Original Article

Effects of Repeated Alcohol Intake on Blood Pressure and Sodium Balance in Japanese Males with Hypertension

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Alcohol consumption causes biphasic changes in blood pressure (BP) in Asians. The aim of the present study was to investigate the effects of repeated alcohol intake on BP and sodium metabolism. Fourteen Japanese males with hypertension (37–67 years old) were examined under standardized conditions (Na intake 120 mmol/day). After 1 week of alcohol restriction, the patients consumed a control drink with dinner for 3 days, 1 ml/kg of alcohol for the next 7 days, then the control drink for 3 days. Supine BP and heart rate were measured 5 times daily, and urinary excretion of water and sodium was determined throughout the study period. Average BP decreased initially, then returned to the baseline level during the alcohol period. Evening BP decreased significantly throughout the alcohol period, although the reduction was attenuated during the late phase. Morning and afternoon BP did not change significantly, but tended to be elevated during the late phase. Heart rate increased both in the morning and evening during the alcohol period. Urine volume did not change during the early phase, but increased significantly during the late phase. Urinary sodium excretion decreased initially, but increased during the middle phase of the alcohol period. In conclusion, BP decreases initially with sodium retention, then returns to the baseline level with restoration of sodium balance during repeated alcohol intake in Japanese males with hypertension. Sodium retention during the early phase appears to be the consequence of BP reduction and may contribute to the subsequent changes in BP. (*Hypertens Res* 2004; 27: 167–172)

Key Words: alcohol, hypertension, blood pressure, sodium, natriuresis

Introduction

The relation between alcohol consumption and hypertension is well known (1, 2), and restriction of alcohol intake is recommended in the management of hypertension (3). Although the pressor effect of alcohol has been well documented (1, 2, 4–6), ethanol has both vasoconstrictive and vasodilatory actions, and a metabolite of ethanol acetaldehyde dilates blood vessels (7). We reported previously that a single intake of alcohol lowers blood pressure (BP) for several hours, while repeated alcohol consumption causes biphasic changes in the

BP of Japanese males with hypertension (8–10). It is also known that cessation of drinking sometimes causes alcohol withdrawal syndrome, which includes transient BP elevation and tachycardia (11). These effects of alcohol appear to be dependent on the duration and amount of consumption, the time from the last drinking, and the presence or absence of alcohol flush, which is common in Asians (12, 13). However, the time-related changes in BP caused by alcohol consumption and its withdrawal have not been clarified precisely.

It has been reported that alcohol has effects on water and electrolyte metabolism, such as diuresis due to the suppres-

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sion of vasopressin release and increases in urinary excretion of magnesium and calcium (14–16). We observed previously that ingestion of alcohol decreased the serum potassium level and intracellular sodium concentration in hypertensive subjects (17). It has also been reported that alcohol acutely reduces urinary sodium excretion (14, 18, 19). This effect of alcohol may be involved in alcohol-induced hypertension, since sodium balance plays an important role in BP regulation and hypertension. However, there have been no studies investigating the effects of repeated alcohol consumption on sodium balance with reference to changes in BP.

In the present study, we examined the effects of repeated intake of alcohol and its withdrawal on BP and sodium and water metabolism in Japanese males with essential hypertension. To investigate the effects of alcohol on BP in detail, BP was measured 5 times per day from early morning to late evening throughout the study period under standardized conditions.

Methods

Subjects

Fourteen Japanese males with essential hypertension and drinking habits were studied. Their ages were 37–68 years old (54 ± 2 years, mean $\pm$ SEM), and average height and weight were 168 ± 1 cm and 67 ± 1 kg, respectively. The amount of their usual alcohol intake ranged from 30–105 ml/day (67 ± 5 ml/day). All patients were diagnosed as having mild to moderate essential hypertension and none of them had serious cardiovascular, hepatic, or renal disorders. Two patients were never treated, and the other 12 patients were treated with antihypertensive drugs before the present study.

Protocol

The study protocol was approved by the Ethics Committee of the National Cardiovascular Center, and informed consent was obtained from each subject. All subjects abstained from alcoholic drinks and stopped antihypertensive medications for at least 1 week before the study. Subjects were hospitalized in a ward of the National Cardiovascular Center where they ate a regular hospital diet (Na 120 mmol/day, 1,600 kcal/day). Before entering the protocol, subjects stayed in the ward for several days to minimize the effect of hospitalization on BP during the study protocol.

The study was divided into three consecutive phases: Control phase—a 3-day period during which nonalcoholic drinks having the same number of calories as the alcoholic drinks were added to the dinners (17:00–18:00); Alcohol phase—a 7-day period during which 1 ml/kg of ethanol was administered with dinner, in the form of vodka, lime juice and water; Recovery phase—a 3-day period during which the nonalcoholic drinks were added to dinners. Additional water intake

was not restricted throughout the study protocol.

Supine BP was measured using mercury sphygmomanometers at 6:00, 10:00, 14:00, 18:00 and 21:00 by trained nurses throughout the study period. Heart rate was measured manually immediately before the BP measurements. Urine collections for 24 h and measurements of fasting body weight were also carried out each day. Venous blood samplings were performed before dinner (17:00), 60–90 min after dinner (19:00), and before breakfast (8:00) on the morning following the last day of the control period and on Days 1 and 7 of the alcohol period.

Biochemical Measurements

Serum electrolytes and urinary excretion of sodium, potassium and creatinine were determined using a biochemical analysis system (TBA-80S; Toshiba, Tokyo, Japan).

Statistical Analysis

Values are expressed as the mean $\pm$ 1 SEM. Comparisons were made by repeated measures analysis of variance followed by the contrast method. Analyses were performed using Stat View (ver. 5) and Super ANOVA software (Abacus Concept Inc., Berkeley, USA). A *p* value of less than 0.05

Systolic Blood Pressure

Fig. 1. Systolic blood pressure at 5 different time points during the control, alcohol, and recovery periods. * *p* < 0.05 vs. the last day of the control period. † *p* < 0.05 vs. the last day of the alcohol period.

Diastolic Blood Pressure

Fig. 2. Diastolic blood pressure at 5 different time points during the control, alcohol, and recovery periods. * $p < 0.05$ vs. the last day of the control period. † $p < 0.05$ vs. the last day of the alcohol period.

was considered statistically significant.

Results

Blood pressure and heart rate at different times of the day during the control, alcohol and recovery periods are shown in Figs. 1–3. Evening BP during the alcohol period was consistently lower than that during the control period (systolic BP at 21:00 was 145.4 ± 4.9 mmHg on the last day of the control period, and 130.7 ± 3.2 mmHg on Day 1 of the alcohol period). Morning and afternoon BPs did not change during the alcohol period, although they tended to increase during the late phase (systolic BP at 14:00 was 146.1 ± 6.2 mmHg on the last day of the control period, and 151.8 ± 4.9 mmHg on Day 7 of the alcohol period). These changes in BP returned to the control level during the recovery period. Heart rate increased significantly both in the morning and evening during the alcohol period, although these changes were attenuated during the late phase. The increases in heart rate returned to baseline during the recovery period.

Daily average BP and heart rate are shown in Fig. 4. Systolic BP decreased significantly during the early phase of the alcohol period (Day 1: 140.2 ± 3.2 mmHg) compared with the control period (147.2 ± 4.7 mmHg); however, the reduction was blunted during the late phase (Day 7: $144.7 \pm$

Heart Rate

Fig. 3. Heart rate at 5 different time points during the control, alcohol, and recovery periods. * $p < 0.05$ vs. the last day of the control period. † $p < 0.05$ vs. the last day of the alcohol period.

Fig. 4. Average systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during the control, alcohol, and recovery periods. * $p < 0.05$ vs. the last day of the control period. † $p < 0.05$ vs. the last day of the alcohol period.

3.6 mmHg). Diastolic BP showed a similar tendency, although its change was not significant. Average heart rate increased during the alcohol period (Control: 64.0 ± 1.0 ; Day

Fig. 5. Body weight (BW), urine volume (UV), urinary sodium excretion (UNaV), and urinary creatinine excretion (UCr) during the control, alcohol, and recovery periods. * $p < 0.05$ vs. the last day of the control period.

1: 68.7 ± 1.4 ; Day 7: 66.5 ± 1.1 beats/min), and returned to baseline during the recovery period.

Body weight decreased slightly but significantly during the late phase of the alcohol period and the recovery period (Fig. 5). Urine volume did not change during the early phase of the alcohol period, but increased significantly on Days 4–6. Biphasic changes in urinary Na excretion were observed during the alcohol period. It decreased from 112 ± 8 mmol/day during the control period to 97 ± 6 mmol/day on Day 2, then increased to 130 ± 8 mmol/day on Day 4. There were no significant changes in urinary excretion of creatinine or K.

Serum Na and K concentrations at 17:00, 19:00 and 8:00 during the control and alcohol periods are shown in Table 1. There were no significant changes in serum Na concentration. Serum K decreased after meals both during the control and alcohol periods; however, the level of serum K after ingestion of alcohol was significantly lower than that during the control period.

The alcohol-induced reductions in BP and urinary sodium excretion were more obvious in two patients who showed marked facial flush after alcohol ingestion than in the rest of subjects. The amount of usual alcohol intake did not relate to the changes in BP or sodium excretion.

Table 1. Serum Concentrations of Sodium and Potassium during the Control and Alcohol Periods

	Control	Alcohol Day 1	Alcohol Day 7
Serum Na (mmol/l)			
17:00	140.1 ± 0.7	140.0 ± 0.5	139.5 ± 0.5
19:00	139.7 ± 0.7	140.0 ± 0.6	139.6 ± 0.6
8:00	140.3 ± 0.7	140.1 ± 0.6	139.6 ± 0.5
Serum K (mmol/l)			
17:00	4.09 ± 0.06	4.06 ± 0.07	3.97 ± 0.05
19:00	$3.84 \pm 0.05^\dagger$	$3.65 \pm 0.05^\dagger, *$	$3.61 \pm 0.04^\dagger, *$
8:00	4.18 ± 0.06	4.16 ± 0.07	4.14 ± 0.06

$^\dagger p < 0.05$ vs. 17:00, * $p < 0.05$ vs. control period.

Discussion

In the present study, repeated intake of alcohol for 7 days caused significant changes in BP and Na balance in Japanese males with hypertension. The alcohol-induced reduction in evening BP was consistently observed throughout the alcohol intake days, while the decrease in average BP was observed in the early but not the late phase of alcohol consumption. These changes in BP were associated with early sodium retention followed by natriuresis during the alcohol period. The present study demonstrates that repeated alcohol intake causes biphasic changes in BP and sodium metabolism, and suggests these changes may interact with each other.

The changes in BP after repeated alcohol consumption confirm previous observations (8–10). The reduction in evening BP was observed throughout the alcohol period in this and our previous studies. This depressor response may be specific to Asian subjects, since alcohol flush syndrome characterized by facial flush and tachycardia is common in Asians but rare in Caucasians and Africans (8, 20). The alcohol-induced BP elevation was not apparent in the present study, but morning and afternoon BPs tended to increase in the late phase (9, 10). The mechanisms of the hypertensive effect of alcohol have not been completely clarified, although neurohumoral substances, vascular smooth muscle, and endothelium may be involved (13, 16). Our studies suggest that the alcohol withdrawal rather than any straightforward action of alcohol itself may play an important role in the BP elevation because BP fell at the time of high blood alcohol level. The average BP measured at 5 different hours decreased during the early phase of the alcohol period, then returned to the baseline level in the present study. These findings suggest that some slow pressor mechanisms may operate in the changes in BP after repeated alcohol intake.

Heart rate increased during the alcohol period in the present study, confirming previous observations (8–10, 16). The change in heart rate was most apparent in the evening but was also seen in the morning. The evening tachycardia appears to be due to the direct action of alcohol and to the re-

flex response to BP reduction. Mechanisms related to alcohol withdrawal, such as activation of the sympathetic nervous system, may be involved in the morning rise in heart rate.

Urinary sodium excretion decreased during the early phase but increased during the middle phase of the 7-day alcohol period in the present study. The early reduction in sodium excretion appears to be related to the initial decrease in BP, since BP is a powerful regulator of renal sodium handling and *vice versa* (21). This sodium retention may contribute to the subsequent BP change, including the rise in daytime BP. The late natriuresis also appears to follow the change in average BP, which returned to the baseline level after repeated alcohol consumption. The acute reduction in urinary sodium excretion after alcohol consumption was also observed in some earlier studies (14, 18, 19). In addition to the hemodynamic mechanism, neurohormonal factors might contribute to the alcohol-induced sodium retention, since activation of the sympathetic nervous system and the renin-angiotensin system acts on the kidney to reduce sodium excretion (22). In the related previous studies, we observed that both plasma norepinephrine concentration and plasma renin activity increased after a single alcohol ingestion (8, 23). However, those changes were attenuated after repeated intake of alcohol (9).

The alcohol-induced changes in BP, heart rate and sodium metabolism may not be restricted to hypertensive patients, but may also be seen in normotensive subjects. Acute reductions in BP and sodium excretion (19, 20) and a chronic increase in BP (24) have also been observed in normotensive individuals. However, these effects of alcohol may be more clinically relevant in hypertensives than in normotensives. The effects of alcohol on BP appear to be dose-dependent, since a linear relationship has been observed between the amount of alcohol consumption and the level of BP (1, 2). A similar dose-related effect would be expected regarding sodium metabolism, although there have been no studies examining the dose-response relationship in humans.

In the present study, urine volume did not change during the early phase but increased during the middle phase of the alcohol period. It is known that alcohol temporally stimulates water excretion from the kidney. This alcohol-induced diuresis is mediated by the suppression of vasopressin secretion (18, 23). The lack of initial diuresis in our study may be related to the decrease in BP, which acts to reduce renal water excretion. The increase in urine volume was observed in parallel with natriuresis when BP returned to the baseline level. However, a precise assessment of water balance was not possible in the present study, since the amount of daily water intake was not measured.

Several studies have shown that serum sodium concentration increases after alcohol ingestion (25, 26). This change in sodium concentration may be related to the alcohol-induced diuresis. In the present study, the level of serum sodium did not change during the alcohol period. The lack of marked diuresis and the free access to water may explain the stable

level of serum sodium. On the other hand, the serum potassium concentration decreased acutely after alcohol intake, confirming earlier observations (8, 26, 27). This alcohol-induced hypokalemia was not due to kaliuresis, but was mediated by activation of the sympathetic nervous system, since propranolol attenuated the change in serum potassium in our previous study (27).

Alcohol consumption may also influence BP through its effects on magnesium and calcium metabolism (13). It has been shown that urinary excretion of these minerals increases after ingestion of alcohol (14, 15), although we did not measure urinary magnesium and calcium in the present study. The alcohol-induced deficiency of these minerals may play a role in BP elevation. An experimental study has shown that magnesium supplementation prevents the development of alcohol-induced hypertension in rats (28). However, the depressor effect of magnesium and calcium supplementation was not significantly different between drinkers and nondrinkers in our previous studies (29, 30).

In conclusion, the findings of the present study show that average BP decreases during the early phase but returns to the baseline level during the late phase during repeated alcohol intake in Japanese males with hypertension. Urinary sodium excretion decreased initially, then increased during the alcohol period. The early sodium retention appears to be the consequence of alcohol-induced BP reduction and may participate in the subsequent BP elevation.

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