NOTE

Renin-Dependency of Glycyrrhizin-Induced Pseudoaldosteronism

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Abstract. A prospective study was carried out on 12 patients with chronic hepatitis who were taking 546 mg/day of glycyrrhizin for 4 weeks in order to identify the factors responsible for the development of hypertension and hypokalemia. In 5 patients, blood pressure increased and serum potassium decreased after the treatment (responders). In the remaining 7 patients, these values were unchanged (nonresponders). There were no significant differences in age, plasma aldosterone, the catecholamine concentrations or serum transaminases. The basal plasma renin activity (PRA) in the responders was more than 1.5 ng/ml/h (2.5 ± 0.3 ng/ml/h), while that in the non-responders was less than 1.5 ng/ml/h (0.7 ± 0.1 ng/ml/h). Furthermore, a positive correlation between the basal RPA and the changes in blood pressure, and a negative correlation between the basal PRA and the changes in potassium were found. These results suggest that patients with higher PRA levels are more likely to develop hypertension and hypokalemia when treated with glycyrrhizin.

LICORICE extract (glycyrrhizia), prepared from the root of the plant Glycyrrhiza glabra, has long been widely used for flavoring in food, beverages and medicines. The active compound in licorice is glycyrrhizin, a conjugate of 2 molecules of glucuronic acid and glycyrrhetic acid [1-3].

Glycyrrhizin is well known to be similar in its metabolic activities to mineralocorticoid [4, 5]. In addition, the development of pseudoaldosteronism, characterized by sodium retention, exaggerated potassium excretion, and suppression of both renin and aldosterone was described in patients who took large amounts of licorice or glycyrrhizin for long periods [1, 6-9]. However, the alterations in blood pressure and electrolyte balance in patients taking licorice or glycyrrhizin were quantitatively variable, with some individuals showing little or no change, whereas others exhibited gross abnormalities [10, 11].

The present study was undertaken in an attempt to identify factors responsible for the development of pseudoaldosteronism in patients with chronic liver disease taking glycyrrhizin.

Subjects and Methods

The study was approved by the human investigation committee of the Tochigi National Hospital. Twelve patients with chronic hepatitis were studied. They were 10 men and 2 women, age 33 to 64 years old (mean ± SEM., 50 ± 3). A diagnosis of chronic hepatitis was made by compiling the patient’s history, laboratory data and liver biopsy. Patients with alcoholic liver diseases, liver cirrhosis (presence of ascites, splenomegaly, thrombocytopenia, abnormal indocyanine green retention, prolongation of prothrombin time), essential hypertension, diabetes mellitus, renal and myocardial disease and patients taking diuretics, steroids and immunosuppressive drugs were excluded from the study.

They were given 546 mg/day of glycyrrhizin (Nihon Chemipha Co., Tokyo) for 4 weeks and
were followed up at our outpatient clinic every 2 weeks. At the time of their visits before and after the treatment, they were kept recumbent for about 15 min and their blood pressure was recorded with a sphygmomanometer. In addition, their blood was collected for the determination of serum electrolytes, transaminases, total protein, plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma epinephrine (PE) and plasma norepinephrine (PNE).

PRA was determined by radioimmunoassay of angiotensin I generated during a 60-min incubation at 37°C [12], PAC as measured with an aldosterone-RIA kit from Dainabot Co., Tokyo [13]. PNE and PE were determined by high-performance liquid chromatography and the trihydroxyindole fluorometric method [14]. Serum electrolytes and chemistries were measured with an autoanalyzer (Hitachi 736-30, Hitachi, Tokyo, [15]). All results were expressed as the mean ± SEM. Statistical comparisons were made by Student's t-test or Chi-square analysis. Statistical significance was considered to be less than 0.05.

**Results**

Five of the 12 patients with chronic hepatitis were the responders whose mean blood pressure (MBP) increased from 92 ± 4 to 104 ± 6 mmHg (p<0.02), and whose mean serum potassium concentration decreased from 4.3 ± 0.1 to 3.3 ± 0.1 mEq/l (p<0.01), while the remaining 7 patients were the nonresponders whose MBP and mean serum potassium concentration remained stable during the 4-week treatment with glycyrrhizin (96 ± 2 to 98 ± 4 mmHg and 4.1 ± 0.1 to 4.2 ± 0.2 mEq/l, respectively, Fig. 1 and 2). The basal data for patients in both groups are shown in Table 1. There were no significant differences between the two groups in age, sex, family history of hypertension, transaminases, or total protein and plasma catecholamines.

The basal levels of PAC were not different. They decreased similarly after the treatment with glycyrrhizin (87 ± 16 to 25 ± 8 pg/ml in the responders, 76 ± 14 to 42 ± 7 pg/ml in the nonresponders). The basal level of PRA in the responders was more than 1.5 ng/ml/h (2.5 ± 0.3 ng/ml/h), while that in the nonresponders was below 1.5 ng/ml/h (0.7 ± 0.1 ng/ml/h), significantly lower than the responders (p<0.01, Fig. 3). After the treatment with glycyrrhizin, PRA in both groups was suppressed, and no differences were found between the two groups (0.5 ± 0.1 ng/ml/h in the responders, 0.5 ± 0.1 ng/ml/h in the nonresponders). Four to six weeks after the discontinuation of glycyrrhizin, MBP, PRA, PAC and serum potassium in the responders returned to the basal levels (MBP; 89 ± 3 mmHg, PRA; 2.1 ± 0.03 ng/ml/h, PAC 75 ± 10 pg/ml, potassium; 4.2

![Fig. 1. Changes in mean blood pressure (MBP) before and after the treatment with glycyrrhizin.](image-url)
Table 1. Clinical characteristics of the patients studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Family history</th>
<th>MBP (mmHg)</th>
<th>GOT (IU/l)</th>
<th>GPT (IU/l)</th>
<th>TP (g/dl)</th>
<th>PE (pg/ml)</th>
<th>PNE (pg/ml)</th>
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<td>2 53 F</td>
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<td>F</td>
<td>-</td>
<td>93</td>
<td>98</td>
<td>156</td>
<td>7.8</td>
<td>0.04</td>
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<tr>
<td>3 57 M</td>
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<td>+</td>
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<td>93</td>
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<td>6.9</td>
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<td>1 64 F</td>
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<tr>
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<td>6 40 M</td>
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<td>65±11</td>
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<td>7.4±0.2</td>
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<td>1.19±0.02</td>
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</table>

Fig. 2. Changes in potassium (K) before and after the treatment with glycyrrhizin.

Discussion

The present study demonstrated two points in patients with chronic hepatitis treated with 546 mg of glycyrrhizin. First, 5 of the 12 patients showed an increase in blood pressure and a decrease in serum potassium (responders), while in the remaining 7 patients, these values remained stable (nonresponders). Second, the basal PRA values in the responders were different from those of the

Furthermore, a significant positive correlation between the basal PRA values and the changes in blood pressure (r = 0.85, p < 0.01), and a significant negative correlation between the basal PRA values and the changes in the serum potassium concentration (r = -0.75, p < 0.01) were found (Figs. 4 and 5). Body weight, the plasma catecholamine concentration, and the serum sodium and chloride concentrations were not altered during the treatment.
nonresponders. The patients with higher PRA were more likely to develop hypertension and hypokalemia.

Since Conn et al. [6] first described a case of pseudoaldosteronism caused by chronic, excessive licorice ingestion, similar cases have been reported in the literature [1, 7–9]. Glycyrrhizin and carbenoxolone, the semisynthetic hemisuccinate derivative of glycyrrhizinic acid, have been shown to have mineralocorticoid activity [3–5].

In the present study, all patients taking glycyrrhizin showed a reduction in both PRA and PAC from the basal levels, indicating that glycyrrhizin acted as an exogenous mineralocorticoid and suppressed the renin-angiotensin-aldosterone system. Although suppression of the renin-angiotensin-aldosterone system was seen in all patients, an increase in blood pressure and a decrease in serum potassium were observed in 5 patients (responders). It has been shown that the development of hypertension and hypokalemia is not always observed in all patients taking glycyrrhizin or carbenoxolone. Indeed, Revers [16] reported the development of edema, shortness of breath and headaches in 20% of the patients treated with licorice; and Hausman et al. [11] described hypertension in 3 of 15 patients treated with carbenoxolone. While it is not entirely clear
what dictates these differences in response, older people, perhaps due to a decreased binding of carbenoxolone to plasma albumin with a diminished plasma clearance rate [17], and those with impaired renal or myocardial function are reported to be reliable indicators for predicting an increase in blood pressure or a decrease in serum potassium [18]. However, none of these factors could predict the development of hypertension and hypokalemia in our patients.

Glycyrrhizin and carbenoxolone are almost entirely removed from the circulation by conjugation in the liver to form glucuronide, and reduced hepatic activity can clearly impair this mechanism [17]. As far as indocyanine green excretion, albumin, transaminases and prothrombin time were concerned, no differences were found between the responders and the nonresponders. Furthermore, since patients who progressed to liver cirrhosis were excluded from the study, we can rule out the possibility that the changes observed in the responders could be derived from the impaired metabolism of glycyrrhizin.

The only difference we found which clearly differentiated the responders from the nonresponders was the PRA value before the treatment, with patients having a PRA of more than 1.5 ng/ml/h being the responders and those having a PRA of less than 1.5 ng/ml/h being the nonresponders. The sympathetic nervous system is one of the major factors which determine the secretion of renin from the juxtaglomerular cells. Furthermore, the activation of the sympathetic nervous system or infusion of catecholamines is known to stimulate renin release [19]. In the present study, however, PNE of the responders, was not different from that of the nonresponder. Therefore, it seems unlikely that the high PRAN levels in the responders derived from activation of the sympathetic nervous system. Sodium balance is another important factor affecting renin secretion. Low sodium intake is associated with increased secretion of renin through activation of the vascular stretch receptor and macula densa receptor [19]. It has been shown that mineralocorticoid cannot induce hypertension or hypokalemia when animals are placed on a low sodium intake [20], and, furthermore, development of hypertension or hypokalemia induced by mineralocorticoid is shown to be sodium-dependent [21]. Therefore, although we did not examine sodium balance, these results suggest that the higher PRA levels observed in the responders were not due to a low dietary sodium intake. Furthermore, in the present study, PRA, PAC, MBP and potassium concentrations in the responders returned to basal levels after discontinuation of glycyrrhizin. PRA levels in the responders were still higher than 1.5 ng/ml/h. These results suggest that differences in the PRA in the responders and nonresponders
were not due to differences in sympathetic nervous activity, blood pressure and sodium intake.

Although the mechanism(s) responsible for the high PRA levels in the responders remain unclear from the present study, it is concluded that patients with higher PRA levels are more likely to develop hypertension and hypokalemia due to glycyrrhizin.

References