Hemodynamic Changes by Drug Interaction of Adrenaline With Chlorpromazine

Hitoshi Higuchi, DDS, PhD,* Akiko Yabuki, DDS,† Minako Ishii-Maruhama, DDS, PhD,* Yumiko Tomoyasu, DDS, PhD,† Shigeru Maeda, DDS, PhD,* and Takuya Miyawaki, DDS, PhD†

*Department of Dental Anesthesiology, Okayama University Hospital, Okayama, Japan, and †Department of Dental Anesthesiology and Special Care Dentistry, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Adrenaline (epinephrine) is included in dental local anesthesia for the purpose of vasoconstriction. In Japan, adrenaline is contraindicated for use in patients receiving antipsychotic therapy, because the combination of adrenaline and an antipsychotic is considered to cause severe hypotension; however, there is insufficient evidence supporting this claim. The purpose of the present study was to clarify the changes in hemodynamics caused by drug interaction between adrenaline and an antipsychotic and to evaluate the safety of the combined use of adrenaline and an antipsychotic in an animal study. Male Sprague-Dawley rats were anesthetized with sodium pentobarbital. A catheter was inserted into the femoral artery to measure blood pressure and pulse rate. Rats were pretreated by intraperitoneal injection of chlorpromazine or chlorpromazine and propranolol, and after 20 minutes, saline or 1 of 3 different doses of adrenaline was administered by intraperitoneal injection. Changes in the ratio of mean arterial blood pressure and pulse rate were measured after the injection of adrenaline. Significant hypotension and tachycardia were observed after the injection of adrenaline in the chlorpromazine-pretreated rats. These effects were in a dose-dependent manner, and 100 µg/kg adrenaline induced significant hemodynamic changes. Furthermore, in the chlorpromazine and propranolol-pretreated rats, modest hypertension was induced by adrenaline, but hypotension and tachycardia were not significantly shown. Hypotension was caused by a drug interaction between adrenaline and chlorpromazine through the activation of the β -adrenergic receptor and showed a dose-dependent effect. Low-dose adrenaline similar to what might be used in human dental treatment did not result in a significant hemodynamic change.

Key Words: Local anesthesia; Drug interaction; Adrenaline; Epinephrine; Antipsychotics.

Vasoconstrictors are included in local anesthetics to increase the duration of anesthesia, to prevent local anesthesia systemic toxicity, and to promote hemostasis in the local operative field.¹ Adrenaline (epinephrine) is

the most common vasoconstrictor that is added to local anesthetics, and lidocaine and articaine with adrenaline are the most widely used local anesthetics for dental treatment. However, adrenaline has drug interactions with some medicines. It is widely believed that the combination of adrenaline with an antipsychotic can cause hypotension because antipsychotics have α -adrenergic blocker effects that can result in decreased peripheral resistance, and adrenaline has been shown to have significant β 2-adrenergic mediated vasodilatory

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Address correspondence to Dr Hitoshi Higuchi, DDS, PhD, Department of Dental Anesthesiology, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8525, Japan; higuti@md.okayama-u.ac.jp.

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effects that also can cause hypotension. Therefore, the combination of adrenaline and an antipsychotic is contraindicated in Japan for fear of causing significant hypotension. However, there is insufficient evidence supporting this claim, and, in clinical settings, there are many situations in which the use of local anesthetics with adrenaline is appropriate for dental treatment of patients receiving antipsychotic therapy. Thus, the purpose of the present study was to clarify the changes in hemodynamics caused by a drug interaction between adrenaline and an antipsychotic and to evaluate the safety of the combined use of adrenaline with an antipsychotic in an animal study.

MATERIALS AND METHODS

Animals

The protocol of the present study was approved by Okayama University Animal Care and Use Committee (approval number: OKU-2012569). We used male Sprague-Dawley rats (weighing 450–500 g) that had been housed at a room temperature of 24°C with a 12-hour light-dark cycle and given free access to food and water.

Agents

Adrenaline (Bosmin), chlorpromazine (Contomin), and propranolol (Inderal) were purchased from Daiichi-Sankyo (Tokyo, Japan), Mitsubishi Tanabe Pharma (Osaka, Japan), and AstraZeneca (Osaka, Japan), respectively.

Preparation for Measurement of Blood Pressure and Pulse Rate

Rats were anesthetized with an intraperitoneal injection of sodium pentobarbital. The femoral artery was dissected out and cannulated with a heparinized polyethylene tube to measure arterial blood pressure and pulse rate. Animals were allowed to breathe spontaneously throughout the experiment. To maintain body temperature within the physiological range, all procedures were performed over a heating pad under continuous monitoring of rectal body temperature.

Administration of Drugs and Evaluation

Chlorpromazine (5 mg/kg), saline, or chlorpromazine (5 mg/kg) and propranolol (5 mg/kg) were administered by

intraperitoneal injection as pretreatment. After 15 minutes, the baseline blood pressure and pulse rate were measured for 5 minutes, and adrenaline (1, 10, or 100 µg/kg) was administered by intraperitoneal injection. Mean arterial blood pressure and pulse rate were measured and recorded every minute for 20 minutes.

We calculated the average mean arterial blood pressure and pulse rate for each 5-minute period, and calculated the ratio of baseline blood pressure and pulse rate before and after the injection of adrenaline and reported it as percentage change. For the investigation of a dose-dependent response, we calculated the ratio of baseline blood pressure and pulse rate to the maximum or minimum after the injection of adrenaline.

Statistical Analysis

We used 2-way analysis of variance (ANOVA) with agents as the main factor and time as repeated measure and a Bonferroni's post hoc test for comparisons of the percentage change of average mean arterial blood pressure and pulse rate at each time point. We also used 1-way ANOVA with a Dunnett's post hoc test for comparisons of the percentage change of average mean arterial blood pressure and pulse rate at different concentrations of adrenaline. $P < .05$ was considered significant. All data are shown as the mean $\pm$ SD.

RESULTS

Figure 1 shows the hemodynamic changes caused by the drug interaction between adrenaline and chlorpromazine. Intraperitoneal injection of 100 µg/kg adrenaline induced significant hypotension immediately in only chlorpromazine-pretreated rats ($P = .008$, 2-way ANOVA with post hoc Bonferroni's test; the interaction of main factor and time was significant), and induced significant tachycardia in chlorpromazine-pretreated rats and saline-pretreated rats ($P = .015$, 2-way ANOVA with post hoc Bonferroni's test; the interaction of main factor and time was significant). In contrast, in chlorpromazine and propranolol-pretreated rats, modest hypertension was induced by 100 µg/kg adrenaline injection ($P = .021$, 2-way ANOVA with post hoc Bonferroni's test; the interaction of main factor and time was not significant), and neither hypotension nor tachycardia was shown (Figure 2).

Figure 3 shows the dose-dependent effect of adrenaline on the drug interaction between adrenaline and chlorpromazine. Thus, adrenaline injection caused hypotension (saline: $101.3 \pm 7.9\%$; 1 µg/kg: $99.0 \pm$

Figure 1. The time course of percentage change of mean blood pressure (MBP) (a) and pulse rate (PR) (b) after the injection of saline or 100 µg/kg adrenaline (AD) in chlorpromazine (Ch)-pretreated rats and saline-pretreated rats (Ch + saline: $n = 4$; Ch + AD: $n = 6$; saline + AD: $n = 4$). P values are for between-agent comparisons (vs the value for Ch + saline) at specified time intervals by using 2-way analysis of variance with Bonferroni's post hoc test. Data represent mean $\pm$ SD.

18.6%; 10 µg/kg: $84.7 \pm 6.2\%$; 100 µg/kg: $71.5 \pm 9.0\%$) and tachycardia (saline: $97.2 \pm 5.8\%$; 1 µg/kg: $99.6 \pm 6.4\%$; 10 µg/kg: $106.8 \pm 9.4\%$; 100 µg/kg: $123.2 \pm 10.0\%$). The injection of 100 µg/kg adrenaline

caused significant hypotension ($P = .0036$, 1-way ANOVA with Dunnett's post hoc test) and tachycardia ($P = .0005$, 1-way ANOVA with Dunnett's post hoc test).

Figure 2. The blockade effect of propranolol (Pro) on hemodynamic changes by drug interaction between adrenaline (AD) and chlorpromazine (Ch) on mean blood pressure (MBP) (a) and pulse rate (PR) (b) (Ch + saline: $n = 4$; Ch + Pro + AD: $n = 3$). AD induced modest hypertension, but did not significantly influence pulse rate change in Pro + Ch-pretreated rats. P values are for between-agent comparisons (vs the value for Ch + saline) at specified time intervals by using 2-way analysis of variance with Bonferroni's post hoc test. Data represent means $\pm$ SD.

Figure 3. The effect of adrenaline at each concentration on mean blood pressure (MBP) (a) and pulse rate (PR) (b) in chlorpromazine-pretreated rats (saline: $n = 4$; 1 $\mu\text{g/kg}$: $n = 6$; 10 $\mu\text{g/kg}$: $n = 4$; 100 $\mu\text{g/kg}$: $n = 6$). Adrenaline at each concentration induced hypotension and tachycardia, and 100 $\mu\text{g/kg}$ adrenaline induced significant hemodynamic changes. P values are for the comparisons at each concentration of adrenaline by using 1-way analysis of variance with Dunnett's post hoc test (vs saline). Data represent means $\pm$ SD.

DISCUSSION

Our results show that the drug interaction between adrenaline and chlorpromazine induced hypotension in rats. In the presence of a nonselective β -blocker (propranolol), modest hypertension by α receptor action of adrenaline was shown and hypotension by the drug interaction between adrenaline and chlorpromazine was not induced. This suggested that the hypotension caused by the drug interaction between adrenaline and chlorpromazine occurred through the β -adrenergic receptor activity. Moreover, this reaction was dose dependent, with the 100 $\mu\text{g/kg}$ adrenaline dose inducing significant hemodynamic changes.

Adrenaline has many drug-drug interactions. Tricyclic antidepressants, monoamine oxidase inhibitors, nonselective β -adrenoceptor antagonists, general anesthetics, cocaine, and antipsychotics such as chlorpromazine are listed as drugs that interact with adrenaline.^{1,2} Of these drugs, some antipsychotics are listed as contraindicated in the adrenaline drug information insert, and it is prohibited in Japan to use adrenaline in patients taking phenothiazine (eg, chlorpromazine) or butyrophenone antipsychotics because they can induce severe hypotension.

Schizophrenia is a severe form of mental illness. The lifetime prevalence and incidence of schizophrenia are 0.33–0.66% and 10.2–22.0 per 100,000 person-years,³ respectively, and schizophrenia affects about 24 million people worldwide.⁴ Antipsychotics block D_2 -dopamine receptors and reduce dopamine neurotrans-

mission, and some also interact with D_1 - and D_4 -dopaminergic, 5-HT_{2A} and 5-HT_{2C}-serotonergic, and α -adrenergic receptors. Among antipsychotic drugs, chlorpromazine produces the most significant α receptor blockade.⁵

Antipsychotics are classed into 2 generations. Typical first-generation drugs include haloperidol, chlorpromazine, pimozide, and perphenazine, and second-generation drugs include clozapine, quetiapine, and risperidone. Second-generation antipsychotics have fewer side effects than first-generation; therefore, second-generation antipsychotics are regarded as a first-line therapy. However, first-generation drugs still remain as important and effective medicines for antipsychotic therapy,^{6,7} and many patients are still taking first-generation antipsychotics.

Adrenaline is a potent stimulant of both α - and β -adrenergic receptors. α -1 adrenergic receptors are located in vascular and genitourinary smooth muscle and cause smooth muscle constriction. Located in pancreatic islets (β cell), platelets, nerve terminals, and vascular smooth muscle, α 2 receptors decrease insulin secretion, increase aggregation, release norepinephrine, and cause vasoconstriction, respectively. On the other hand, β 1 and β 2 receptors are located in the heart and smooth muscle (vascular, bronchial, gastrointestinal, and genitourinary), respectively. Activation of β receptors increases the force and rate of the heart and the relaxation of smooth muscle. The effect of intravenous infusion of adrenaline in humans⁵ is increased systolic pressure and heart rate. Diastolic pressure usually falls

and the mean blood pressure is not greatly elevated because of β_2 -mediated vasodilator action that is partially counterbalanced by vasoconstriction by α receptor activity. If an α receptor antagonist is given in the presence of adrenaline, the vasodilatation is more pronounced, total peripheral resistance is decreased, and mean blood pressure falls; this is known as adrenaline (epinephrine) reversal.⁵

Some previous reports have shown a drug interaction between adrenaline and chlorpromazine. Foster et al.⁸ and Ginsburg and Duff⁹ studied the drug interaction between adrenaline and chlorpromazine by measuring blood flow in humans. Foster et al.⁸ demonstrated the reversal of adrenaline vasoconstriction by chlorpromazine; however, Ginsburg and Duff⁹ showed no reversal action. Yagiela et al.¹⁰ also reported hemodynamic changes caused by drug interaction between adrenaline and chlorpromazine in dogs. They found that low-dose adrenaline (0.33 $\mu\text{g}/\text{kg}$) did not influence blood pressure or heart rate; however, high-dose adrenaline (2.5 $\mu\text{g}/\text{kg}$) induced hypotension and tachycardia.

Adrenaline prolongs the duration of the local anesthetic effect, and commercially prepared local anesthetics with adrenaline are available in dental local anesthetic cartridges. These products are very efficient, effective, and convenient. In the dental field, there are generally 4 different concentrations of adrenaline available in local anesthetics: 1 : 50,000 (20 $\mu\text{g}/\text{mL}$), 1 : 80,000 (12.5 $\mu\text{g}/\text{mL}$), 1 : 100,000 (10 $\mu\text{g}/\text{mL}$), and 1 : 200,000 (5 $\mu\text{g}/\text{mL}$). In the present study, only 100 $\mu\text{g}/\text{kg}$ of adrenaline induced significant hemodynamic changes, and this adrenaline dose is equivalent to 300 mL local anesthetic with 1 : 50,000 adrenaline (assumed 60-kg patient). However, this huge dose would be inconceivable in human dental treatment. These findings suggest that a clinical amount of local anesthetic used with adrenaline in dental treatment should not induce severe hypotension in patients taking an antipsychotic. However, it is unclear whether we can equate the dose in rats with that in humans, and therefore this is a limitation of the present study.

In conclusion, we showed that hypotension and tachycardia were caused by a drug interaction between

adrenaline and chlorpromazine, and this change was dose dependent. Our animal study therefore provides additional evidence that low-dose adrenaline added to local anesthetics may not induce severe hemodynamic changes, and that the use of local anesthetics with adrenaline may be safe for patients undergoing dental treatment who are taking antipsychotics such as chlorpromazine.

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