Journal of Human Hypertension (2001) 15, 549–552

www.nature.com/jhh

ORIGINAL ARTICLE

Liquorice-induced rise in blood pressure: a linear dose-response relationship

HÁ Sigurjónsdóttir[1], L Franzson[2], K Manhem[1], J Ragnarsson[3], G Sigurdsson[3] and S Wallerstedt[1]

[1]*Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden;* [2]*Department of Chemical Pathology, and* [3]*Department of Medicine, Reykjavik City Hospital, University of Iceland, Iceland*

To clarify the dose-response and the time-response relationship between liquorice consumption and rise in blood pressure and explore the inter-individual variance this intervention study was designed and executed in research laboratories at University hospitals in Iceland and Sweden. Healthy, Caucasian volunteers who also served as a control for himself/herself consumed liquorice in various doses, 50–200 g/day, for 2–4 weeks, corresponding to a daily intake of 75–540 mg glycyrrhetinic acid, the active substance in liquorice. Blood pressure was measured before, during and after liquorice consumption. Systolic blood pressure increased by 3.1–14.4 mm Hg ($P < 0.05$ for all), demonstrating a dose-response but not a time-response relationship. The individual response to liquorice followed the normal distribution. Since liquorice raised the blood pressure with a linear dose-response relationship, even doses as low as 50 g of liquorice (75 mg glycyrrhetinic acid) consumed daily for 2 weeks can cause a significant rise in blood pressure. The finding of a maximal effect of liquorice after only 2 weeks has important implications for all doctors dealing with hypertension. There does not seem to be a special group of responders since the degree of individual response to liquorice consumption followed the normal distribution curve.
Journal of Human Hypertension (2001) **15,** 549–552

Keywords: 11 β-hydroxysteroid dehydrogenase; liquorice; glycyrrhetinic acid

Introduction

Liquorice has been well known by mankind for a long time and was used medicinally long before the time of Christ. The earliest evidence of the use of liquorice is reputed to be the stores of liquorice found in the ancient tombs of Egyptian pharaohs, including that found in the 3000-year-old tomb of King Tut.[1] During the last couple of decades, our knowledge of the real effects of liquorice has increased. Case reports in which patients have reacted with hypertension, hypokalaemia, muscle weakness and even hypertensive encephalopathy with hemiparesis have been published.[2–5] Even apparently marginal doses of liquorice as in liquorice-flavoured chewing gum, chewing tobacco and Pontefract cakes have proved to cause hypokalaemia and hypertension.[2,6,7] The aim of the present study was to investigate the dose-response relationship, the time-response relationship and the inter-individual response variability to glycyrrhetinic acid.

Correspondence: Dr HÁ Sigurjónsdóttir, Department of Endocrinology, Gröna Stråket 8, Sahlgrenska University Hospital/Sahlgrenska, 413 45 Göteborg, Sweden, Fax: +46 31 821524
Received 4 November 2000; revised and accepted 7 March 2001

Subjects and methods

Study plan and collection of data

Three similarly designed experiments were conducted. General results from the first and second study have been published previously[8] but have not been used for analyse of the dose-response relationship. In order to avoid salt-induced influence on the results, with increased fluid retention, sweet liquorice was used and not salt liquorice. In the first and second studies the subjects were investigated without regard to the menstrual cycle. In the third study, where 75 mg of glycyrrhetinic acid was consumed, the women started the consumption on day 1–4 of the menstrual cycle. All subjects were normotensive and while participating in the study they had their usual home diet, containing on average 122 mmol of sodium estimated by 24-h urinary excretion. All volunteers signed an informed consent form. In each study the same nurse measured the blood pressure throughout the study period and monitored the well being of each participant. The local Ethics Committee approved each of the studies.

Study group 1

Ten healthy volunteers, one man and nine women, with a mean age of 30 years (23–37 years), consumed

200 g of sweet liquorice, ie 540 mg of glycyrrhetinic acid, daily for 2 weeks. Blood pressure was measured with a standard mercury sphygmomanometer with a standard cuff in the sitting position after at least 5 min of rest, three times per week, twice each visit. Baselines were obtained from a run-in period of 2 weeks, which was followed by a liquorice consumption period of 2 weeks and a follow-up period of 2 weeks. A physical examination was performed at the beginning of the study, at the end of the liquorice consumption, and at the end of the study.

Study group 2

Thirty healthy volunteers, 19 women and 11 men, with a mean age of 27.6 years (20–33 years) consumed 100 g of sweet liquorice, ie 270 mg of glycyrrhetinic acid, daily for 4 weeks. Other methods were as in study 1, but here the liquorice consumption period lasted 4 weeks.

Study group 3

Twenty-four healthy volunteers, 12 men and 12 women, with a mean age of 31.7 years (25–43 years) consumed 50 g of sweet liquorice, ie 75 mg of glycyrrhetinic acid, daily for 4 weeks. The discrepancy in the glycyrrhetinic acid concentration compared with that in study 1 and 2 is explained by the use of a product from another factory. Blood pressure was measured with a standard mercury sphygmomanometer with a standard cuff in the supine position after at least 15 min of rest. Blood pressure was measured twice during each visit, before the liquorice consumption and after 2 and 4 weeks consumption, and finally 4 weeks after liquorice consumption was ended. A physical examination was performed at the beginning of the study, at the end of the period of active treatment and, finally, 4 weeks after the consumption was concluded.

Statistical methods

In studies 1 and 2 a mean value for the blood pressure was calculated from the available measurements the last 2 measuring days before the liquorice consumption was started (baseline) and the last 2 measuring days in the second and fourth week of liquorice consumption. In study 3 a mean value was calculated for each visit before liquorice consumption (baseline) and after 2 and 4 weeks of consumption. The 95% confidence interval (CI) was determined and the two-tailed paired *t*-test was used to see if there was a significant change of blood pressure from the period before liquorice consumption (baseline period) and after consumption for 2 and 4 weeks respectively (in study 1 only for 2 weeks). The two-tailed paired *t*-test was also used to measure the change in plasma/serum potassium from baseline to 2 weeks after initiating liquorice consumption except in study 2 where the 2-week periods were compared.

Regression analysis was used to calculate the dose-response and time-response relationship. The response variance was calculated by variance analysis, using the data from study 2. A *P*-value of 0.05 or less was considered statistically significant.

Results

Study group 1

Baseline systolic blood pressure was 117.5 mm Hg (CI = ±6.0).[8] The mean value for systolic blood pressure after 2 weeks of liquorice consumption was 131.9 mm Hg (CI = ±7.5). The rise in systolic blood pressure of 14.4 mm Hg (Table 1) was significant ($P = 0.003$).

The baseline value for diastolic blood pressure was 72.6 mm Hg (CI = ±0.4) and the mean value after 2 weeks consumption 81.9 mm Hg (CI = ±0.2). The rise was 9.3 mm Hg and statistically significant ($P = 0.01$). Heart rate did not change significantly. Plasma potassium decreased by 0.36 mmol/L after 2 weeks ($P = 0.02$).

Study group 2

General results of this study have been published earlier. Baseline systolic blood pressure was 114.2 mm Hg (CI = ±3.5).[8] The mean value for the systolic blood pressure after 2 weeks of liquorice consumption was 119.4 mm Hg (CI = ±2.9). The rise in blood pressure of 5.2 mm Hg was highly significant ($P = 0.00087$). The mean value for the systolic blood pressure after 4 weeks of liquorice consumption was 119.6 mm Hg (CI = ±4.0) and equals a rise of 5.4 mm Hg compared with baseline (Table 1) and is significant ($P = 0.0002$).

The diastolic blood pressure increased from 73.2 mm Hg (CI = ±0.2) to 76.0 mm Hg (CI = ± 0.5) after 2 weeks was not significant. Neither did the heart rate change significantly. Plasma potassium decreased by the mean value of 0.24 mmol/L after 2 weeks ($P < 0.001$).

Study group 3

Baseline systolic blood pressure was 113 mm Hg (CI = ±4.5) and after 2 weeks of liquorice consumption the systolic blood pressure was increased (Table 1) by 3.1 mm Hg mean to 116.1 mm Hg (CI = ±4.5 and $P = 0.028$). After 4 weeks of liquorice consumption the mean value of the systolic blood pressure was 114.9 mm Hg (CI = ±4.8); this increase was not statistically significant compared with baseline ($P = 0.4$).

Diastolic blood pressure, heart rate and serum potassium did not change significantly.

Table 1 Mean rise in systolic blood pressure in relation to dose of glycyrrhetinic acid and duration of consumption

Dose of glycyrrhetinic acid (mg)	*No. of volunteers*	*Mean rise in systolic blood pressure (mm Hg) after liquorice consumption for:*		*P-value*	
		2 weeks	4 weeks	2 weeks	4 weeks
540	10	14.4	NP	0.003	NP
270	30	5.2	5.4	0.000	0.000
75	24	3.1	1.9	0.03	NS

NP, not performed; NS, not significant.

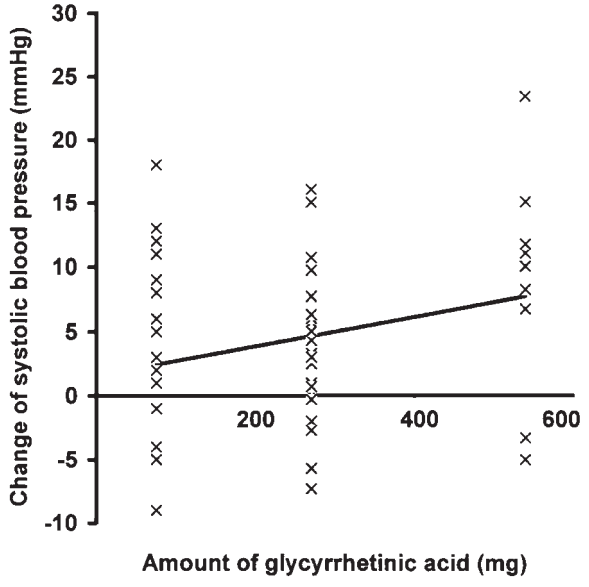

Figure 1 Dose-response relationship.

Dose-response relationship/time-response relationship

The dose-response relationship was clear, using data from 2 weeks of liquorice consumption for systolic blood pressure. Regression analysis revealed a linear relationship between dose and response (Figure 1). The response (rise in blood pressure) after 2 weeks of consumption gave the equation $y = 1.60 + 0.011 \times$ dose, where the regression coefficient is 0.011 with 95% CI (0.0010, 0.021). The regression coefficient is significantly different from 0, $P = 0.03$. The equation for the response after 4 weeks of consumption was; $y = 0.88 + 0.014 \times$ dose. The regression coefficient is 0.014 with 95% CI (–0.0098, 0.037), which is not significantly different from 0, $P = 0.25$. This coefficient did not differ significantly from that of the 2-week equation.

Individual variance

Variance analysis of the results in study 2 measured the systolic blood pressure response after 4 weeks of liquorice consumption. The response followed the normal curve where the probability of an individual's exhibiting the maximum rise of 1 mm Hg in blood pressure after 4 weeks of daily consumption of 270 mg glycyrrhetinic acid was 4%, the probability of a maximum rise of 2 mm Hg was 10%, and the probability of a rise of more than 8 mm Hg was 7%.

Discussion

Until recently it has been generally held that the consumption of liquorice has to be almost heroic to have an effect on the blood pressure.[5,9,10] Our results indicate the contrary.[8] We now know that the effects of eating liquorice depends on the dose but prolongation of the consumption from 2 to 4 weeks does not influence the response. The maximal blood pressure rise is reached after the first 2 weeks. These results are in accordance with previous studies, which reveal that the liquorice-induced hormonal changes can be measured as soon as 1 week after the start of consumption of 100 g of liquorice.[11] It is interesting to note that there is not a great inter-individual variance in the rise of blood pressure, and the rise is rather a question of dose. This is important when liquorice is discussed as cause of secondary hypertension.[12] The linear regression between dose and change in blood pressure was demonstrated 2 weeks after the start of liquorice intake, which possibly could be influenced by hormonal changes during the menstrual cycle. On the other hand, the women in the two higher dose groups started their consumption irrespective of the time in the cycle, which may neutralise this influence. Although the regression coefficient was similar for the dose-response relationship after 2 and 4 weeks, it was not possible to find a significant correlation after 4 weeks. This is possibly explained by the use of a substantially reduced number of observations and lack of results from the study with the highest dose due to the study design.

We would also like to stress that the amount of glycyrrhetinic acid varies between different liquorice products, which makes the total weight of the sweet less important. The linear dose-response relationship should make it easier to compare pro-

ducts as regards the risk of increasing blood pressure, considering the glycyrrhetinic acid content.

It is our clinical impression that liquorice-induced hypertension is underestimated and could be misunderstood. Doctors should consider this diagnosis more often and inform their patients with essential hypertension about the effect of liquorice. We have in this paper focused on the blood pressure rise due to liquorice, but inhibiting 11 β-HSD also results in fluid and sodium retention, and a decreased serum potassium concentration as expected. The inhibition of 11 β-HSD leads to inhibition of the catabolism of cortisol to cortisone making the half-life of the cortisol longer. As cortisol has the same affinity to the aldosterone receptors as aldosterone this gives the cortisol the effect of mineralocorticoid, leading to pseudohyperaldosteronism with fluid and sodium retention as well as serum potassium reduction.[6–11,13]

Liquorice can also lead to a suppressed renin concentration, either secondary to the hypervolaemia or by direct inhibition of the renin production.[7,11,14–16] The diagnosis of liquorice-induced hypertension should thus be suspected if the renin concentration in plasma or plasma-renin activity is suppressed, depending on the method used by the respective laboratory. The diagnosis is then confirmed by measuring the metabolites of cortisol and cortisone in the urine, since the ratio of the metabolites of cortisol/cortisone in the urine rises with liquorice consumption.[9,13] In clinical practice, the easiest way to confirm the diagnosis is to stop the liquorice consumption and follow the patient for several weeks, up to a maximum of 4 months, when the renin suppression should have vanished.

Acknowledgements

We thank Mr O Petursson, the Drift liquorice sweet factory in Iceland and the Malaco sweet factory in Sweden for kindly supplying all liquorice, and to Sverker Jern head of the Clinical Experimental Laboratory, Sahlgrenska University Hospital/Östra for constructive discussion and statistical help. This study was supported by a grant from the Science Fund of the Reykjavik City Hospital and The Göteborg Medical Society. (Competing interests: None declared.)

References

1 Lucas R. *Nature's Medicines (the folklore, romance, and value of herbal remedies)*. Awards books, A916N. 1976: New York (Universal-Award House, c1966), pp 89–94.
2 Blachley JD, Knochel JP. Tobacco chewer's hypokalemia: licorice revisited. *N Engl J Med* 1980; **302**: 784–785.
3 Sigurjonsdottir HA, Ragnarsson J. Hathrystingur af völdum lakkriss. *Laeknabladid/The Icelandic Med J* 1993; **79**: 87–91.
4 Folkerssen L, Knudsen NA-L, Teglbjaerg PS. Licorice. A basis for precautions one more time. *Ugeskr Laeger* 1996; **158**: 7420–7421.
5 van der Zwan A. Hypertension encephalopathy after liquorice ingestion. *Clin Neurol Neurosurg* 1993; **95**: 35–37.
6 de Klerk GJ, Nieuwenhuis MG, Beutler JJ. Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. *BMJ* 1997; **314**: 731–2.
7 Dellow EL, Unwin RJ, Honour JW. Pontefract cakes can be bad for you: refractory hypertension and liquorice excess. *Nephrol Dial Transplant* 1999; **14**: 218–220.
8 Sigurjonsdottir HA *et al*. Is blood pressure commonly raised by moderate consumption of liquorice? *J Hum Hypertens* 1995; **9**: 345–348.
9 van Uum SHM *et al*. The role of 11 beta-hydroxysteroid dehydrogenase in the pathogenesis of hypertension. *Cardiovasc Res* 1998; **38**: 16–24.
10 Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994; **23**: 359–377.
11 Farese Jr RV *et al*. Licorice induced hypermineralcorticoidism. *N Engl J Med* 1991; **325**: 1223–1227.
12 Störmer FC, Reistad R, Alexander J. Glycyrrhizic acid in liquorice – evaluation of health hazard. *Food Chem Toxicol* 1993; **31**: 303–312.
13 Palermo M *et al*. Urinary free cortisone and the assessment of 11 beta-hydroxysteroid dehydrogenase activity in man. *Clin Endocrinol (Oxf)* 1996; **45**: 605–611.
14 Epstein MT *et al*. Liquorice toxicity and the renin-angiotensin-aldosterone axis in man. *BMJ* 1977; **1**: 209–210.
15 Hollifield JW. Clinical significance of plasma renin activity. *J Tenn Med Ass* 1973; **66**: 947–948.
16 Megia A *et al*. Angiotensin I-converting enzyme levels and renin-aldosterone axis recovery after cessation of chronic licorice ingestion. *Nephron* 1993; **65**: 329–330.