthetic agents have depressant effects on the cardiovascular system (ie, decreased myocardial contractility, decreased cardiac output, and vasodilation), a further reduction in blood pressure may occur if epinephrine-containing lidocaine is administered to antipsychotic users during anesthesia. The purpose of the present study was to clarify the hemodynamic response of regular antipsychotic users given epinephrine-containing lidocaine for dental procedures under general anesthesia.

METHODS AND MATERIALS

This prospective pilot study was performed at Nippon Dental University Hospital, Tokyo, Japan and included 30 patients who regularly used typical and/or atypical antipsychotics for more than 3 months and were scheduled for restorative dental procedures and/or extractions under general anesthesia. Exclusion criteria for the study were as follows: age <18 or >65 years; an American Society of Anesthesiologists physical status >2; concurrent use of cardiovascular and/or antidepressant drugs; allergy to lidocaine or any other study agents; and history of hypertension, heart failure, diabetes mellitus, or hyperthyroidism.

This study was approved by the Ethics Committee of the Nippon Dental University School of Life Dentistry, Tokyo, Japan (approval number NDU-T-2015-14). It was performed in accordance with the guidelines of that institution and of the Declaration of Helsinki and was conducted after clinical trial registration, as certified by the International Committee of Medical Journal Editors (trial identification number: UMIN000016644). Informed consent was obtained from all individual participants or legal guardians included in the study.

No premedication was administered to any patient. Upon arrival to the operating room, routine anesthesia monitors were applied, consisting of electrocardiography, pulse oximetry, a noninvasive blood pressure cuff, capnography, and bispectral index (BIS) monitoring. General anesthesia was induced with a target-controlled infusion of propofol 3 to 5 mcg/mL and a continuous infusion of remifentanil 0.2 to 0.3 mcg/kg/min using a syringe pump (TE-332S, Terumo) after an intravenous (IV) line was secured. The patient was administered 100% oxygen via a face mask during this process. If venous access was difficult to establish, a slow mask induction using sevoflurane was performed to facilitate IV placement, then anesthesia was switched to the same propofol and remifentanil infusions listed previously. Remifentanil administration was terminated immediately after nasotracheal intubation and following neuromuscular blockade with rocuronium bromide (0.6 mg/kg). Anesthesia was maintained with oxygen 2 L/min, air 4 L/min, and propofol at levels yielding BIS values of 40 to 60.

Five minutes after the discontinuation of remifentanil, baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), and percutaneous oxygen saturation (SpO_2) were recorded. Immediately after the baseline values were measured, 1.8 mL of 2% lidocaine (36 mg) with 1:80,000 epinephrine (22.5 mcg) was slowly administered with a 30-gauge needle via buccal infiltration in the right posterior mandibular region over a period of 30 seconds. The SBP, DBP, HR, and SpO_2 measurements were repeated at 2-, 4-, 6-, 8-, and 10-minute intervals after the local anesthetic injection. If the SBP decreased below 70 mm Hg, phenylephrine 0.1 mg was administered as a rescue for hypotension, and the administration time and dosage were recorded. The planned dental treatment was initiated 10 minutes after administration of the local anesthetic. At that time, remifentanil administration was restarted, and anesthesia was maintained with oxygen 2 L/min, air 4 L/min, propofol 2 to 3 mcg/mL, and remifentanil 0.2 to 0.3 mcg/kg/min at levels yielding BIS values of 40 to 60. The SBP, DBP, HR, and SpO_2 were continually measured at 5-minute intervals throughout the dental procedure, and adverse events up to 1 hour after the local anesthetic administration were examined.

All numerical data are expressed as mean ± SD. Differences from baseline to each time point for SBP, DBP, HR, and SpO_2 were analyzed using Dunnett test. All statistical analyses were performed using SPSS Version 24.0 (IBM; Armonk, NY). A P value <.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the 30 sample patients are presented in Table 1. All patients had American Society of Anesthesiologists scores of 1, and perioperative data are detailed in Table 2. Slow mask induction using sevoflurane was required in 4 cases, whereas an IV line could be secured without this technique in the other 26 cases.

Changes in SBP, DBP, HR, and SpO_2 over time are presented in Table 3. No statistically significant changes were observed in the SBP, DBP, HR, or SpO_2 for the 10-minute period after the administration of epinephrine-

Table 1. Subject Demographics ($n = 30$)

Age, mean ± SD, y	24.6 ± 4.9
Sex, male/female	26/4
Weight, mean ± SD, kg	75.4 ± 19.2
Height, mean ± SD, cm	168.6 ± 8.3
Body mass index, mean ± SD, kg/m^2	26.5 ± 5.9
Prescribed antipsychotics	*n* (includes overlaps)
Typical antipsychotics	
Butyrophenones	
Haloperidol	5
Bromperidol	1
Phenothiazines	
Propericiazine	1
Levomepromazine	5
Atypical antipsychotics	
Risperidone	16
Olanzapine	3
Aripiprazole	10
Reason for prescription	
Intellectual disability	20
Autism	16
Schizophrenia	2

containing lidocaine. No abnormalities in the hemodynamic parameters were noted over the 1-hour period following the local anesthetic injection.

DISCUSSION

In the present study, we assessed changes in the SBP, DBP, HR, and SpO_2 for 10 minutes after administering epinephrine-containing lidocaine to patients taking antipsychotic medications, and no significant change was noted in any measurement over time. This study demonstrated that low-dose epinephrine (22.5 mcg) added to local anesthetics administered for dental treatment under general anesthesia is unlikely to affect the hemodynamic parameters of patients taking antipsychotic medications.

Epinephrine is a potent stimulant of both α- and β-adrenergic receptors. α-1 adrenergic receptors are located in vascular smooth muscle and cause vasoconstriction when activated. However, β-1 and β-2 adrenergic receptors are primarily located in the heart and smooth muscle (vessels in skeletal muscle, bronchi, and gastrointestinal tract), respectively. Activation of β-1 adrenergic receptors increases the rate and force of contraction of the heart, whereas activation of β-2 adrenergic receptors induces dilation of vessels in skeletal muscle. The effects of epinephrine depend on the specific receptors being stimulated as well as the dosage, as epinephrine displays preferential binding depending on dose (high dose = α-1 activity, moderate dose = β-1 activity, and β-2 activity with lower doses). Therefore, the effect of epinephrine on blood pressure and HR differs depending on the dose; a small dose increases SBP and HR slightly, but vasodilation of skeletal muscle predominates, and DBP decreases. Mean blood pressure, however, does not change. When high-dose epinephrine is administered for conditions in which α-adrenergic receptors have been pharmacologically blocked, the β-adrenergic receptor effects predominate, potentially leading to a lower blood pressure due to β-2 receptor-mediated vasodilation; this is known as epinephrine or "adrenaline" reversal.[5]

Table 2. Perioperative Data*

TCI rate of propofol at time of induction, mcg/mL	3.7 ± 0.8
Remifentanil infusion rate at time of induction, mcg/kg/min	0.25 ± 0.06
Rocuronium dose for intubation, mg	50.7 ± 9.4
Propofol TCI rate at time of injection, mcg/mL	2.7 ± 0.5
Surgical time, min	59.8 ± 33.4
Anesthesia time, min	113.4 ± 36.2
Total dose of propofol, mg	772.1 ± 339.5
Total dose of remifentanil, mcg	1083.3 ± 572.2

* TCI indicates target-controlled infusion; $n = 30$; values are presented as mean ± SD.

Antipsychotics have been broadly classified as *typical*, which include phenothiazines (eg, chlorpromazine, levomepromazine, perphenazine) and butyrophenones (eg, haloperidol), and *atypical* (eg, risperidone, olanzapine, aripiprazole). Typical and atypical antipsychotic medications have α-adrenergic receptor antagonistic action. In Japan, epinephrine-containing local anesthetics are used cautiously in patients regularly taking antipsychotic medications. However, except during cardiopulmonary resuscitation, relatively high-dose epinephrine administration is contraindicated in these patients. In general, epinephrine doses ranging from 200 to 1000 mcg are used when managing medical urgencies and emergencies such as advanced cardiac life support and severe bronchospasms. Epinephrine dosages used in conjunction with local anesthetics in dentistry are smaller than those used for medical purposes. Commercially prepared local anesthetics with epinephrine for dental use are supplied in cartridges, and in Japan the most common concentration of epinephrine in lidocaine is 1:80,000 (12.5 mcg/mL). In this study, a 1.8-mL local anesthetic dental cartridge with an epinephrine concentration of 1:80,000 was administered, for a total epinephrine dose of 22.5 mcg.

Some previous reports have shown a drug interaction between epinephrine and the typical antipsychotic chlorpromazine. Yagiela et al[7] reported hemodynamic changes caused by the interaction between these 2 medications in dogs. They found that low-dose epinephrine (0.33 mcg/kg) did not influence blood pressure

Table 3. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Percutaneous Oxygen Saturation (SpO_2) Measured Over Time Following Injection of Lidocaine With Epinephrine*

Time, min	*Baseline*	*2*	*4*	*6*	*8*	*10*
SBP, mm Hg	106.5 ± 13.2	105.7 ± 15.9	105.6 ± 19.1	106.0 ± 15.9	106.0 ± 15.3	106.4 ± 15.2
DBP, mm Hg	57.6 ± 11.7	57.8 ± 13.0	57.6 ± 14.0	57.2 ± 13.1	58.1 ± 12.9	58.7 ± 12.9
HR, bpm	73.9 ± 15.1	77.2 ± 13.7	79.6 ± 12.7	79.2 ± 11.2	79.1 ± 11.7	80.2 ± 11.9
SpO_2, %	99.4 ± 0.8	99.3 ± 0.9	99.4 ± 0.8	99.4 ± 0.8	99.4 ± 0.8	99.4 ± 0.8

* Data are expressed as mean ± SD ($n = 30$). No significant differences in the SBP, DBP, HR, and SpO_2 were noted over time. Baseline was defined as time immediately preceding injection of 1.8 mL of 2% lidocaine with 1:80,000 epinephrine. Dunnett test was used to evaluate differences between baseline measurements and each time point. P values $<.05$ were considered statistically significant.

or HR, whereas high-dose epinephrine (2.5 mcg/kg) induced hypotension and tachycardia. Higuchi et al[8] also reported that in rats, an intraperitoneal injection of chlorpromazine followed by an intraperitoneal injection of epinephrine resulted in marked hypotension and tachycardia, depending on the epinephrine dose. However, administration of chlorpromazine and propranolol, a nonselective β-blocker, followed by the administration of epinephrine resulted in only a slight increase in blood pressure, instead of a decrease. These animal studies demonstrated that hypotension was caused by an interaction between epinephrine and chlorpromazine mediated by the dose-dependent activation of β-2 adrenergic receptors.

In the study by Yagiela et al,[7] low-dose epinephrine (0.33 mcg/kg) did not cause hemodynamic changes. When applied to the average body weight (75.4 kg) of the subjects in this study, the equivalent amount of low-dose epinephrine would be 24.8 mcg, which is close to that used in our study (22.5 mcg). It is necessary to consider whether epinephrine doses used in canines are comparable with those used in humans, but our findings are consistent with those of Yagiela et al[7] and suggest no significant change in hemodynamic parameters. These findings suggest that the relatively low dose of epinephrine used with lidocaine in dental treatment does not show a strong β-adrenergic receptor stimulatory effect and does not induce hypotension when used in patients taking antipsychotics.

Patients taking antipsychotics for schizophrenia, autism, and intellectual disability often undergo dental treatment under general anesthesia because of their uncooperative nature, poor compliance, and/or dental phobia. We chose propofol as the general anesthetic agent in this study. Propofol does not directly induce bradyarrhythmias because it does not depress sinoatrial node activity or atrioventricular conduction at therapeutic doses.[9] However, propofol does demonstrate simultaneous afterload reduction and decrease in heart contractility, which leads to potentially significant reductions in systolic, diastolic, and mean arterial pressures.[10,11] Therefore, it is presumed that during general anesthesia with propofol, blood pressure is more likely to decrease due to the interaction between antipsychotics and epinephrine than during routine dentistry without general anesthesia. Our results indicate that even with the use of propofol for general anesthesia, the interaction between low-dose epinephrine and antipsychotics did not impact blood pressure. However, severe hypotension may occur when propofol, antipsychotics, and epinephrine are used in combination in patients with low cardiovascular reserve and elderly patients. Phenylephrine may be suitable as a vasoconstrictive agent in those situations.

In general, inhibition of a receptor by antagonists produces an "upregulation" phenomenon.[12] Regular use of antipsychotic drugs may result in upregulation of α-adrenergic receptors, which in turn could produce tolerance to the α-blocking properties of these drugs. Therefore, patients who are just beginning antipsychotic therapy might be at risk for this interaction under general anesthesia, as they have not yet become tolerant to the α blockade induced by antipsychotics.

When using epinephrine-containing local anesthetics, it is important to closely monitor the patient's hemodynamic parameters. Furthermore, remifentanil, the opioid analgesic used during anesthesia induction and tracheal intubation in this study, can cause hypotension and bradycardia.[13] The modelled context-sensitive half-life (the time required for the drug's plasma concentration to decrease by 50% after infusion cessation) following a 3-hour infusion of remifentanil is ~3 minutes.[14] Therefore, in our protocol, remifentanil was discontinued immediately after intubation, and lidocaine with epinephrine was administered 5 minutes later. This waiting period was deemed sufficient for any influence of the remifentanil on hemodynamic responses to be considered negligible at the time of measurement. During dental treatment, needle placement and injection of local anesthetic is occasionally associated with systemic complications like vasovagal syncope and rarely with more serious cardiac issues, such as arrhythmias or angina.[15] Even under general anesthesia, it is possible for bradycardia to be induced by the

intense noxious stimulation of rapid local anesthetic injection.[16] In this study, we believe that a vasovagal reflex was avoided because we performed local anesthesia slowly over 30 seconds.

This study had some limitations. First, as a pilot study, our sample size was relatively small, which may have limited its statistical power. Second, the strength of the α-1 adrenergic receptor blocking action was not consistent for each antipsychotic drug. For example, chlorpromazine and risperidone have a higher affinity for the α-1 receptor.[17] Therefore, further studies are needed to examine the interaction with epinephrine according to each individual antipsychotic.

CONCLUSION

This is the first prospective study on the hemodynamic effects of the interaction between antipsychotics and epinephrine-containing lidocaine administered during dental treatment. Our study suggests that the injection of 2% lidocaine with 1:80,000 epinephrine at clinically relevant volumes (1.8 mL) under general anesthesia with propofol is unlikely to affect the hemodynamic parameters of patients regularly taking antipsychotic medications.

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