Ompi-to prevents the progression of renal failure

Takako YOKOZAWA,* Xiao Qi WU and Hikokichi OURA

Department of Applied Biochemistry, Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University

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Abstract

The effects of Ompi-to were examined in rats with irreversible uremia induced by administration of a 0.75% adenine diet for 40 days and then an 18% casein diet (ordinary diet) for another 40 days. In rats given Ompi-to at a dose of 30 mg/rat/day (for 35 days at maximum), the levels of blood urea nitrogen and serum creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphorus were decreased significantly, whereas calcium was increased significantly, reflecting prevention of the progression of renal failure.

Key words Ompi-to (Onpi-tô), uremia, renal failure, rat.
Abbreviation Ompi-to (Wen-Pi-Tang), 湯脾湯.

Introduction

We have previously reported the metabolism-improving effect and complex effect of Ompi-to in rats with renal failure, and have demonstrated its effectiveness through various experiments.[1-9] However, in these experiments, suppression of the progression of uremic symptoms was mainly examined in animals given adenine and Ompi-to at the same time. In the present study, in order to prepare continuous chronic renal failure, rats were fed with an ordinary diet after a long period of adenine-diet feeding, and the effects of Ompi-to administration were then investigated in these animals.

Materials and Methods

Animals and treatment : Male rats of the LWH : Wistar strain with a body weight of about 200 g were kept in an animal room at an ambient temperature of 22±1℃ under a 12-hr dark : 12-hr light cycle. They were fed *ad libitum* on an 18% casein diet containing 0.75% adenine, which produced experimental renal failure in the animals.[10-16] After adenine-diet feeding for 40 days, animals were then fed an 18% casein diet (ordinary diet). During the period of ordinary-diet feeding, Ompi-to extract was given orally for 35 days as drinking water, while control rats received tap-water. At intervals of 5 days, blood urea nitrogen (BUN) was determined. On the 35th day of the Ompi-to administration period, the rats were stunned by a sharp blow on the head. Blood was collected into a conical centrifuge tube and the serum was separated by centrifugation immediately in order to determine the levels of creatinine, methylguanidine, guanidinosuccinic acid, inorganic phosphorus and calcium. Throughout the experimental period, there were no statistically significant differences between the control and Ompi-to-treated rats with regard to changes in body weight. The food intake of each rat was essentially proportional to weight change. No case of diarrheal symptom was found. Five rats were used for each experimental group. Values were expressed as means ± S.E.

Ompi-to : The Ompi-to preparation was the same as that described previously.[1] The composition of Ompi-to used in this experiment was as

*〒930-01 富山市杉谷2630
富山医科薬科大学和漢薬研究所臨床利用部門 横澤隆子
Sugitani, Toyama 930-01, Japan

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follows : 15 g of Rhei Rhizoma (*Rheum officinale* BAILLON), 3 g of Ginseng Radix (*Panax ginseng* C. A. MEYER), 5 g of Glycyrrhizae Radix (*Glycyrrhiza glabra* LINN. var. *glandulifera* REGEL et HERDER), 3 g of Zingiberis Rhizoma (*Zingiber officinale* ROSCOE) and 9 g of Aconiti Tuber (*Aconitum japonicum* THUNBERG). Ginseng Radix was a product of Korea, Aconiti Tuber was from Japan, and the other ingredients were from China.

Analyses : Levels of BUN, inorganic phosphorus and calcium were determined using commercial reagents (BUN KAINOS obtained from Kainos Laboratories, Inc., Tokyo, Japan ; Phosphor B-Test Wako from Wako Pure Chemical Industries, Ltd., Osaka, Japan ; Calcium C-Test Wako from Wako Pure Chemical Industries, Ltd.). For determination of creatinine, methylguanidine and guanidinosuccinic acid, the serum was deproteinized by addition of trichloroacetic acid (final concentration, 10%). The supernatant obtained by centrifugation at 3000 rpm for 10 min was injected into a Japan Spectroscopic liquid chromatograph using a step-gradient system. A fluorescence spectrometer (excitation 365 nm, emission 495 nm ; model FP-210, Japan Spectroscopic Co., Tokyo, Japan) was used for detection of the substances on the column.

Statistics : The significance of differences between the control and Ompi-to extract-treated groups was tested using Student's t test.

Results

In rats given the 0.75% adenine diet for 10, 20, 30 and 40 days, the BUN levels were 51 ± 3, 80 ± 8, 136 ± 12 and 200 ± 22 mg/dl, respectively, showing an increase with prolonged adenine administration, as shown in Fig. 1. There were no deaths among rats given the diet for up to 30 days, whereas about 20% of the rats given the adenine diet for 40 days died. Then, changes in the BUN level were observed in rats fed with an ordinary 18% casein diet after 10–40 days of adenine administration. It was found that the BUN level decreased until 30 days of casein-diet feeding following 10–30 days of adenine administration, and became stable thereafter. On the other hand, in rats given the ordinary diet after 40 days of adenine administration, the level decreased markedly to 101 ± 6 mg/dl at 10 days of casein-diet

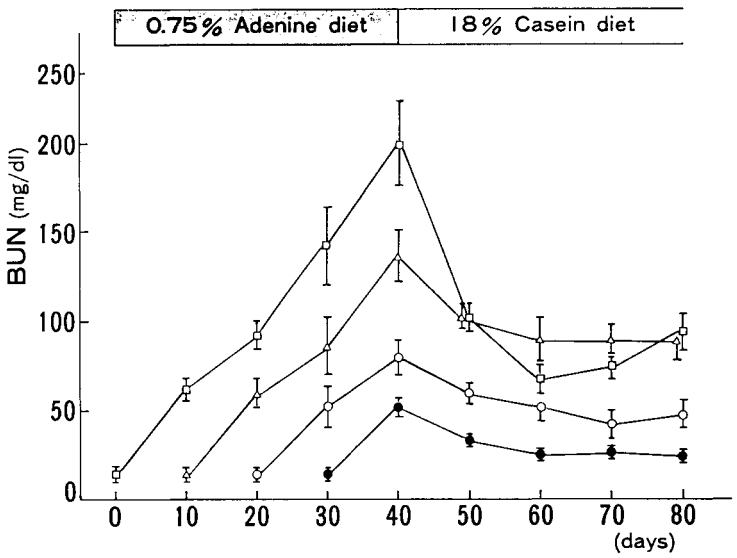

Fig. 1 Changes in the level of blood urea nitrogen over a 40-days period of 18% casein-diet (ordinary diet) feeding following 10, 20, 30 or 40 days of adenine administration.

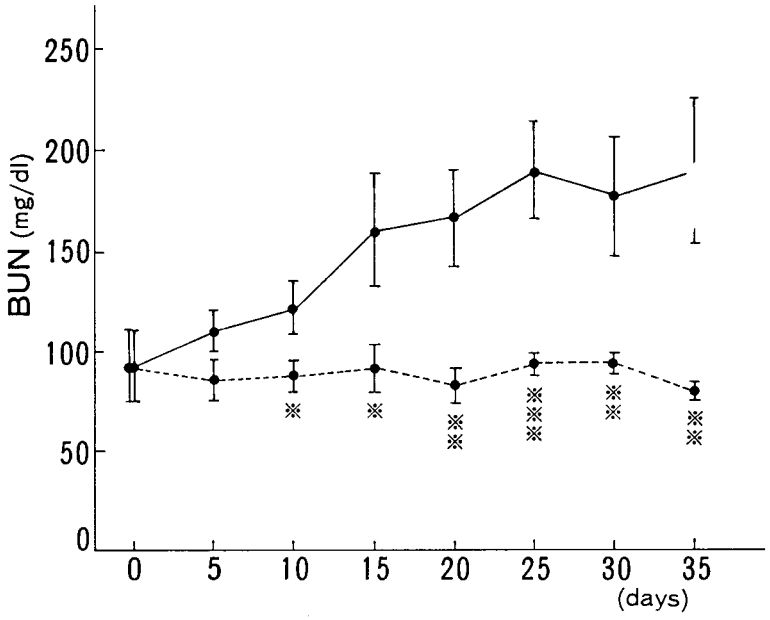

Fig. 2 Effect of Ompi-to on blood urea nitrogen during period of ordinary-diet feeding. ●——●, Control group ; ●·····●, Ompi-to-treated group. * Significantly different from the control value. $p<0.05$, $**p<0.01$, $***p<0.001$.

Table I Serum Constituents in rats given Ompi-to for 35 days.

Group	Cr (mg/dl)	MG (μg/dl)	GSA (μg/dl)	P (mg/dl)	Ca (mg/dl)
Normal rat	0.43±0.04	N.D.	N.D.	8.15±0.09	10.95±0.15
Renal failure rat					
Control	4.54±0.12[a]	18.20±2.60	607±170	15.63±1.75[a]	5.91±0.36[a]
Ompi-to	3.19±0.16[a,**]	4.16±0.59**	104±5*	8.47±0.81**	9.44±0.35[a,**]

Cr=creatinine ; MG=methylguanidine ; GSA=guanidinosuccinic acid ; P=inorganic phosphorus ; Ca=calcium. Statistical significance : a $p<0.001$ *vs.* normal rat, * $p<0.01$, ** $p<0.001$ *vs.* renal failure control rat. N.D., not detectable.

feeding and 69±5 mg/dl at 20 days. Although the level at 30 days (74±5 mg/dl) was similar to that obtaind at 20 days, the BUN level was increased at 40 days, indicating the progression of deterioration in renal function. The effects of Ompi-to were examined in these rats with induced renal failure. The rats were divided into two groups in terms of the BUN level at 40 days of ordinary-diet feeding, and Ompi-to was administered to one group at a dose of 30 mg/rat/day (equivalent to 150 mg/kg body weight/day).

As shown in Fig. 2, the BUN level in control rats increased gradually to reach 160±29 mg/dl at 15 days, 189±25 mg/dl at 25 days, and 191±36 mg/dl at 35 days, reflecting chronic progressive uremia. In contrast, in rats given Ompi-to at a dose of 30 mg/rat/day, the level was 92±11 mg/dl at 15 days, 94±5 mg/dl at 25 days, and 80±2 mg/dl at 35 days, showing evident suppression of the increase in BUN.

The serum levels of creatinine, methylguanidine, guanidinosuccinic acid and inorganic phosphorus in rats given Ompi-to for 35 days were decreased significantly by 30%, 77%, 83% and 46%, respectively, whereas the calcium level was increased significantly by 60%, showing marked improvement of renal failure parameters in blood (Table I).

Discussion

In China, Ompi-to has been used routinely for patients with moderate chronic renal failure. In previous studies aimed at elucidating the effects of this drug scientifically, the authors administered adenine and Ompi-to to animals at the same time, and found that the rats given Ompi-to showed decreases of BUN and serum creatinine, markedly reduced accumulation of methylguanidine and guanidinosuccinic acid and improvement of hypoalbuminemia and hyperphosphatemia. Also, the pattern of variation in blood hormones was partially improved (decrease in calcitonin, increase in testosterone, improved renin-angiotensin-aldosterone system parameters, increase triiodothyronine and thyroxine), and blood pressure was decreased.[1,3-6] Thus, Ompi-to prevented the progression of renal failure. However, the value of this drug as a medicament for renal failure remained unclear, because its actions after the induction of renal failure were not fully considered. Therefore, in the present study, the effects of Ompi-to were examined in rats with progressive chronic renal failure prepared in such a way as to simulate the drug's clinical application. The results showed that parameters of renal failure in blood were partially improved in rats given Ompi-to. Ompi-to clearly prevented renal failure from becoming chronic and advanced, suggesting its usefulness as a therapeutic drug. Ompi-to is a prescription composed of Rhei Rhizoma as the main ingredient, together with Ginseng Radix, Glycyrrhizae Radix, Zingiberis Rhizoma and Aconiti Tuber. Of these components, Rhei Rhizoma markedly decreased or eliminated BUN, creatinine, methylguanidine and guanidinosuccinic acid in rats given adenine ; hyperphosphatemia and hypocalcemia were also improved, suggesting an overall improvement of parameters of renal failure.[17] A significant decrease in blood methylguanidine level was noted in rats given Ginseng Radix.[18] However, unlike the former two crude drugs, there were no particular variations in the uremic toxins after Glycyrrhizae Radix, Zingiberis Rhizoma or Aconiti Tuber administration (unpublished data). The uremia-improving action of Ompi-to is thus probably based on the action of crude drugs such as Rhei Rhizoma and Ginseng Radix. On the other hand, although rats with renal failure were given Ompi-to extract in drinking water *ad libitum*, they showed hardly any difference in water and food consumption in comparison with the control rats, and there were no side effects such as diarrhea and weight loss. These results suggest a wide range of applications for Ompi-to therapy, unlike the usual forms of therapy including a strict low-protein diet, essential amino acid therapy, and administration of activated charcoal or lactulose.[19-21] However, since the range of metabolic regulation decreases in parallel with the progression of renal failure, the dose and the dosing interval should be altered according to the level of renal function. In this regard, Ompi-to therapy requires further investigation.

和文抄録

臨床応用へのモデル実験を志向して進行性の慢性腎不全ラットを作製し，温脾湯の効果を検討した。温脾湯 30 mg/rat/day（最長35日間）投与群では血清尿素窒素，クレアチニン，メチルグアニジン，グアニジノコハク酸，無機リンが有意に低下し，逆にカルシウムは有意に上昇し，腎不全の進行を抑制する作用が認められた。

References

1) Oura, H., Zheng, P.D. and Yokozawa, T. : Effect of Onpi-tô in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **1**, 209-217, 1984.
2) Oura, H., Chung, H.Y. and Yokozawa, T. : Effect of each component crude drug of the traditional Chinese prescription "Onpi-tô" on rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **2**, 351-356, 1985.
3) Oura, H., Chung, H.Y., Zheng, P.D., Yokozawa, T., Wakaki, K. and Koizumi, F. : Effect of Onpi-tô administered orally for a long term on rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **2**, 365-371, 1985.
4) Zheng, P.D., Yokozawa, T., Oura, H. and Nakada, T. : Effect of orally administered Onpi-tô to rats with

chronic renal failure on blood flow in renal tissue, blood pressure, and hormone levels in blood. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 37-44, 1986.

5) Zheng, P.D., Yokozawa, T. and Oura, H. : Effect of Onpi-tô on extrarenal hormones in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 65-70, 1986.

6) Zheng, P.D., Yokozawa, T. and Oura, H. : Effect of Onpi-tô in adenine-induced chronic renal failure rats. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 83-88, 1986.

7) Yokozawa, T., Zheng, P.D., Mo, Z.L. and Oura, H. : The effect of Onpi-tô on urinary excretion of methylguanidine in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 198-201, 1986.

8) Yokozawa, T., Wu, X.Q., Lee, T.W. and Oura, H. : Onpi-tô administration increases renal function in rats with renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **5**, 179-183, 1988.

9) Yokozawa, T., Wu, X.Q., Fujioka, K. and Oura, H. : Effects of crude drug extract of Ompi-to on renal function in rats with renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **6**, 64-69, 1989.

10) Yokozawa, T., Zheng, P.D., Oura, H. and Koizumi, F. : Animal model of adenine-induced chronic renal failure in rats. *Nephron* **44**, 230-234, 1986.

11) Yokozawa, T., Chung, H.Y. and Oura, H. : Urinary constituents and renal function in rats administered with adenine. *Jap. J. Nephrol.* **29**, 1129-1135, 1987.

12) Yokozawa, T. and Oura, H. : Distribution of guanidino compounds in rats with chronic renal failure induced by adenine. *Jap. J. Nephrol.* **29**, 1137-1143, 1987.

13) Yokozawa, T., Oura, H. and Nakada, T. : Blood flow in renal tissue, blood pressure, and blood hormone levels in rats with adenine-induced renal failure. *Jap. J. Nephrol.* **29**, 1145-1151, 1987.

14) Koeda, T., Wakaki, K., Koizumi, F., Yokozawa, T. and Oura, H. : Early change of the proximal tubules in adenine-ingesting rat kidneys with reference to biochemical and electron microscopic studies. *Jap. J. Nephrol.* **30**, 239-246, 1988.

15) Yokozawa, T., Mo, Z.L. and Oura, H. : Comparison of toxic effects of methylguanidine, guanidinosuccinic acid and creatinine in rats with adenine-induced chronic renal failure. *Nephron* **51**, 388-392, 1989.

16) Yokozawa, T., Fujitsuka, N. and Oura, H. : Variations in the distribution of methylguanidine with the progression of renal failure after methylguanidine loading. *Nephron* **52**, 347-351, 1989.

17) Yokozawa, T., Suzuki, N., Zheng, P.D., Oura, H. and Nishioka, I. : Effect of orally administered rhubarb extract in rats with chronic renal failure. *Chem. Pharm. Bull.* **32**, 4506-4513, 1984.

18) Yokozawa, T., Zheng, P.D., Chung, H.Y., Fukumoto, J. and Oura, H. : Effect of red ginseng powder in rats with chronic renal failure. *J. Med. Pharm. Soc. WAKAN-YAKU* **3**, 136-142, 1986.

19) Mitch, W.E. and Walser, M. : Nutritional therapy of the uremic patient. In "The Kidney"(Eds. by B.M. Brenner and F.C. Rector), W.B. Saunders Company, Philadelphia, pp. 1759-1790, 1986.

20) Kumano, K., Takara, S., Izumi, H., Shimizu, T., Sakai, T., Kuwao, S., Ise, M. and Takahashi, H. : The modifications of dietary protein and administration of oral adsorbent AST-120 in chronic renal failure rats. *Jap. J. Nephrol.* **29**, 185-194, 1987.

21) Miyazaki, M., Aoyagi, K. and Tojo, S. : Lactulose therapy for chronic renal failure. *Jap. J. Nephrol.* **26**, 1091-1098, 1984.