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The Antipsychotic and Antiemetic Drug Prochlorperazine Delays the Ventricular Repolarization of the In Situ Canine Heart

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Abstract. Electropharmacological effect of the antipsychotic and antiemetic drug prochlorperazine was assessed using the halothane-anesthetized in vivo canine model (n = 5). Up to 10 times higher than the clinically relevant doses of prochlorperazine (≤ 3 mg/kg, i.v.) did not induce cardiohemodynamic collapse in the model. Meanwhile, clinically relevant to suprathera-peutic doses (0.3 – 3 mg/kg, i.v.) prolonged the ventricular repolarization period in a dose-related and reverse-use dependent manner that could become proarrhythmic substrates. Thus, caution has to be paid on the use of prochlorperazine particularly for patients with risks of the elevated plasma drug concentration, compromised cardiac repolarization, and/or frequent ventricular premature beats.

Keywords: prochlorperazine, antipsychotic drug, monophasic action potential, long QT syndrome, torsades de pointes

Introduction

The efficacy of the antipsychotic and antiemetic drug prochlorperazine against acute migraine has been demonstrated (1), whereas its potential adverse effect on compromised cardiac repolarization was recently suspected (2). Indeed, numerous other antipsychotic drugs have been shown to prolong QT interval via the blockade of cardiac K^+ channels, occasionally resulting in the onset of fatal ventricular arrhythmias, namely, torsades de pointes (3 – 8). However, information is still lacking regarding the in vitro as well as in vivo electro-physiological effects of prochlorperazine despite its clinical importance.

The present study was designed to analyze the pro-arrhythmic potential of prochlorperazine. For this pur-pose, we used the halothane-anesthetized in vivo canine model to simultaneously assess its cardiohemodynamic and electrophysiological effects (7 – 10). To better analyze the electrophysiological effects of the drug on the depolarization and repolarization phases, we recorded the His bundle electrogram and monophasic action potential (MAP), respectively, in addition to the standard lead II electrocardiogram (ECG). Moreover, a MAP recording/pacing combination catheter was used to simultaneously measure both MAP and effective refractory period (ERP) at the same site and directly compare the drug effects on the repolarization and refractoriness (11).

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Materials and Methods

Experiments were carried out using five beagle dogs of either sex weighing approximately 10 kg. Animals were obtained through the Animal Laboratory for Research of the University of Yamanashi. All experi-ments were performed according to Guidelines for Animal Experiments, University of Yamanashi.

Cardiohemodynamic parameters

Dogs were initially anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, 1.0% halothane vaporized with 100% oxygen was inhaled with a volume-limited ventilator

(SN-480-3; Shinano, Tokyo). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. To prevent blood clotting, heparin calcium (100 IU/kg) was intravenously administered. A heparinized catheter was inserted through the right femoral artery for continuous monitoring of the systemic blood pressure. A thermodilution catheter (TC-704; Nihon Kohden, Tokyo) was positioned at the right side of the heart via the right femoral vein. The cardiac output was measured by a standard thermodilution method using a cardiac output computer (MFC-1100, Nihon Kohden). Total peripheral resistance was calculated using the basic equation: mean blood pressure/cardiac output. A pig-tail catheter was positioned at the left ventricle through the right femoral artery to measure the left ventricular pressure. The maximum upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$) and the left ventricular end-diastolic pressure (LVEDP) were obtained during the sinus rhythm to estimate the contractility and preload of the left ventricle, respectively.

Electrophysiological parameters

The surface lead II ECG was obtained from the limb electrodes. Corrected QT intervals were calculated with the formulas by Bazett (QTc-b) (12) and Van de Water et al. (QTc-v) (13). A quad-polar electrodes catheter was positioned at the non-coronary cusp of the aortic valve through the left femoral artery to obtain the His bundle electrogram. A bi-directional steerable MAP recording/pacing combination catheter (1675P; EP Technologies Inc., Sunnyvale, CA, USA) was positioned at the endocardium of the interventricular septum in the right ventricle through the left femoral vein to obtain MAP signals. The signals were amplified with a DC preamplifier (300, EP Technologies Inc.). The duration of the MAP signals was measured as an interval, along a line horizontal to the diastolic baseline, from the MAP upstroke to the desired repolarization level, and the interval (ms) at 90% repolarization was defined as MAP_{90}.

The heart was electrically driven using a cardiac stimulator (SEC-3102, Nihon Kohden) with the MAP recording/pacing combination catheter placed in the right ventricle. The stimulation pulses were rectangular in shape, 1 – 2 V (about twice the threshold voltage), and of 1-ms duration. MAP_{90} was measured during the sinus rhythm ($MAP_{90(sinus)}$) and at a pacing cycle length of 400 ms ($MAP_{90(CL400)}$) and 300 ms ($MAP_{90(CL300)}$). The ERP was assessed by the programmed electrical stimulation to the right ventricle. The pacing protocol consisted of five beats of basic stimuli in a cycle length of 400 ms followed by an extra stimulus of various coupling intervals. Starting in the late diastole, the coupling interval was shortened in 5- to 10-ms decrements until refractoriness occurred. The duration of the terminal repolarization phase of the ventricle (TRP) was calculated by the difference between the $MAP_{90(CL400)}$ and ERP at the same site, which reflects the extent of electrical vulnerability of the ventricular muscle (11).

Experimental protocol

The cardiohemodynamic and electrophysiological parameters were continuously monitored using a polygraph system (RM-6000, Nihon Kohden), and analyzed using a real time full automatic data analysis system (MP/VAS 3 for Macintosh ver 1.0; Physio-Tech, Tokyo). Each measurement of ECG, MAP, atrio-His (AH), and His-ventricular (HV) intervals was the mean of three consecutive recordings. The cardiovascular variables were assessed in the following order: The cardiac output was measured twice. Next, the ECG, His bundle electrogram, systemic and left ventricular pressure, and MAP signals were recorded under the sinus rhythm. Then, the MAP signals were recorded at a pacing cycle length of 400 and 300 ms. Finally, the ERP was assessed with the programmed electrical stimulation as described above.

After the basal assessment, prochlorperazine in a low dose of 0.03 mg/kg was administered over 10 min, and each parameter was assessed 5, 10, 15, 20, and 30 min after the start of the infusion. Next, prochlorperazine in a middle dose of 0.3 mg/kg, which is a clinically relevant daily dose, was additionally administered over 10 min and each parameter was observed in the same manner. Finally, prochlorperazine in a high dose of 3 mg/kg was administered over 10 min, and each parameter was observed 5, 10, 15, 20, 30, 45, and 60 min after the start of the infusion.

Drugs

Commercially available prochlorperazine mesilate (Novamin® for injection; Shionogi Co., Ltd., Osaka) was used, which was diluted with saline in concentrations of 0.03, 0.3, and 3 mg/ml. The following drugs were purchased: thiopental sodium (Tanabe Seiyaku, Osaka), halothane (Takeda Chemical Industries, Tokyo), and heparin calcium (Mitsui Pharmaceuticals, Tokyo).

Statistical analyses

Data are expressed as the mean ± S.E.M. The statistical significances within a parameter were evaluated by one-way, repeated-measures analysis of variance (ANOVA) followed by Contrast for mean values comparison. A P value <0.05 was considered statistically significant.

Results

Effects on the blood pressure and heart rate

The time courses of changes in the heart rate and mean blood pressure are summarized in Fig. 1 (n = 5), of which the pre-drug control values were 128 ± 10 beats/min and 113 ± 5 mmHg, respectively. After the low-dose infusion (0.03 mg/kg prochlorperazine), no significant change was detected in the heart rate or mean blood pressure. After the middle-dose infusion (0.3 mg/kg), the heart rate and mean blood pressure decreased at 30 min and 5 – 30 min, respectively. After the high-dose infusion (3 mg/kg), the heart rate and mean blood pressure decreased further for 5 – 60 min.

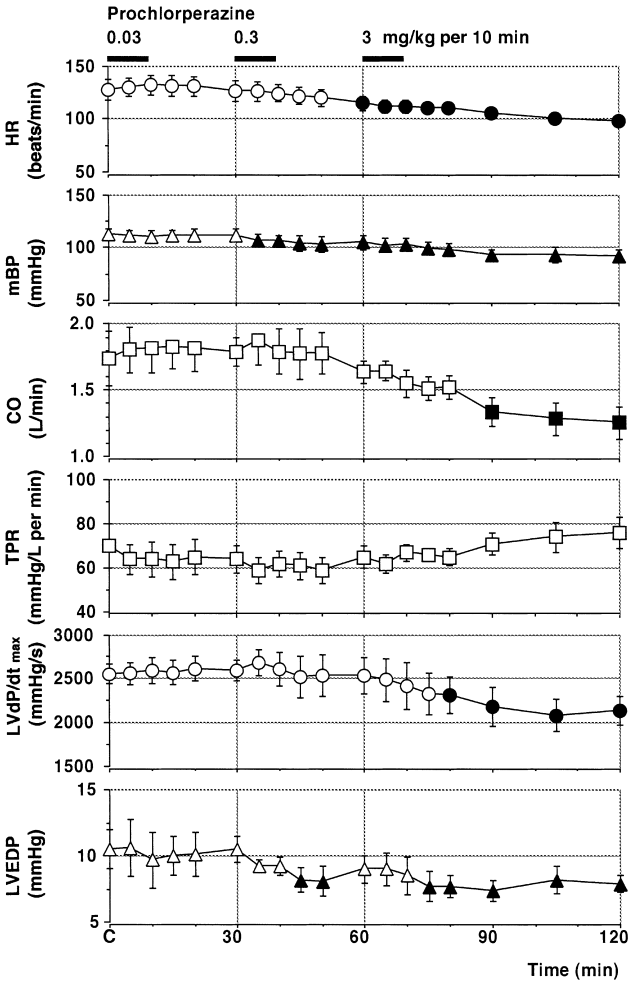

Fig. 1. Time courses of the heart rate (HR), mean blood pressure (mBP), cardiac output (CO), total peripheral resistance (TPR), maximum upstroke velocity of the left ventricular pressure ($LVdP/dt_{max}$), and left ventricular end-diastolic pressure (LVEDP). Data are presented as the mean ± S.E.M. (n = 5). The closed symbols represent the significant differences from the respective pre-drug control values (C) at $P<0.05$.

Effects on the cardiac output and total peripheral resistance

The time courses of changes in the cardiac output and total peripheral resistance are summarized in Fig. 1 (n = 5), of which the pre-drug control values were 1.74 ± 0.21 L/min and 70 ± 10 mmHg/L per min, respectively. After the low- and middle-dose infusion, no significant change was detected in the cardiac output, whereas after the high-dose infusion, it decreased for 30 – 60 min. On the other hand, no significant change was detected in the total peripheral resistance during the observation period.

Effects on the $LVdP/dt_{max}$ and LVEDP

The time courses of changes in the $LVdP/dt_{max}$ and LVEDP are summarized in Fig. 1 (n = 5), of which the pre-drug control values were 2,552 ± 110 mmHg/s and 10.5 ± 1.5 mmHg, respectively. After the low-dose infusion, no significant change was detected in the $LVdP/dt_{max}$ or LVEDP. After the middle-dose infusion, no significant change was detected in the $LVdP/dt_{max}$, whereas the LVEDP decreased for 15 – 20 min. After

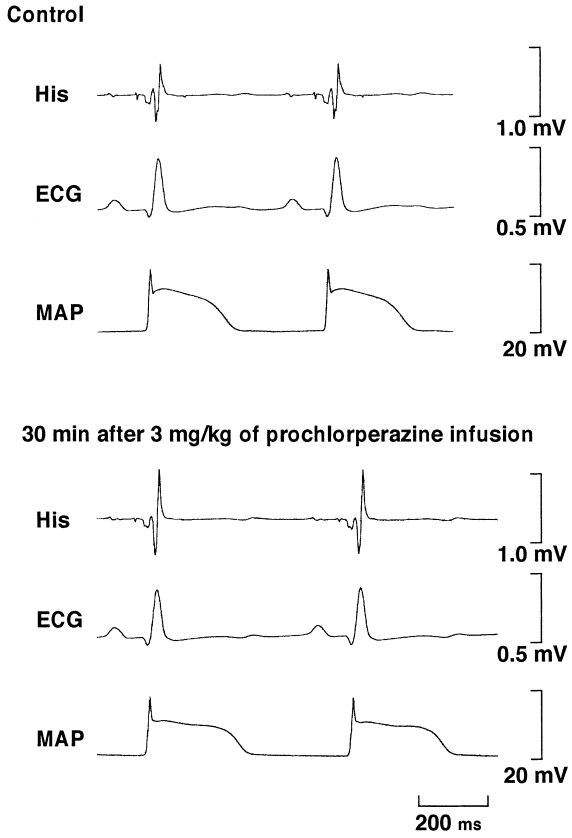

Fig. 2. Typical tracings of His bundle electrogram (His), lead II surface electrocardiogram (ECG), and monophasic action potentials (MAP) recorded from the right ventricle during the sinus rhythm at the pre-drug control (Control) and 30 min after starting the infusion of 3 mg/kg of prochlorperazine.

the high-dose infusion, the $LVdP/dt_{max}$ and LVEDP decreased for 20 – 60 min and for 15 – 60 min, respectively.

Effects on the ECG

Typical tracings of the effects of prochlorperazine on ECG are depicted in Fig. 2, and the time courses of changes in ECG parameters are summarized in Fig. 3 (n = 5). The pre-drug control values of the PR interval, QRS width, QT interval, QTc-b, and QTc-v were 108 ± 6, 73 ± 2, 312 ± 21, 450 ± 14, and 358 ± 18 ms, respectively. After the low- and middle-dose infusions, no significant change was detected in any of the ECG parameters. After the high-dose infusion, the QRS width, QT interval, and QTc-v were prolonged for 10 – 30 min, for 20 – 60 min, and for 20 – 60 min, respectively. Meanwhile, no significant change was detected in the PR interval or QTc-b during the observation period. No ventricular premature beat was observed during the whole experimental period.

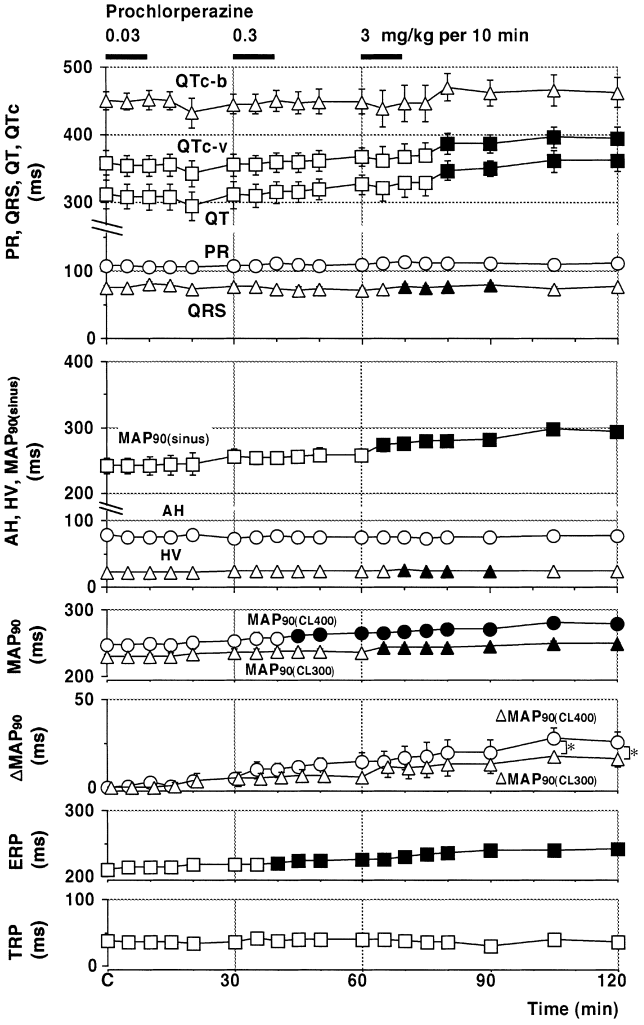

Fig. 3. Time courses of PR interval (circles), QRS width (triangles), and QT interval (squares); QTc-b (triangles: corrected by Bazett's formula); QTc-v (squares: corrected by Van de Water's formula); atrio-His interval (AH, circles); His-ventricular interval (HV, triangles); duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) during the sinus rhythm ($MAP_{90(sinus)}$, squares); MAP_{90} during the electrical pacing at a cycle length of 400 ms ($MAP_{90(CL400)}$, circles) and 300 ms ($MAP_{90(CL300)}$, triangles); increments in $MAP_{90(CL400)}$ ($\Delta MAP_{90(CL400)}$, circles) and $MAP_{90(CL300)}$ ($\Delta MAP_{90(CL300)}$, triangles) from the respective pre-drug control values (C); effective refractory period (ERP); and terminal repolarization period (TRP). Data are presented as the mean ± S.E.M. (n = 5). The asterisks represent significant differences between $\Delta MAP_{90(CL400)}$ and $\Delta MAP_{90(CL300)}$ at $P<0.05$. The closed symbols represent the significant differences from the respective pre-drug control values (C) at $P<0.05$.

Effects on the His bundle electrogram and MAP signals during the sinus rhythm

Typical tracings of the effects of prochlorperazine on the His bundle electrogram and MAP signals are depicted in Fig. 2, and the time courses of changes in the AH and HV intervals and $MAP_{90(sinus)}$ during the sinus rhythm are summarized in Fig. 3 (n = 5). The pre-drug control values of the AH and HV intervals and $MAP_{90(sinus)}$ were 78 ± 6, 23 ± 1, and 243 ± 12 ms, respectively. After the low- and middle-dose infusions, no significant change was detected in these parameters. After the high-dose infusion, the HV interval and $MAP_{90(sinus)}$ were prolonged for 10 – 30 min and for 5 – 60 min, respectively. Meanwhile, no significant change was detected in the AH interval during the observation period.

Effects on the monophasic action potential, effective refractory period, and terminal repolarization period during the ventricular pacing

The time courses of changes in the $MAP_{90(CL400)}$, $MAP_{90(CL300)}$, ERP, and TRP are summarized in Fig. 3 (n = 5), of which the pre-drug control values were 247 ± 6, 229 ± 4, 210 ± 5, and 37±3 ms, respectively. After the low-dose infusion, no significant change was detected in any of these parameters. After the middle-dose infusion, the $MAP_{90(CL400)}$ and ERP were prolonged for 15 – 30 min and for 10 – 30 min, respectively, whereas no significant change was detected in the $MAP_{90(CL300)}$ or TRP. After the high-dose infusion, the $MAP_{90(CL400)}$, $MAP_{90(CL300)}$, and ERP were prolonged for 5 – 60 min, whereas no significant change was detected in the TRP. The time courses of the increment in the $MAP_{90(CL400)}$ and $MAP_{90(CL300)}$ were also calculated as shown in Fig. 3. Increment of the $MAP_{90(CL400)}$ was greater than that of the $MAP_{90(CL300)}$ for 45 – 60 min after the high-dose infusion, indicating that prochlorperazine can prolong the repolarization period in a reverse use-dependent manner.

Discussion

Since information is still lacking regarding the proarrhythmic potential of prochlorperazine, we simultaneously assessed its electrophysiological and cardiohemodynamic effects using the well-established, halothane-anesthetized in vivo canine model (7 – 10).

Drug doses

Since clinically recommended doses of prochlorperazine have been 5 – 10 mg/body, i.v. (1, 2, 14, 15), the doses of the drug used in this study can be considered to provide sub- to supra-therapeutic levels of plasma drug concentrations. It should be noted that the plasma drug concentration will increase in patients with the liver dysfunction like liver cirrhosis and with the concomitant use of other drugs that may inhibit the drug metabolism, since prochlorperazine is metabolized and eliminated by the liver.

Electrophysiological and cardiohemodynamic effects

The present in vivo study provides a causal link between the clinical observation and the drug effects on the cardiac ion channels. More importantly, the extent of QT interval prolongation by several I_{Kr} blockers in the current in vivo model has been shown to be similar to that observed in the clinical phase I studies (A. Sugiyama et al., unpublished observation). As clearly shown in the results, prochlorperazine delayed the repolarization process in a dose-related and reverse-use dependent manner, indicating that the drug may inhibit I_{Kr} channels in vivo (7 – 10). Such an electrophysiological profile has to be confirmed by in vitro study. Also, prochlorperazine delayed the intraventricular conduction, indicating that the drug can inhibit fast Na^+ channels of the heart, since the intraventricular conduction solely depends on the Na^+ channel activity (16 – 19). Furthermore, ERP was also prolonged after the middle- and high-dose administrations, which would reflect the Na^+ and/or K^+ channels inhibition (17, 18). It should be noted that no significant change was detected in the atrioventricular nodal conduction during the study, suggesting that the drug hardly affects cardiac Ca^{2+} channels in vivo.

Prochlorperazine decreased the mean blood pressure and LVEDP in a dose-related manner, indicating the reduction of after- and pre-load of the left ventricle, which may be in part explained by a previous in vitro report that prochlorperazine inhibits α_1-adrenoceptor (20). Prochlorperazine also decreased the heart rate and left ventricular contraction in a dose-related manner together with the reduction of cardiac output. Since prochlorperazine can be considered to suppress Na^+ and K^+ channels of the heart as discussed above, the negative chronotropic effect of prochlorperazine can be possibly exerted through the blockade of both channels, whereas the negative inotropic action may be in part explained by the Na^+ channel inhibition. It should be noted that the negative chronotropic effect of prochlorperazine will enhance the prolongation of the repolarization period via the reverse-use dependent property of K^+ channel inhibition.

Proarrhythmic potentials

It is well known that impulses that reach the ventricles during the middle and terminal portions of the T wave can initiate ventricular tachycardias and fibrillation, since the repolarization is most heterogeneous and Na^+ channels are in different phases of recovery in this phase (11). In the halothane-anesthetized animal model, the extent of such electrical vulnerability can be estimated by the TRP, and drug-induced prolongation and backward shift of the TRP have been known to increase the potential for slow conduction and reentry that allows perpetuation of torsades de pointes (7 – 10, 17, 18). As demonstrated in this study, prochlorperazine did not prolong the TRP. Thus, the extent of the proarrhythmic potential of prochlorperazine may be less than that of other well-known proarrhythmic antipsychotics, including haloperidol, sulpiride, and risperidone, each of which prolonged the TRP significantly in addition to its backward shift (7, 8, 21). Lack of TRP prolongation by prochlorperazine may be explained by the concomitant Na^+ channel inhibition which will prolong the ERP (17 – 19), whereas the backward parallel shift of the TRP itself may increase the dangerous chance of "R on T" phenomenon in the presence of frequent ventricular premature beats (11).

Conclusions

While up to 10 times higher than the clinically relevant doses of prochlorperazine did not induce the cardiovascular collapse in the current study, the therapeutic to supratherapeutic doses of prochlorperazine prolonged the ventricular repolarization in a dose-related and reverse-use dependent manner together with the backward parallel shift of the electrically vulnerable period. Thus, caution has to be paid on the use of the drug for patients with risks of the elevated plasma drug concentration, compromised cardiac repolarization and/or frequent ventricular premature beats.

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