Yozinkodakuto, a traditional Chinese (Japanese Kampō) medicine, improves the creatinine level in chronic renal failure

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Chinese herbal medicine has historically been used for the treatment of renal disease. The clinical efficacy of Yozinkodakuto and its additional prescription was investigated in 28 patients (19 males and 9 females) with chronic renal failure (CRF). The underlying diseases for CRF were 14 cases of chronic glomerulonephritis, 8 cases of diabetic nephropathy, 2 cases of nephrosclerosis, 1 case of polycystic kidney, 1 case of gouty kidney, and 2 cases of unknown origin. Serum creatinine (Cr) concentrations were improved significantly with Yozinkodakuto at 6 months independent of the underlying disease. There were no remarkable changes in the levels of serum phosphorus, karium and uric acid between before and after treatment. Adverse effects were itching in 5 cases and stomatitis in 2 cases, but no major side effects were seen. This study suggests that Yozinkodakuto is a useful agent in the treatment of CRF.

Key words chronic renal failure, Chinese herbal medicine, Yozinkodakuto.

Introduction

In Asian countries numerous kinds of plants have been used as food, sources for food additives, spices and traditional herbal medicines. Some examples of drugs developed from traditional herbal medicines are ephedrine from Ephedra sinica, morphine from Papaver somniferum, quinine from Cinchona, and cocaine from Erythroxylon coca, among others.

Chinese herbal medicine has been used over the centuries for the treatment of renal disease. However, experimental studies of Kampō medicine for chronic renal failure (CRF) have just started in these past twenty years. Rhubarb and rhubarb containing Ompito (Wen-Pi-Tang in Chinese) can delay the progression of CRF, but can not reduce the level of creatinine (Cr). Western medicines such as carbon absorbant (AST-120) or angiotensin-converting enzyme inhibitors (ACEIs) improves the 1/Cr-time slope, but it can not decrease the Cr level as well. Under the present situation, there is still no complete cure for CRF.

The clinical efficacy of Yozinkodakuto and its additional prescription was investigated in 28 patients with CRF. The serum Cr level was improved significantly from 3.9 ± 1.6 (S.D.) to 3.5 ± 1.9 (S.D.) at 6 months later. No major side effects were seen. There is every possibility that Chinese medicine can become the first treatment of choice for CRF.

Patients and Methods

Patients. We investigated CRF patients treated for at least six months with Yozinkodakuto and its additional prescription during the period of August 2003 to December 2005. There were 19 men and 9 women with an average age of 60.3 ± 11.8 (S.D.) years (range 41 - 81). The cause of CRF was chronic glomerulonephritis in 14, diabetic nephropathy in 8, nephrosclerosis in 2, polycystic kidney in 1, gouty kidney in 1, and unknown origin in 2 patients. Twenty-six cases had been using a hypotensive drug and 10 cases were on ATS-120. The mean value of serum Cr was 3.9 (range 1.5 - 6.7), and its value at six months later was used to assess the efficacy of Yozinkodakuto. Cases for whom steroid drugs and immunosuppressive agents, etc., had been newly used within three months before starting the Kampō medication were excluded from this study. Administration of Yozinkodakuto was terminated at the indication of dialysis therapy. The one-way repeated-measured ANOVA was used to evaluate the significance of differences between before and after treatment. A P value of 0.05 or less was considered as statistically significant. The judgment of side effects was performed at every examination.

Preparation of Yozinkodakuto. Hot water-extract of Yozinkodakuto was prepared from a mixture of five dried traditional herbal medicines - Astragalus membranaceus Bge (Radix, 30g, Neimenggu), Paeonia lactiflora Pall (Radix, 15g, Anhui province), Smilax glabra Roxb (Radix, 30g, Hunan province), Houttuynia cordata Thunb (whole herb, 10g, Sichuan province), and Dioscorea sativa L. (Radix, 10g, Guangdong province) - according to standard methods with minor modification as reported previously.3–5 Briefly, the mixture of dried traditional herbal medicines was mixed in 600 ml of water and boiled down to 300 ml. The aqueous extract was filtered with a sieve and the resulting decoction was administered 3 times a day before meals.

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Results

Twenty-five out of 28 patients received Yozinkodakuto or its additional prescription treatment for 6 months. As shown in Fig. 1(a), serum Cr improved significantly at 6 months after treatment with Yozinkodakuto. However, Yozinkodakuto did not reduce BUN. Fig. 1(b) shows values of Cr of individual patients determined before, during, and at the completion of 6-month Yozinkodakuto therapy. Passage was excellent except for one case. There were no remarkable changes in the levels of serum karium (K), phosphorus (P), and uric acid (UA) between before and after treatment (Table 1). Yozinkodakuto also did not reduce the amount of urinary protein (data not shown).

Table 2 shows the result of Yozinkodakuto treatment with different underlying disease. Yozinkodakuto was effective independent of the underlying disease. Three cases interrupted treatment at 126, 129 and 142 days because of itching, but this unfavorable symptom was resolved within a few weeks by cessation. While they were taking Yozinkodakuto, Cr was improved successfully. But after interruption of the Yozinkodakuto treatment, one case needed dialysis and the other two showed worsening Cr levels. Two cases showed stomatitis at 196 and 223 days, but with the use of an ointment they were able to continue the treatment.

Table 1 Change of Cr, BUN, K, P, and UA between pre- and post-treatment

<table>
<thead>
<tr>
<th></th>
<th>pre-treatment</th>
<th>post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td>BUN</td>
<td>42.7</td>
<td>47.3</td>
</tr>
<tr>
<td>K</td>
<td>5.0</td>
<td>4.7</td>
</tr>
<tr>
<td>P</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>UA</td>
<td>7.5</td>
<td>7.0</td>
</tr>
</tbody>
</table>

There were no remarkable changes in the levels of serum BUN, K, P, and UA before and after treatment with Yozinkodakuto.

Table 2 Changes in Cr concentration by Yozinkodakuto treatment of the different underlying disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>before</th>
<th>6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic glomerulonephritis (n=13)</td>
<td>3.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Diabetic nephropathy (n=6)</td>
<td>4.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Nephrosclerosis (n=2)</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Polycystic kidney (n=1)</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Gouty kidney (n=1)</td>
<td>4.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Unknown origin (n=2)</td>
<td>3.3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Yozinkodakuto was effective independent of basal disease. Three cases interrupted treatment because of itching. The number of patients in each group is indicated in parentheses.

Discussion

In recent years, growing numbers of patients have progressed to end-stage renal disease and the medical costs of dialysis have been increasing. Preventing the aggravation of CRF has become a most important problem for nephrologists. There are some medicines such as Rhubarb, Ompito and AST-120 that delay the need for dialysis. ACEIs and angiotensin II receptor antagonist have been reported to retard the progression in patients with early CRF and albuminuria. However, they only attenuate the 1/Cr-time slope but can not reduce the Cr level.

Kampo formulae have been used for medical purposes for centuries. Its prescription is not a single, but a mixture of several herbs. In the present study, Yozinkodakuto significantly improved serum Cr concentrations (p<0.01) at 6 months. However, improvement of Cr stopped in three months. An obvious problem of this study is that it was not a double-blind placebo controlled trial. Kampo formulae are decoctions made from several herbs, and the color, smell and taste vary with each formula. Therefore, it is difficult to produce a placebo to resemble a certain Kampo formula. Until today there have been few clinical studies on the efficacy of Kampo medicines in comparison with a placebo.
In Japan, documentations of the pharmacological effects of herbs started in the third decade of the 19th century. Astragali Radix has a diuretic effect, antihypertensive effect, proteinuria-decreasing effect and renal function-improving effect.\(^7\)\(^8\) Paeoniae Radix is known not only Asia but also in Europe as a blood-flow improvement agent.\(^9\) It is believed that Houttuynia Herb, Smilax Rhizoma and Dioscoreae Colletti Rhizoma possess an anti-inflammatory effect and a diuretic effect,\(^10\) although detailed studies have not been performed. In recent years, investigations of herbs have begun to flourish, but they are still insufficient.

The quantity of Yozinkodakuto we used in this study was equivalent to 3-5 times the usual dosage in Japan, but it is the usual dosage in China. As a result of deteriorating renal function, we administered the larger quantity comparable to the dosage used in China. Three cases interrupted treatment because of itching and two cases showed stomatitis. But no major side effects were incurred.

Yozinkodakuto appears to be effective regardless of the basal disease at any time from the early stage of renal insufficiency to the end-stage of renal failure.\(^1\)\(^1\) Even though patients with dialysis Yozinkodakuto reduce Cr level.\(^2\) Yozinkodakuto improved the Cr level but could not change BUN. The diuretic action of Yozinkodakuto might be one of the reasons for this, but we cannot explain all of it. In any case, it is certain that Yozinkodakuto is effective for CFR because modified creatinine clearance (Cockcroft-Gault's method) was statistically improved (p<0.01) at 6 months, and those who interrupted Yozinkodakuto treatment had rapid deterioration of renal function. This strongly suggests that this Chinese medicine may become a first-choice therapeutic option for CFR.

References


Japanese abstract

漢方薬は2000年以降から腎疾患に用いられてきた。しかし、生化学的、病理学的な検討は始まったばかりである。大変あるいは大黄含有剤である温脾湯の報告はあるが、これらは腎不全の進行を抑えるだけで、腎機能を改善するわけではない。一方、西洋医学的にはクレアチニンや低蛋白食療法などが行われているが、これらクレアチニンを低下するまでには至っていない。

今回我々は、血清クレアチニンが1.5mg/dl以上の患者28例に養腎降濁湯を投与したところ、6ヶ月後のクレアチニン値の平均は3.9mg/dlから3.5mg/dlに有意に改善した。養腎降濁湯は、腎不全の基礎疾患に関わらず有効であった。また、重篤な副作用も認めなかった。養腎降濁湯は腎不全の第一選択薬となりうる。

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