A Rabbit Model for Evaluation of Chlorpromazine-Induced Orthostatic Hypotension

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The present study was conducted to develop an experimental model for evaluation of chlorpromazine-induced orthostatic hypotension in rabbits. In addition, the α -adrenoceptor blocking effect of chlorpromazine was investigated in isolated rabbit aorta and saphenous vein in comparison with prazosin. Chlorpromazine (0.1 and 1 mg/kg, i.v.) potentiated significantly a decrease in mean blood pressure at 1 min after the onset of head-up tilt in rabbits anesthetized with urethane alone, urethane + α -chloralose or nitrous oxide alone, but not in conscious and morphine + urethane + α -chloralose-anesthetized rabbits. There was a negative correlation ($r = -0.986$, $p < 0.01$) between the extent of chlorpromazine-induced orthostatic hypotension and the amplitude of tilt-induced reflex tachycardia before chlorpromazine treatment. Both prazosin and pentolinium elicited orthostatic hypotension under all four anesthetic conditions. The pA_2 value for chlorpromazine to antagonize norepinephrine-induced contraction in aorta was significantly larger than that in saphenous vein, whereas prazosin blocked aortic and venous contractions to a similar extent. These results suggest that a rabbit under an anesthesia which impairs tilt-induced reflex tachycardia may be useful for evaluation of orthostatic hypotension by chlorpromazine. The relatively low potential of chlorpromazine to produce orthostatic hypotension may be partly due to its weak venodilating action.

Key words chlorpromazine; orthostatic hypotension; rabbit; α -adrenoceptor blocking action

Orthostatic hypotension is one of the clinical side effects for a diverse group of drugs including α_1 -adrenoceptor blocking agents, ganglion blocking agents, neuroleptics and antidepressants.^{1–3} This side effect may cause physicians to decrease doses or change treatment, leading to a possible therapeutic failure. The orthostatic hypotension elicited by α_1 -adrenoceptor blocking agents and ganglion blocking agents has also been observed in experimental animals,^{4–6} which may result from a reduced cardiac output due to decreased venous return and a blockade of baroreflex arch at autonomic ganglia level during orthostatic stress, respectively. On the other hand, there are few reports on neuroleptic-induced orthostatic hypotension in experimental animals, although neuroleptics such as chlorpromazine frequently cause orthostatic hypotension in humans, particularly during the initial phase of treatment.

The main purpose of the present study was to develop a model for evaluation of orthostatic hypotension produced by chlorpromazine in rabbits. This animal was chosen because of its lax abdominal wall, making it peculiarly ill-adapted to postural change. In addition, we compared the abilities of chlorpromazine to block α -adrenoceptors in arterial and venous smooth muscles isolated from rabbits, because chlorpromazine has α -adrenoceptor blocking properties⁷ and because α_1 -adrenoceptor blocking agents cause orthostatic hypotension by lowering total peripheral resistance and by reducing cardiac output as a consequence of venodilatation.⁸

MATERIALS AND METHODS

Male Japanese white rabbits, weighing 2.0–3.2 kg were used in the study. All rabbits were fed a normal chow diet.

Blood Pressure Responses to Head-Up Tilt in Conscious and Anesthetized Rabbits Rabbits were anesthetized with one of the following four anesthetics; 1) urethane 1.2 g/kg, i.p. (group U), 2) urethane 600 mg/kg, i.p. and

α -chloralose 60 mg/kg, i.p. (group U+C), 3) morphine 1 mg/kg, i.m., urethane 450 mg/kg, i.p. and α -chloralose 45 mg/kg, i.p. 1 h after morphine 1 mg/kg, i.m. (group M+U+C) and 4) induction dose of sodium thiopental 25 mg/kg, i.v., followed by 2 to 3% halothane in a 7:3 mixture of nitrous oxide and oxygen for about 10 min and withdrawal of halothane from gas mixture (group G). Rabbits in group G were intubated, ventilated with an artificial respirator and immobilized with tubocurarine 1 mg/kg, i.m. every 1 h. Arterial blood gases in group G were maintained within the physiological range by supplying 95% O₂ and 5% CO₂ gas. The right femoral artery was cannulated to measure arterial blood pressure. The cannulation in conscious rabbits was done under a local anesthesia with 1% dibucaine. All anesthetized rabbits were placed in a supine position on a tilt table, and the head and the extremities were firmly fixed to the table thereby preventing their movement during tilt. On the other hand, conscious rabbits were placed in plastic restraining cages that allowed the animals to adopt a normal position resting on their four legs, and the head was fixed outside the cage. Arterial blood pressure and heart rate (HR) were measured by a pressure transducer (TP-200TL, Nihon Kohden, Tokyo) and by a heart rate counter (AT-600G, Nihon Kohden, Tokyo) triggered by arterial blood pressure waves, respectively, and the two parameters were recorded on an ink-writing recticorder (WI-681G, Nihon Kohden, Tokyo). The transducer was fixed at the level of the heart irrespective of any change in posture by tilt. Rectal temperature was maintained at about 37 °C by a heating lamp. Drugs were injected *via* the catheter inserted into the marginal vein of the ear.

Anesthetized rabbits were intermittently tilted for 1 min to 30, 45 and 60° in a head-up position every 4 min, which was designated as one series of tilts. This procedure was repeated 3 times in the prazosin- and pentolinium-treated rabbits and 5 times in the chlorpromazine-treated rabbits. The interval among each series of tilts was 15 min. Conscious rabbits

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were tilted from horizontal to vertical position. Drugs were injected 5 min before each beginning of the third to fifth series of tilts.

α -Adrenoceptor Blocking Action in Aorta and Saphenous Vein Rabbits were anesthetized with sodium pentobarbital 35 mg/kg, i.v. and sacrificed by bleeding from the common carotid arteries. Thoracic aorta and saphenous vein were excised and cut into ring segments (5 mm in length). The rings were mounted in an organ bath containing 20 ml Krebs-bicarbonate solution (118.2 mM NaCl, 4.6 mM KCl, 1.2 mM MgSO_4 , 2.5 mM CaCl_2 , 1.2 mM KH_2PO_4 , 24.8 mM NaHCO_3 and 10.0 mM glucose) which was bubbled with 95% O_2 and 5% CO_2 gas at 37°C. The resting tension was adjusted to 2.0 g in the aorta and to 1.0 g in the vein. Developed tension was isometrically measured by a force-displacement transducer (TB-611T, Nihon Kohden, Tokyo) and recorded on an ink-writing recticorder (WI-681G, Nihon Kohden, Tokyo). Propranolol (10^{-6} M) and *N*^ω-nitro-L-arginine methyl ester (3×10^{-4} M) were added to the bath solution to block β -adrenoceptors and nitric oxide synthesis, respectively. After a 60 min equilibration period, the experiment was started.

A preliminary study on the reproducibility of the concentration-response curves for norepinephrine was made. The results showed that there was no significant difference among the sixth to eighth curves in the aorta and among the fifth to seventh ones in the vein. Therefore, α -adrenoceptor blocking agents at increasing concentrations were treated after the sixth curve in the aorta and after the fifth one in the vein. The pretreatment period was 30 min. The effect of α -adrenoceptor blocking agents was evaluated by calculating the pA_2 value according to the method of Arunlakshana and Schild.⁹⁾

Drugs The following drugs were used; chlorpromazine hydrochloride, prazosin hydrochloride, pentolinium hydrogen tartrate, urethane, α -chloralose, norepinephrine bitar-

trate, dibucaine hydrochloride, propranolol hydrochloride, *N*^ω-nitro-L-arginine methyl ester (Sigma), halothane, morphine hydrochloride (Takeda Yakuhin), sodium pentobarbital (Dainippon Seiyaku), sodium thiopental (Tanabe Seiyaku), tubocurarine chloride (Yoshitomi Seiyaku).

Statistical Analysis All data are expressed as means $\pm$ S.E.M. Statistical analyses were performed by using an unpaired Student's *t* test for two-sample comparisons and a one-way analysis of variance followed by Dunnett's test for multiple comparisons. In each case, *p* values less than 0.05 were considered significant.

RESULTS

Effects of Chlorpromazine, Prazosin and Pentolinium on Blood Pressure Changes by Head-Up Tilt in Conscious and Anesthetized Rabbits

Initial (before starting the first series of tilts) values for mean blood pressure (MBP) and HR in both conscious and anesthetized rabbits are summarized in Table 1. Initial MBP in group M+U+C and group G rabbits was significantly higher than that in conscious rabbits. On the other hand, initial HR in group U and group U+C rabbits was significantly higher than that in conscious rabbits. How-

Table 1. Initial Mean Arterial Blood Pressure (MBP) and Heart Rate (HR)

	MBP (mmHg)	HR (beats/min)
Conscious	98.5 $\pm$ 2.8	286 $\pm$ 6
Urethane	100.0 $\pm$ 3.6	348 $\pm$ 8 ^{b)}
Urethane + α -chloralose	103.0 $\pm$ 3.3	321 $\pm$ 6 ^{a)}
Morphine + Urethane + α -chloralose	120.4 $\pm$ 2.0 ^{b)}	283 $\pm$ 13
Nitrous oxide	112.5 $\pm$ 2.5 ^{b)}	294 $\pm$ 7

Values represent the mean $\pm$ S.E.M. of 15 experiments. a) *p* < 0.05, b) *p* < 0.01; significantly different from the value in conscious animals.

Fig. 1. Left of Each Panel: Original Tracings Illustrating Blood Pressure (BP) Response to Vertical Tilt during 1 min (Horizontal Bars) before (Control) and after Chlorpromazine (Panel A), Prazosin (Panel B) and Pentolinium (Panel C) in Conscious Rabbits. Right of Each Panel: Effects of Drugs on Mean Blood Pressure (MBP) at 1 min after the Onset of Vertical Tilt

% Change in MBP at 1 min tilt was calculated in each rabbit from the following equation: (MBP at 1 min tilt - MBP just before tilt) $\times$ 100 / MBP just before tilt. Open and closed columns represent the values obtained before and after drug treatment, respectively. Control: response to the second series of tilts. Values represent the mean $\pm$ S.E.M. from 5 experiments.

ever, the significant increases in initial MBP and HR levels were not related to the ability of chlorpromazine to produce orthostatic hypotension. A 90° tilt for 1 min caused either a slight elevation or almost no change in blood pressure of conscious rabbits (control in Fig. 1), while it produced about

16% increase in HR (data not shown). Chlorpromazine at 0.01–1 mg/kg, i.v. hardly affected the blood pressure changes by vertical tilt (Fig. 1A). In rabbits treated with prazosin (0.1 mg/kg, i.v.) or pentolinium (1 mg/kg, i.v.), the tilt gradually lowered blood pressure and the hypotension corresponded to approximately 20% of the pre-tilt value at 1 min after the onset of tilt (Figs. 1B and 1C). However, these orthostatic hypotensions were not significantly different from the blood pressure response before drug treatment because of a marked interindividual variability.

In the rabbits anesthetized with urethane as well as the other three anesthetics, blood pressure was promptly decreased by 30–60° tilts in a tilt angle-dependent manner and then returned gradually toward or above the pre-tilt level during 1-min tilt (control in Fig. 2). There was no significant difference among the amplitudes of the initial hypotension induced by tilt in the rabbits anesthetized with the four anesthetics, although the hypotension tended to be smaller in group M+U+C rabbits compared with the other three groups (data not shown). HR was increased in response to tilt in anesthetized rabbits, the rank order of tachycardia during 45° tilt being group M+U+C > group G ≈ group U+C ≈ group U rabbits. This was also true for 30 and 60° tilts. The amplitude of tachycardia during 45° tilt in group M+U+C rabbits was similar to that during 90° tilt in conscious rabbits (data not shown).

Although chlorpromazine at 0.1 mg/kg, i.v. did not affect the initial reduction in blood pressure in response to 30–60° tilts in the rabbits anesthetized with urethane as well as the other three anesthetic agents, chlorpromazine markedly delayed the restoration of blood pressure to the pre-tilt level during tilt (Fig. 2). When a decrease in MBP at 1 min after the onset of tilt was taken as an index of orthostatic hypotension, chlorpromazine at 0.1 and 1 mg/kg, i.v. augmented significantly the orthostatic hypotension during 30–60° tilts and 30 and 45° tilts, respectively, in group U rabbits (Fig. 3). Chlorpromazine at 0.1 and 1 mg/kg, i.v. also reinforced sig-

Fig. 2. Original Tracing Illustrating Effects of Chlorpromazine on Blood Pressure (BP) Response to 30–60° Tilt for 1 min (Horizontal Bars) in Urethane-Anesthetized Rabbit

Fig. 3. Effects of Chlorpromazine on Mean Blood Pressure (MBP) at 1 min after the Onset of 30–60° Tilt in the Rabbits Anesthetized with Urethane, Urethane + α -Chloralose, Morphine + Urethane + α -Chloralose and Nitrous Oxide

% Change in MBP at 1 min tilt was calculated as in the legend for Fig. 1. Values represent the mean $\pm$ S.E.M. from 5 experiments. a) $p < 0.05$, b) $p < 0.01$; significantly different from the corresponding control.

Fig. 4. Correlation between Maximum Reflex Tachycardia during Tilt without Chlorpromazine and Orthostatic Hypotension after Chlorpromazine in Conscious and Anesthetized Rabbits

Maximum reflex tachycardia during tilt without drug was calculated in each rabbit from the following equation: (maximum change in heart rate during the second series of tilts – heart rate just before the tilt) $\times$ 100/heart rate just before the tilt. Orthostatic hypotension after chlorpromazine was calculated in each rabbit by subtracting % change in mean blood pressure at 1 min tilt just before chlorpromazine from that after chlorpromazine (0.1 mg/kg, i.v.). % Change in mean blood pressure at 1 min tilt was calculated as in the legend for Fig. 1. Tilt angle was 90° in conscious rabbits and 45° in anesthetized ones. U; urethane anesthesia, U+C; urethane + α -chloralose anesthesia, M+U+C; morphine + urethane + α -chloralose anesthesia.

nificantly the orthostatic hypotension during 60° tilt in group U+C rabbits, while it failed to produce orthostatic hypotension in group M+U+C rabbits (Fig. 3). In group G rabbits chlorpromazine (1 mg/kg, i.v.) potentiated significantly the orthostatic hypotension during 30 and 45° tilts (Fig. 3). When the relationship between the ability of chlorpromazine (0.1 mg/kg, i.v.) to induce orthostatic hypotension and the amplitude of reflex tachycardia in response to head-up tilt before chlorpromazine treatment was examined in conscious and anesthetized rabbits, there was a negative correlation between the two parameters (Fig. 4).

Prazosin at 0.03 and 0.1 mg/kg, i.v. enhanced significantly the initial reduction in MBP during tilt (45 and 60°) in group U and group G rabbits, respectively, and pentolinium at 0.3 mg/kg, i.v. potentiated it significantly only in group U rabbits (data not shown). As shown in Figs. 5 and 6, prazosin (0.03 or 0.1 mg/kg, i.v.) and pentolinium (0.3 or 1 mg/kg, i.v.) augmented significantly the orthostatic hypotension in group U, group U+C and group G rabbits. The amplitude of orthostatic hypotension by prazosin at 0.03 and 0.1 mg/kg, i.v. under the three anesthetics was similar to that by chlorpromazine at

0.1 and 1 mg/kg, i.v., respectively. In group M+U+C rabbits both prazosin (0.1 mg/kg, i.v.) and pentolinium (1 mg/kg, i.v.) converted the pressor response at 1-min tilt to a depressor one in group M+U+C rabbits. The effects of prazosin and pentolinium were observed in a tilt angle-dependent fashion.

Chlorpromazine at 0.01–1 mg/kg, i.v. lowered basal MBP dose-dependently in conscious and anesthetized rabbits with the following rank order of potency: group U $\cong$ group G $\cong$ group U+C > group M+U+C > conscious rabbits (Table 2). Both prazosin and pentolinium also reduced basal MBP in conscious and anesthetized rabbits (Table 2).

α -Adrenoceptor Blocking Action in Aorta and Saphenous Vein Both chlorpromazine (10^{-7} and 10^{-6} M) and prazosin (10^{-8} and 10^{-7} M) caused a concentration-dependent rightward parallel shift of the concentration–response curve for norepinephrine in the aorta with no inhibition of maximum contractile response, the pA_2 values for chlorpromazine and prazosin being 7.72 ± 0.16 and 8.19 ± 0.12 , respectively

Fig. 5. Effects of Prazosin on Mean Blood Pressure (MBP) at 1 min after the Onset of 30–60° Tilt in the Rabbits Anesthetized with Urethane, Urethane + α -Chloralose, Morphine + Urethane + α -Chloralose and Nitrous Oxide

% Change in MBP at 1 min tilt was calculated as in the legend for Fig. 1. Values represent the mean $\pm$ S.E.M. from 5 experiments. a) $p < 0.05$, b) $p < 0.01$; significantly different from the corresponding control.

Fig. 6. Effects of Pentolinium on Mean Blood Pressure (MBP) at 1 min after the Onset of 30–60° Tilt in the Rabbits Anesthetized with Urethane, Urethane + α -Chloralose, Morphine + Urethane + α -Chloralose and Nitrous Oxide

% Change in MBP at 1 min tilt was calculated as in the legend for Fig. 1. Values represent the mean $\pm$ S.E.M. from 5 experiments. a) $p < 0.05$, b) $p < 0.01$; significantly different from the corresponding control.

Table 2. Drug-Induced Decrease in Mean Arterial Blood Pressure under Different Anesthetic Conditions

Drugs	Dose (mg/kg, i.v.)	Conscious	Urethane	Urethane + α -chloralose	Morphine+Urethane + α -chloralose	Nitrous oxide
Chlorpromazine	0.01	-0.8 ± 1.3	-7.8 ± 2.1	-5.0 ± 2.8	-2.8 ± 1.2	-5.4 ± 1.2
	0.1	-5.2 ± 1.5	-18.2 ± 5.0	-22.6 ± 5.1	-15.4 ± 6.0	-19.2 ± 3.0
	1	-13.2 ± 2.0	$-30.0 \pm 4.8^{a)}$	$-37.2 \pm 4.3^{b)}$	-28.4 ± 4.5	$-38.8 \pm 5.5^{b)}$
Prazosin	0.03	—	-23.2 ± 2.9	-27.4 ± 3.9	—	—
	0.1	-22.5 ± 4.6	—	—	-29.4 ± 2.8	-29.6 ± 2.7
Pentolinium	0.3	—	-14.0 ± 2.9	-14.2 ± 2.6	—	—
	1.0	-24.2 ± 10	—	—	-23.2 ± 5.0	-25.0 ± 7.0

Values represent the mean $\pm$ S.E.M. (mmHg) of 5 experiments. a) $p < 0.05$, b) $p < 0.01$; significantly different from the value in conscious animals.

Table 3. pA_2 Values and Schild Slopes for Chlorpromazine and Prazosin against the Contraction Induced by Norepinephrine in Aortae and Saphenous Veins Isolated from Rabbits

	Chlorpromazine		Prazosin	
	pA_2	Slope	pA_2	Slope
Aorta	7.72 ± 0.16	0.99 ± 0.04	8.19 ± 0.12	1.03 ± 0.08
Saphenous vein	$6.67 \pm 0.19^{a)}$	1.20 ± 0.11	7.80 ± 0.18	0.72 ± 0.11

Values represent the mean $\pm$ S.E.M. of 4 or 5 experiments. a) $p < 0.01$; significantly different from the value in the aorta.

(Table 3). In the saphenous vein, chlorpromazine (5×10^{-7} and 3×10^{-6} M) and prazosin (10^{-7} and 10^{-6} M) shifted concentration-dependently the norepinephrine concentration-response curve to the right with about 10–20% inhibition of maximum contraction. The pA_2 values were 6.67 ± 0.19 for chlorpromazine and 7.80 ± 0.18 for prazosin (Table 3). The pA_2 value for chlorpromazine, but not prazosin, was significantly smaller in the saphenous vein than in the aorta. In all experiments, the slope of the regression line from Schild plots was not significantly different from unity (Table 3).

DISCUSSION

Drug-induced orthostatic hypotension is generally evaluated by measuring the blood pressure response of experimental animals to head-up tilt. In the present study, the blood pressure of anesthetized rabbits was initially reduced by 30, 45 and 60° tilts and gradually returned toward or above the pre-tilt pressure during 1-min tilt, but blood pressure of conscious rabbits was scarcely altered even by vertical tilt. When the decrease in MBP at 1 min after the onset of tilt was taken as an index of orthostatic hypotension, chlorpromazine produced a significant orthostatic hypotension in group U, group U+C and group G rabbits, but not in conscious and group M+U+C rabbits. The chlorpromazine-induced orthostatic hypotension was observed with three tilt angles under urethane anesthesia, whereas it was observed with one or two angles under the other two anesthetics. From these results, of the anesthetics used in the present study, urethane may be the most suitable anesthetic for evaluating the chlorpromazine-induced orthostatic hypotension. HR was increased in response to tilt in conscious and anesthetized rabbits, the rank order of this reflex tachycardia being conscious $\approx$ group M+U+C > group G $\approx$ group U+C $\approx$ group U rabbits. When the relationship between the orthostatic hypotension induced by chlorpromazine at 0.1 mg/kg, i.v. and the amplitude of re-

flex tachycardia during 45° or 90° tilt before the treatment with chlorpromazine was examined in conscious and anesthetized rabbits, there was a negative correlation between the two parameters. This finding implies that chlorpromazine can produce orthostatic hypotension under conditions that impair baroreflex. Therefore, special care should be taken to avoid accidents due to orthostatic hypotension when chlorpromazine is administered to patients with neuropathy (e.g. diabetes mellitus) or elderly patients, whose baroreflex system is likely to be impaired. On the other hand, prazosin as well as pentolinium induced orthostatic hypotension not only in group U, group U+C and group G but also in group M+U+C rabbits whose reflex tachycardia was hardly impaired. This result implies that prazosin and pentolinium may cause orthostatic hypotension irrespective of neuropathy or age. The orthostatic hypotension inducing effect of prazosin was observed with two or three tilt angles under each anesthesia. The amplitudes of the orthostatic hypotension induced by prazosin at 0.03 and 0.1 mg/kg, i.v. were similar to those by chlorpromazine at 0.1 and 1 mg/kg, i.v., respectively. Thus, the ability of prazosin to induce orthostatic hypotension was three to ten times more potent than that of chlorpromazine, judging from the dose employed.

Head-up tilt decreases cardiac output in human^{10,11)} and in experimental animal,⁵⁾ which is attributable to pooling of blood in the venous vascular bed.¹⁰⁾ In normal conditions, however, this pooling is counteracted by the baroreflex, leading to an immediate recovery of cardiac output and blood pressure during tilt. Prazosin suppresses the recovery of cardiac output during tilt by dilating the venous vasculature as well as the arterial one. This contributes to orthostatic hypotension induced by prazosin. In the present *in vitro* experiments using rabbit aorta and saphenous vein as a model of artery and vein, the pA_2 value for chlorpromazine but not prazosin against the norepinephrine-induced contraction was significantly smaller in the saphenous vein than in the aorta, suggesting that the α -adrenoceptor blocking effect of chlorpromazine is significantly weaker in the venous vascular bed. From these results, it seems that the lower potency of chlorpromazine to block α -adrenoceptors in veins may be responsible for the inability of chlorpromazine to produce orthostatic hypotension under M+U+C anesthesia where baroreflex activity is hardly suppressed and where prazosin, which blocked α_1 -adrenoceptors to a similar extent in the aorta and saphenous vein, was able to cause orthostatic hypotension. Take *et al.*¹²⁾ showed recently that the mRNAs of α_{1d} - and α_{1b} -adrenoceptor subtypes were expressed predominantly in the rat aorta and portal vein, respectively, and that naftopidil,

a relatively selective α_{1d} -adrenoceptor antagonist with a significantly weaker α_1 -adrenoceptor blocking potency in the portal vein than in the aorta, did not elicit orthostatic hypotension in anesthetized rats, but prazosin with a similar potency in both blood vessels produced it. If the different expression of α_1 -adrenoceptor-subtype mRNAs in the rat aorta and portal vein is the case for the rabbit aorta and saphenous vein, it is possible that chlorpromazine, like naftopidil, may be a relatively selective α_{1d} -adrenoceptor antagonist, resulting in a low potential of chlorpromazine to induce orthostatic hypotension.

In conclusion, the rabbit under anesthetic conditions which impair reflex tachycardia during tilt may be a useful experimental model for evaluation of orthostatic hypotension induced by chlorpromazine. In addition, a relatively low potential of chlorpromazine to produce orthostatic hypotension may be partly due to its weak venodilating action.

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