Antihypertensive effects of the herbal drugs of Kampo medicine (traditional Japanese medicine): report of a single case who took six different Kampo formulas in turn

Hiroshi Odaguchi,* Akino Wakasugi, Tetsuro Oikawa, Toshihiko Hanawa

Oriental Medicine Research Center, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8642, Japan. (Received August 17, 2011. Accepted December 6, 2011.)

Abstract

Objective: A considerable number of hypertensive patients believe that the herbal drugs of Kampo medicine (traditional Japanese medicine) have antihypertensive effects. However, the antihypertensive effects of these drugs have not yet been substantiated. We report a single case study that evaluated the efficacies of 6 Kampo formulas, which are widely used for hypertension.

Methods: We administered the following 6 different Kampo formulas in the given order to a 43-year-old male with mild hypertension who was not receiving any antihypertensive drugs: hangeękobokuto (HK), oregenedokuto (OG), shichimotsukokato (SK), chotosan (CT), saikokaryukotsubureito (SR), and hachimijigōan (HJ). Each formula was administered exclusively for 4 weeks, and a washout period of 4 weeks was maintained between the administrations of 2 consecutive formulas.

Results: Prior to the commencement of this study, the patient was diagnosed as a candidate for treatment with HJ from the viewpoint of Kampo medicine. Interestingly, our results also showed that HJ exhibited the strongest antihypertensive effect in daytime blood pressure (BP), nighttime BP, and 24-h BP in this patient. The systolic daytime BP, systolic nighttime BP, and diastolic nighttime BP were reduced by more than 10 mmHg after HJ therapy. In contrast, the other formulas did not produce any significant effects, except HK that exhibited a pressor effect.

Discussion and conclusion: Kampo formulas can be candidates for antihypertensive drugs. However, it is suggested that Kampo formulas should be prescribed according to not only the diagnosis of Western medicine, for example, hypertension, but also the diagnosis of Kampo medicine.

Key words  hypertension, Kampo, Sho, hachimijigōan.

Introduction

Kampo medicine was not originally aimed for the treatment of hypertension because the concept of hypertension emerged only in the 20th century. However, it is probable that various complications associated with hypertension have been treated with Kampo medicines that have the ability to lower the high BP. Some animal studies1-3 have documented the antihypertensive effect of Kampo medicines; however, such an effect in humans has not been clarified yet.4)

In this paper, we report a single case study that evaluated the efficacies of 6 Kampo formulas for hypertension. Because diagnosis in Kampo medicine is extremely different from that in Western medicine, Kampo...
formulas should be prescribed according to not only the
diagnosis of Western medicine, for example, hyperten-
sion, but also the diagnosis of Kampo medicine. The
current study aimed to examine the efficacy of Kampo
medicine in hypertension in relation to the diagnosis of
Kampo medicine.

Methods

Subject: For this study, we recruited a 43-year-old male
who was diagnosed with essential hypertension 6 years
ago. He had not taken any antihypertensive drugs and
his office BP was classified as mild hypertension
according to the Guidelines for the Management of
Hypertension (JSH 2009).3) There were no physical
signs indicating a complication of cardiovascular dis-
 ease, renal disease, or other diseases.

A detailed explanation about the protocol of this
study was provided, and a written informed consent was
obtained.

Study design (Figure 1): The protocol of this study was
approved by Ethics committee of Oriental Medicine
Research Center of the Kitasato Institute. This study
was conducted in keeping with “World medical associa-
tion declaration of Helsinki 1989”.

<table>
<thead>
<tr>
<th>HK</th>
<th>washout</th>
<th>OG</th>
<th>washout</th>
<th>SK</th>
<th>washout</th>
<th>CT</th>
<th>washout</th>
<th>SR</th>
<th>washout</th>
<th>HJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Study schedule. HK, hangekobokuto; OG, orendogokuto;
SK, shichimotsukokato; CT, chotosan; SR, saikokaryukotsuboreito;
HJ, hachimijijigogan

The office BP of this subject was measured twice on
different occasions at an interval of more than 2 weeks,
and the values were confirmed to be almost identical.
Subsequently, he was administered the following 6 dif-
erent Kampo formulas in the given order: hangekobokuto
(TJ-16: HK), orendogokuto (TJ-15: OG), shichimotsu-
kokato (TJ-46: SK), chotosan (TJ-47: CT), saikokaryu-
kotsuboreito (TJ-12: SR), and hachimijijigogan (TJ-7: HJ).
The formulas were provided in a spray-dried powder
form (TSUMURA & Co., Tokyo, Japan). The daily
dose of each formula was determined to be 7.5 g. Each
formula was tested for 4 weeks (test period), and a 4-
week washout period was maintained between the
administrations of 2 consecutive formulas. Prior to and
after the completion of each test period, the subject was
evaluated by office BP measurement, 24-h ambulatory
BP monitoring (ABPM), cardio-ankle vascular index
(CAVI) assessment, and blood examination. Prior to the
completion of the entire study, a medical check-up was
conducted according to the conventions of Kampo
medicine.

Data acquisition: BP was measured in accordance with
the recommendation of American Heart Association.6)
The office BP was measured using an automated de-
vice (ES-P110, Terumo, Tokyo, Japan) and the mea-
surement was repeated at intervals of at least 1 minute.
The average of the multiple readings was considered
the office BP. ABPM was conducted using a portable au-
mated sphygmomanometer (TM-2431, A&D, Tokyo,
Japan). BP was measured every 30 minutes from 0 AM
to 6 AM and every 15 minutes during the rest of the
day. The obtained data was analyzed using a software
(TM-2430-15, A&D) specially designed for this sphy-
gmomanometer. The parameters were defined as follows.7)
We defined 24-h BP as the average of all BP readings
throughout 24 h. Nighttime BP was defined as the aver-
age of all BPs recorded from 0 AM to 6 AM, while day-
time BP was the average of all BPs recorded from 8 AM
to 10 PM. Nocturnal BP fall was calculated as the day-
time systolic BP minus the nighttime systolic BP.
Morning BP was defined as the average of the BPs re-
corded during the first 2 h after waking. The lowest BP
was defined as the average of 3 BP readings centered on
the lowest systolic nighttime reading. Morning BP surge
was calculated as the morning systolic BP minus the
lowest systolic BP.

CAVI was obtained using a specific measurement de-
vice (Vasera VS-100, FUKUDA DENSHI, Tokyo,
Japan). CAVI is regarded as an indicator of arterial stiff-
ness, and the theory of its measurement has been de-
scribed previously.8) CAVI of the both sides was
measured independently during cuff deflation, and the
mean values were described as CAVI.

Blood examination was conducted to establish the
safety of each formula. We also assessed the lipid pro-
file and insulin resistance to examine the effect of each
formula on these parameters. As an index of insulin re-
sistance, we calculated homeostasis model assessment
of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting blood glucose (mg/dL) × fasting immuno-reactive insulin (μU/mL)/405. The serum high-sensitive C-reactive protein (HS-CRP) level, which is considered a useful predictor of early atherosclerosis, was also measured.

Results

Overall course: The subject underwent all the examinations and consumed all the drugs as scheduled. During the study period, he did not report any symptoms that suggested the emergence of side effects of Kampo formulas, and his sleeping status during each ABPM was good.

Kampo diagnosis: The medical check-up conducted according to the conventions of Kampo medicine prior to the study revealed the following findings: Excessive sweating, light headedness on standing, cold and burning sensations on his feet, discomfort or tenderness at the hypochondrium, stuck feeling in the pit of the stomach, lack of resistance at the lower abdomen, and palpable linea alba. Based on the theory of Kampo medicine, these findings were most compatible with the “HJ Sho (Kampo diagnosis indicating the clinical state where HJ is most applicable),” and we diagnosed the subject likewise.

BP values: The values of BP and heart rate before the administration of each Kampo formula are presented in Table 1. Baseline differences were marked for the lowest BP, with a maximum difference of more than 20 mmHg, while those for the other BP parameters were within approximately 10 mmHg.

Table 1 Blood pressure and heart rate values before the administration of each Kampo formula. HK, hangekobokuto; OG, orengekokuto; SK, shichimotsukokato; CT, chotosan; SR, saikokaryukotsuboreito; HJ, hachimijiogan; BP, blood pressure; and HR, heart rate.

<table>
<thead>
<tr>
<th></th>
<th>HK</th>
<th>OG</th>
<th>SK</th>
<th>CT</th>
<th>SR</th>
<th>HJ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Office</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>121.0</td>
<td>125.0</td>
<td>130.3</td>
<td>128.0</td>
<td>132.5</td>
<td>130.5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>94.7</td>
<td>99.5</td>
<td>98.7</td>
<td>94.0</td>
<td>96.8</td>
<td>94.0</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>85.0</td>
<td>79.5</td>
<td>65.3</td>
<td>74.5</td>
<td>77.8</td>
<td>77.5</td>
</tr>
<tr>
<td><strong>24-h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>142.6</td>
<td>143.2</td>
<td>144.7</td>
<td>146.1</td>
<td>148.4</td>
<td>150.6</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>98.1</td>
<td>96.9</td>
<td>98.7</td>
<td>100.6</td>
<td>100.6</td>
<td>100.6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>85.9</td>
<td>81.3</td>
<td>80.7</td>
<td>80.1</td>
<td>84.3</td>
<td>88.5</td>
</tr>
<tr>
<td><strong>Daytime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>146.0</td>
<td>149.2</td>
<td>149.7</td>
<td>150.2</td>
<td>152.6</td>
<td>155.1</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>101.3</td>
<td>101.9</td>
<td>103.5</td>
<td>105.1</td>
<td>103.6</td>
<td>102.1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89.6</td>
<td>86.6</td>
<td>85.3</td>
<td>84.0</td>
<td>88.5</td>
<td>93.1</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132.9</td>
<td>127.9</td>
<td>131.5</td>
<td>135.2</td>
<td>136.2</td>
<td>137.2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>88.8</td>
<td>84.0</td>
<td>86.3</td>
<td>88.5</td>
<td>92.2</td>
<td>95.8</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.5</td>
<td>67.7</td>
<td>68.7</td>
<td>69.6</td>
<td>72.2</td>
<td>74.7</td>
</tr>
<tr>
<td><strong>Morning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>144.5</td>
<td>154.1</td>
<td>152.5</td>
<td>150.9</td>
<td>152.9</td>
<td>154.9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>103.0</td>
<td>99.4</td>
<td>100.2</td>
<td>101.0</td>
<td>105.8</td>
<td>110.5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>86.9</td>
<td>91.8</td>
<td>90.0</td>
<td>88.3</td>
<td>91.1</td>
<td>93.9</td>
</tr>
<tr>
<td><strong>Lowest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>116.3</td>
<td>123.0</td>
<td>129.8</td>
<td>136.7</td>
<td>136.5</td>
<td>136.3</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.3</td>
<td>80.7</td>
<td>79.3</td>
<td>78.0</td>
<td>87.8</td>
<td>97.7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>76.3</td>
<td>67.0</td>
<td>66.5</td>
<td>66.0</td>
<td>71.7</td>
<td>77.3</td>
</tr>
</tbody>
</table>
The changes in the office BP due to each formula are shown in Figure 2. HK increased the office BP, both systolic and diastolic, while OG reduced only the diastolic pressure. Other formulas did not show any definite changes.

Regarding the ABPM parameters, HJ produced the most prominent changes (Figure 3); the systolic daytime BP, systolic nighttime BP, and diastolic nighttime BP were reduced by more than 10 mmHg. On the other hand, HK showed a pressor effect on all these BP parameters, for both systolic and diastolic components, although the magnitude of the changes was not large. The other formulas did not produce any significant effects. Table 2 shows the trends in nocturnal BP fall and morning BP surge. These values exhibited a relatively minimal change due to any Kampo formula.
Table 2  Trends in nocturnal BP fall and morning BP surge. HK, hangekokobokuto; OG, orengedokuto; SK, shichimotsukokato; CT, chotosan; SR, saikokaryokotsuboreito; HJ, hachimijiogan; and BP, blood pressure.

<table>
<thead>
<tr>
<th></th>
<th>HK</th>
<th>OG</th>
<th>SK</th>
<th>CT</th>
<th>SR</th>
<th>HJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal BP fall (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-administration</td>
<td>13.1</td>
<td>21.2</td>
<td>18.1</td>
<td>15.1</td>
<td>16.4</td>
<td>17.8</td>
</tr>
<tr>
<td>Post-administration</td>
<td>11.8</td>
<td>27.6</td>
<td>16.2</td>
<td>16.3</td>
<td>21.3</td>
<td>18.5</td>
</tr>
<tr>
<td>Morning BP surge (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-administration</td>
<td>28.2</td>
<td>31.1</td>
<td>22.7</td>
<td>14.2</td>
<td>16.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Post-administration</td>
<td>24.2</td>
<td>34.3</td>
<td>18.5</td>
<td>10.3</td>
<td>14.8</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Table 3  Changes in the values of CAVI, parameters of lipid profile, HOMA-IR, and HS-CRP. HK, hangekokobokuto; OG, orengedokuto; SK, shichimotsukokato; CT, chotosan; SR, saikokaryokotsuboreito; HJ, hachimijiogan; CAVI, cardio-ankle vascular index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; and HS-CRP, high-sensitive C-reactive protein.

<table>
<thead>
<tr>
<th></th>
<th>HK</th>
<th>OG</th>
<th>SK</th>
<th>CT</th>
<th>SR</th>
<th>HJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>6.28</td>
<td>6.39</td>
<td>6.84</td>
<td>7.19</td>
<td>6.40</td>
<td>6.60</td>
</tr>
<tr>
<td>post-administration</td>
<td>6.32</td>
<td>6.07</td>
<td>6.69</td>
<td>6.45</td>
<td>6.56</td>
<td>6.49</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>179</td>
<td>170</td>
<td>171</td>
<td>176</td>
<td>191</td>
<td>168</td>
</tr>
<tr>
<td>post-administration</td>
<td>162</td>
<td>165</td>
<td>181</td>
<td>176</td>
<td>179</td>
<td>189</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>60</td>
<td>58</td>
<td>60</td>
<td>57</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>post-administration</td>
<td>58</td>
<td>52</td>
<td>59</td>
<td>55</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>79</td>
<td>90</td>
<td>133</td>
<td>77</td>
<td>95</td>
<td>106</td>
</tr>
<tr>
<td>post-administration</td>
<td>96</td>
<td>71</td>
<td>82</td>
<td>69</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>1.69</td>
<td>0.61</td>
<td>0.76</td>
<td>0.63</td>
<td>1.30</td>
<td>1.28</td>
</tr>
<tr>
<td>post-administration</td>
<td>0.92</td>
<td>0.48</td>
<td>1.23</td>
<td>0.70</td>
<td>0.54</td>
<td>1.01</td>
</tr>
<tr>
<td>HS-CRP (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-administration</td>
<td>172</td>
<td>257</td>
<td>251</td>
<td>280</td>
<td>240</td>
<td>159</td>
</tr>
<tr>
<td>post-administration</td>
<td>164</td>
<td>409</td>
<td>283</td>
<td>311</td>
<td>218</td>
<td>171</td>
</tr>
</tbody>
</table>

Other measurement items: Table 3 presents the changes in the values of CAVI, parameters of lipid profile, HOMA-IR, and HS-CRP. All the parameters were almost within normal limits and did not exhibit any change. The data obtained from the blood examination did not suggest the emergence of any side effects of the Kampo formulas.

Discussion

Baseline status before the administration of each formula: In order to examine whether the 4-week washout period between 2 consecutive formulas was adequate, we compared the baseline status before administering each Kampo formula.

Our data showed that baseline differences in all BP parameters, except the lowest BP, were within approximately 10 mmHg. These results were almost consistent with those of this previous study.11) We considered that carry-over effect of each Kampo formula did not significantly influence the baseline status before its administration and that the 4-week washout period was sufficient.

Efficacy of the Kampo formulas with regard to BP:
HK raised the systolic office BP by more than 15 mmHg, while OG decreased the diastolic office BP by almost 10 mmHg. These changes appeared to have some positive implication. However, considering that office BP has limited reproducibility because of the white-coat effect and the placebo effect, we believe that the changes should be evaluated not exclusively but along with the results of ABPM or home BP.

Concerning ABPM, HJ produced the most prominent changes. Regardless of whether it was day or night, it reduced the systolic and diastolic BPs. Its BP-lowering effect did not seem to be far behind from that of angiotensin-receptor blocker or calcium antagonists, which were reported to cause 15–17 mmHg reduction in systolic pressure and 8–10 mmHg reduction in diastolic pressure during a mean follow-up period of 4.2 years. In contrast, HK exhibited a pressor action during day and night in this subject, although the range of variation was not large. Considering the fact that HK exhibited a pressor action also on the office BP, there exists a possibility that HK had an adverse effect on this subject.

Recently, some studies have suggested that morning BP surge or nocturnal BP fall have a close relationship with the risk of cardiovascular diseases. In this study, no Kampo formula caused a significant change in these values. These results may be attributable to the fact that the baseline values of the patient prior to the administration of each Kampo formula were almost within normal limits.

Efficacy of the Kampo formulas with regard to other measurement items and the safety of Kampo medicines: On similar lines, the normal baseline values of CAVI, parameters of lipid profile, HOMA-IR, and HS-CRP might have resulted in nonsignificant changes in these values even after the consumption of any Kampo formula. Our results could not speculate the relationship between these parameters and the effects of Kampo drugs.

Other laboratory data also did not show any changes, and the subject did not report any symptoms that could be attributed to each formula. We consider that no formula exhibited a side effect, except HK that had a pressor effect.

Consideration from the viewpoint of Kampo medicine: Prior to the commencement of this study, the subject was diagnosed as “HJ Sho,” and the results of our study showed that only HJ produced significant antihypertensive effects. In contrast, the other formulas were not only ineffective but also sometimes harmful like HK. These results appear to be thoroughly reasonable from the viewpoint of Kampo medicine and suggest the close relationship between the antihypertensive effects of Kampo drugs and the “Sho” of an individual.

Study design for Kampo medicine: Because Kampo medicine has been developed mainly by accumulating numerous experiences and expert opinions, randomized controlled trials (RCTs) of Kampo medicine are certainly required. We believe that the other traditional medicines share the same problem.

However, there exists a large obstacle for conducting RCTs of Kampo medicine. The approach for diagnosis in Kampo medicine is different from that in Western medicine, which usually assigns each condition a specific disease name; the diagnosis in the former is based on the “Sho” of the patient. Hence, it is assumed that participants for RCTs of Kampo medicine should be recruited not according to the disease diagnosis by Western medicine, for example, hypertension, but according to “Sho.” We consider that the results of this study which suggested only a specific Kampo formula (HJ) was effective in the patient with the corresponding “Sho” validated the above-mentioned assumption.

Currently, our greatest challenge is to formulate an adequate trial design to prove the efficacy of Kampo medicine. Responder-limited design wherein an RCT is conducted only with the subjects who respond to a specific Kampo formula is an example which may resolve the problem of RCT design from the viewpoint of Kampo medicine.

Limitations of this study: In order to fulfill the purpose to clarify the relationship between the antihypertensive effects of Kampo drugs and the “Sho” of an individual, we should have ideally conducted this study with multiple subjects and performed appropriate statistical analysis. However, considering the burden of the subject in this study, we could not conduct it on multiple subjects. Instead, we tested relatively large number, six, of drugs on a single subject. In any case, we could not draw a
definite conclusion from the results of this study wherein only one subject was tested.

As previously mentioned, some baseline differences existed in BP parameters. This problem is common in crossover trial design that may be affected by a carry-over effect. We do not have data about the carry-over effect of any Kampo formulas. However, because the differences appeared compatible with physiological and weather-related changes in BP profile, we believe that the existence of a carry-over effect can be ignored.

Conclusion

The results of our study suggested Kampo formulas can be candidates for antihypertensive drugs having a close relationship with the “Sho” of an individual.

References


12) Trazzi, S., Mutti, E., Frattola, A., Imholz, B., Parati, G., and Mancia, G.: Reproducibility of non-invasive and


