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Rhubarb therapy for chronic renal failure

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Abstract

Daiô-kanzô-tô (Da-Huang-Gan-Cao-Tang) was administered to 18 patients with chronic renal failure to evaluate whether or not Daiô-kanzô-tô has a clinically demonstrable effect in decreasing BUN and improving renal function in patients with chronic renal failure. In all patients, administration of Daiô-kanzô-tô for 8 weeks resulted in no significant decrease in BUN levels. However, discontinuation of Daiô-kanzô-tô caused a significant increase in BUN and Cr levels, and re-administration of the drug caused a significant decrease in BUN levels. In order to further evalute the relationship between Daiô-kanzô-tô, BUN, Cr and renal function, the data was re-evaluated after classifying the patients into two groups. Patients with a significant decrease in BUN levels were placed in the "good-response" group, and the others in a "poor-response" group. Renal function was better in the good response group. Mean age tended to be higher in the good response group than in the poor response group. In comparison with the suspended administration period, a significant increase in the total serum protein and albumin levels was found with a resumption of drug therapy. These results suggest that Daiô-kanzô-tô administration in the treatment of chronic renal failure may partially alleviate diet limitations and be useful as a conservative therapy to maintain a better nutritional status for long periods.

Key words Daiô-kanzô-tô, rhubarb therapy, chronic renal failure
Abbreviation Daiô-kanzô-tô (Da-Huang-Gan-Cao-Tang), 大黄甘草湯

Introduction

In the treatment of chronic renal failure,[1] few pharmacotherapies are available and low-protein and high-calorie diet, so-called renal failure diet,[2] is mainly employed as conservative therapy except for hemodialysis and renal transplantation for terminal stage patients. The diet therapy is effective only when it is performed for a long period under strict control, and thus it is fairly difficult to successfully perform this therapy. A similar situation is seen for administration of essential amino acids[3] and/or keto acids,[4] which is performed for some patients as drug therapy ; only a temporary effect is achieved due to difficulty of long-term ingestion.

Moreover, recently, an increase in the mean age of patients is a minor problem. Due to various limitations, even diet therapy—which is almost the only available therapy in clinics—cannot be performed correctly. Also, when hemodialysis is planned, there are problems such as social adaptation. Therefore, we must strive to maintain residual renal function of a patient as long as possible. If drugs which can improve renal failure over a long period are available, we can expect to perform more active therapy than the conventional passive therapy.

Recently, attention is being paid to oriental drugs[5] as a means which may achieve the above-described purpose. Especially, regarding rhu-

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barb, there are reports[6-8] which state that rhubarb may have a BUN-decreasing activity and renal failure-improving activity. Thus, the effect of this oriental drug has high clinical expectations.

We recently administered drugs consisting of mainly rhubarb to patients with chronic renal failure studied whether or not rhubarb has the clinically reported BUN-decreasing activity and the effect to improve renal failure.

Subjects and Methods

The subjects of this study were 18 patients with chronic renal failure. They consisted of 8 males and 10 females, and their ages ranged from 17 years to 79 years [Mean age ; 56.8±19.3 (S.D.) years].

The causative disease of their chronic renal failure was mostly chronic glomerulonephritis, that is in 16 cases, and there were 2 cases of diabetic nephropathy. One patient with chronic glomerulonephritis (Case 3) underwent renal biopsy for one year and 4 months before this study and was definitely diagnosed as having mesangioproliferative glomerulonephritis (accompanied by hyaline degenerated glomeruli). Hypertension was seen as a complication in 11 cases. In addition, one case each of Banti's syndrome, idiopathic thrombocytopenic purpura and spinal tumor was seen as complications.

During the present study, Cases 5, 6, 7, and 14 were treated as inpatients, while the other patients were treated as outpatients.

The details of each patient are compiled in Table I. The renal function in terms of 24-hour creatine clearance (Ccr) ranged from 7.6 l/day to 42.6 l/day [mean Ccr 28.7±10.1 (S.D.) l/day].

Diet control was performed by dietary prescription starting from 4 weeks before administration of TSUMURA Daiô-kanzô-tô extract granules. In principle, low-protein and high calorie diet was given to the patients. However, since the main purpose of the diet was to continue the low-protein/high-calorie diet almost constantly for a long period, it was impossible to follow a rigid low-protein, high-calorie renal failure diet. During the present study, the patients were instructed to take meals of which the content was as fixed and constant as possible. The content of meals was as follows : mean calorie intake : 33.2±6.5 (S.D.) kcal/kg/day ; mean protein intake : 0.77±0.16 (S.D.) g/kg/day ; salt : 0.15±0.03 (S.D.) g/kg/day.

Use of concominant drugs was limited to the minimum required, and no change was made in the quality and quantity of drugs during the present study.

Daiô-kanzô-tô administration and laboratory tests were carried out in accordance with the protocol shown in Fig. 1. That is, the patients were observed for their disease condition during the first 4 weeks during which the content of meals became almost constant. Then, for the first 4 days, Daiô-kanzô-tô was administered in a dosage of 5.0 g per day in 3 divided doses. Subsequently, after it was confirmed that no serious cathartic activity was exerted by the drug, the patients were administered 7.5 g per day divided doses after each meal. This regimen was continued for 8 weeks, and administration of Daiô-kanzô-tô was suspended for the following 4 weeks. Afer this suspension period, the patients were again administered the drug for another 8 weeks in a dosage of 7.5 g a day.

In most patients, administration of Daiô-kanzô-tô caused soft stool or sludgy stool but no watery stool. In the course of administration, when the stool became very sludgy, administration of the drug had to be reduced to 2.5 g to 5.0 g per day in a few patients, however, in no patients did the administration of Daiô-kanzô-tô have to be discontinued. In Case 18, however, due to small constitution, Daiô-kanzô-tô was administered in a dosage 5.0 g per day in 3 divided doses throughout the administration period.

During the present study, each patient was observed for general condition and clinical findings at least once every 2 weeks. Laboratory tests including determination of BUN and serum creatinine (Cr) were performed every 4 weeks. That is, laboratory tests were performed before administration (Stage 0), 4 weeks after initiation of administration (Stage I), 8 weeks after initia-

Table I Details of subject patients.

Case		Age (Y.O.)	Sex	Body Weight (kg)	Clinical diagnosis	Ccr (l/day) 0	II	V	BUN (mg/dl) 0	I	II	Cr (mg/dl) 0	I	II	Calorie (Cal.) Protein (g)	Progress after completion of the study and continuous administration of Daiô-kanzô-tô
									III	IV	V	III	IV	V		
1	KM	61	F	42	CGN HT	20.9	26.2	24.6	69.5 65.5	57.3 64.0	57.2 62.1	3.0 3.1	2.7 3.0	2.7 2.8	1800 30	Moved to another hospital. Whether continuously administered unknown. Not introduced to HD.
2	KK	67	M	60	CGN, Gont HT	42.6	48.3	47.0	36.0 38.9	34.3 31.3	33.1 30.7	2.5 2.7	2.5 2.5	2.4 2.1	1800 40	After completion of the study administration was stopped at patient's requset.
3	IN	74	F	41	PGN HT	27.0	30.0	33.6	55.5 62.3	50.7 58.1	55.4 52.2	2.3 2.6	2.3 2.4	2.3 2.3	1600 40	December 13, 1983 underwent renal biopsy (many hyalinized glomeruli were observed. Mesangical cells had proliferated to a medim degree, administration still continued (17 months) at IF, IgG (+), C_{3c} (+), Fib (+).
4	KF	46	F	63	CGN	38.6	43.8	36.4	29.8 30.4	24.1 29.8	20.6 27.4	2.5 2.2	1.8 2.1	1.8 2.2	1600 45	Administration continued (16 months).
5	TT	74	M	42	CGN, Spinal Cord Tumor	30.0	32.2	32.8	21.3 34.7	30.3 18.2	29.6 17.8	1.6 2.4	1.7 1.5	1.8 1.6	1600 45	After discharge from the hospital in September 1985, moved to another hospital. Administration unknown. Not introduced to HD.
6	SS	79	F	57	CGN, Nephrotic Syndrome	32.0	32.7	20.3	50.8 52.6	47.5 46.8	38.8 32.8	1.5 1.7	1.4 1.6	1.4 1.6	1600 40	Still in hospital. Administration continued (18 months).
7	JS	71	M	57	DM HT	34.0	30.0	42.9	67.9 52.1	55.9 42.5	58.1 31.1	2.2 2.1	2.0 1.6	2.1 1.6	1500 30	Still in hospital. Administration continued (18 months).
8	MY	75	M	58	CGN, Gout HT	28.3	34.6	33.0	72.4 68.8	47.7 68.2	57.3 62.1	4.9 4.6	4.2 4.4	3.7 4.2	1600 35	Moved to another hospital. Continuation of administration, unknown.
9	EO	51	F	48	CGN	34.5	37.4	38.3	24.2 26.8	20.2 20.3	22.5 31.5	2.2 2.1	2.0 1.8	1.8 1.8	1800 45	Stopped visiting hospital. Continuation of administration, unknown.
10	AW	32	F	57	CGN HT	42.0	39.0	30.2	34.7 36.2	33.7 34.6	31.1 41.9	2.2 2.5	2.2 2.6	2.4 2.8	1800 40	Moved to another hospital. No continuation of Daiô-kanzô-tô administration. Introduced to HD on August 14, 1986.
11	YI	35	F	53	CGN	20.0	20.0	19.0	27.1 31.5	21.0 30.2	26.5 32.2	2.6 2.7	2.6 2.7	2.7 2.7	1800 40	Administration continued (16 months).
12	MI	57	F	60	DM, Banti's Syndrome	35.0	39.2	34.3	53.1 61.5	60.1 60.8	56.9 50.4	1.8 1.9	2.1 2.0	1.8 1.8	1600 65	Administration continued (16 months).
13	KG	76	M	42	CGN HT	35.1	21.0	26.9	50.8 70.1	62.6 63.1	76.6 67.3	2.8 3.1	2.9 3.3	3.2 3.2	1700 35	Stopped visiting hospital. Continuation of administration, unknown.
14	YO	70	F	60	CGN, HT ITP	20.0	20.0	23.2	60.9 70.2	71.6 62.8	61.2 62.7	3.2 3.8	3.8 3.6	3.5 3.7	1800 40	Administration continued (17 months).
15	KI	17	M	58	CGN	38.0	36.0	23.2	32.8 33.6	28.3 31.4	34.8 42.4	3.2 4.3	3.5 4.1	4.0 4.6	2000 50	Moved to another hospital. Continuation of administration, unknown. Not introduced to HD.
16	TS	41	M	55	CCN HT	17.0	12.0	10.0	83.5 113.4	100.1 106.2	101.1 110.7	6.1 6.3	6.5 7.1	6.3 7.5	1800 40	Eight months since the completion of the study (March 12, 1986). Introduced to HD (March 12, 1986).
17	RM	67	M	63	CGN HT	13.7	14.1	14.7	76.9 101.4	127.4 83.4	112.4 94.6	6.0 7.5	8.0 6.3	8.0 6.8	1900 45	Administration continued (15 months) December 25, 1986. BUN 136 mg/dl, Cr 8.1 mg/dl.
18	KS	36	F	36	CGN HT	7.6	9.5	5.0	84.2 119.5	103.6 127.8	105.5 105.7	7.4 8.2	7.5 8.0	7.8 7.6	1800 30	One month after the completion of the study (December 12, 1985). Introduced to HD (December 12, 1985).

CGN, chronic glomerulonephritis ; PGN, mesangioproliferative glomerulonephritis ; HT, hypertention ; HD, hemodialysis ; DM, diabetes mellitus (diabetic nephropathy) ; ITP, idiopathic thromboeytopenic purpura ; IF, immunofluoresense findings.

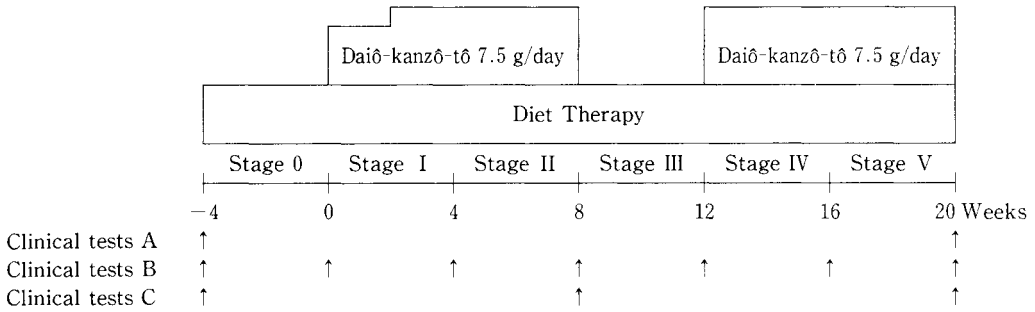


Fig. 1 Administration method of Daiô-kanzô-tô and schedule of laboratory tests.
Satge 0−Satge V : see text.
Clinical tests A : chest X-ray, ECG, peripheral blood, total bilirubin, GOT, GPT, γ-GTP, LDH, ALp., total cholesterl, serum Na · K · Cl · Ca · P.
Clinical tests B : serum total protein, albumin, BUN, Cr, uric acid, urinalysis (protein, sugar, sediment and urinary volume) and physical examination findings.
Clinical tests C : mean value of two 24-hour creatinin clearance (Ccr) values.

tion of administration (Stage II), during no-administration period (Stage III), 4 weeks after initiation of the second administration (Stage IV) and 8 weeks after initiation of the second administration (Stage V). ECG, chest X-rays, peripheral blood analysis and the hepatic function tests including determination of serum total cholesterol were performed before administration of Daiô-kanzô-tô and at the time of completion of present study (20 weeks after initiation of the study). The renal function was evaluated by the mean value of 2 determinations of Ccr and was performed at Stage 0, Stage II and Stage V.

The results were analyzed for significant difference by the paired t-test or the Student's t-test, and difference was judged to be significant when the level of significance was $p<0.05$.

Paired-t formulas

$$t=\frac{d-0}{S_d/\sqrt{n}} \qquad S_d=\sqrt{\frac{\Sigma d^2-(\Sigma d)^2/n}{n-1}}$$

Results

Study on all patients

Regarding blood pressure, a significant decrease in both the systolic and diastolic pressure was observed in Stages I and II in comparison with that in Stage 0. In Stage III (no-administration period), the blood pressure tended to be higher than that in Stage II, but there was no significant difference between the blood pressure. Also, there was no significant difference in the blood pressure between Stage III, Stages IV and V (the second administration period) (Table II).

Regarding BUN, there was no significant difference between Stage 0, Stages I and II. However, a significant increase was seen in the level of BUN in Stage III due to no administration of Daiô-kanzô-tô in comparison with Stage II. There was also a significant differece between Stage III and Stage IV and between Stage III and Stage V (Table III-1).

Regarding Cr, no significant difference was seen between Stage 0 and Stage I, and between Stage 0 and Stage II. There was also no significant difference between the serum creatinine levels in Stage III and Stage IV, and between Stage III and Stage V. However, as was the case for the level of BUN, suspension of administration of Daiô-kanzô-tô caused a significant increase in Cr (Table III-2).

In the case of uric acid, no significant difference was odserved between any Stages (Table III-3).

No significant difference was observed between any Stages for serum electrolytes.

Table II Study on blood pressure in each Stage in all patients (18 cases).

Table II-1 Systolic pressure.

Stage	0	I	II	III	IV	V
m±S.D. (mmHg)	148±26.4	137±29.3	133±18.4	136±16.2	139±16.6	144±19.8

paired-t $^{*}p<0.05$, $^{**}p<0.01$.

Table II-2 Diastolic pressure.

Stage	0	I	II	III	IV	V
m±S.D. (mmHg)	85.9±10.6	78.9±12.4	76.8±11.5	78.2± 9.1	81.2±11.2	81.3±10.1

paired-t $^{*}p<0.05$, $^{**}p<0.01$.

Table III Study on BUN, Cr, and uric acid in each Stage in all patients (18 cases).

Table III-1 BUN (18 cases).

Stage	0	I	II	III	IV	V
m±S.D. (mg/dl)	51.7±21.0	54.2±30.3	54.3±28.7	59.4±28.4	54.4±29.4	59.1±27.4

paired-t, $^{*}p<0.05$.

Table III-2 Cr (18 cases).

Stage	0	I	II	III	IV	V
m±S.D. (mg/dl)	3.2±1.7	3.3±2.0	3.3±2.0	3.5±1.9	3.4±1.9	3.4±2.0

paired-t, $^{*}p<0.05$.

No.	Stage II	Stage III	d*1	d²
1	2.7	3.1	−0.4	0.16
2	2.4	2.7	−0.3	0.09
3	2.3	2.6	−0.3	0.09
4	1.8	2.2	−0.4	0.16
5	1.8	2.4	−0.6	0.36
6	1.4	1.7	−0.3	0.09
7	2.1	2.1	0	0
8	3.7	4.6	−0.9	0.81
9	1.8	2.1	−0.3	0.09
10	2.4	2.5	−0.1	0.01
11	2.7	2.7	0	0
12	1.8	1.9	−0.1	0.01
13	3.2	3.1	0.1	0.01
14	3.5	3.8	−0.3	0.09
15	4.0	4.3	−0.3	0.09
16	6.3	6.3	0	0
17	8.0	7.5	0.5	0.25
18	7.8	8.2	−0.4	0.16
			−4.1	2.47

With regard to Ccr, there was no significant difference between Stage 0 and Stage II, and between Stage 0 and Stage V (Table III-4).

$$S_d=\sqrt{\frac{2.47-(-4.1)^2/18}{18-1}}=0.300599$$

$$t=\frac{-0.227778}{0.30059/\sqrt{18}}=-3.21$$

$t_{0.05}=2.110$

*1 : Stage II − Stage III

A similar comparison was also made for serum total protein and serum albumin, of which level was thought to change in view of the action mechanism of rhubarb.[5,6,9] As a result, a significant increase was seen in serum total protein in Stage V in comparison with Stage III, and in serum albumin in Stages IV and V in comparison with Stage III (Tables IV-1 and IV-2).

In order to more clearly understand the relationships between rhubarb and BUN, Cr, *etc.*, a study was made by classifying the patients into 2 groups. That is, one group consisted of patients

Table III-3 Uric acid (18 cases).

Stage	0	I	II	III	IV	V
m±S.D. (mg/dl)	7.5±1.7	7.7±2.1	7.8±2.3	7.3±2.0	7.6±2.2	7.5±2.3

Table III-4 Ccr (18 cases).

Stage	0	II	V
m±S.D. (l/day)	28.7±10.1	29.2±11.1	27.5±11.1

Table IV Study on total protein and albumin in each Stage in all patients (18 cases).

Table IV-1 Total protein (18 cases).

Stage	0	I	II	III	IV	V
m±S.D. (g/dl)	7.5±0.9	7.4±0.7	7.4±0.7	7.4±0.8	7.5±0.8	7.6±0.9

paired-t, $^*p<0.05$.

No.	Stage III	Stage IV	d*1	d²
1	7.6	7.4	0.2	0.04
2	7.2	7.7	−0.5	0.25
3	8.0	8.2	−0.2	0.04
4	7.7	7.9	−0.2	0.04
5	8.0	8.8	−0.8	0.64
6	8.3	8.2	0.1	0.01
7	8.0	8.3	−0.3	0.09
8	7.8	7.8	0	0
9	7.0	7.2	−0.2	0.04
10	6.9	7.1	−0.2	0.04
11	6.1	6.6	−0.5	0.25
12	7.6	8.4	−0.8	0.64
13	5.7	5.7	0	0
14	6.0	5.9	0.1	0.01
15	7.2	6.9	0.3	0.09
16	8.0	8.1	−0.1	0.01
17	7.6	8.3	−0.7	0.49
18	7.6	7.6	0	0
			−3.8	2.68

$$S_d=\sqrt{\frac{2.67-(-3.8)^2/18}{18-1}}=0.300599$$

$$t=\frac{-0.211111}{0.332351/\sqrt{18}}=-2.69$$

$t_{0.05}=2.110$

*1 : Stage III − Stage V

whose level of BUN in Stages I and II were lower than that in Stage 0 [good response group (Case 1, 2, 3, 4, 6, 7, 8, 9, 10, 11)] and the other group [poor response group (Case 5, 12, 13, 14, 15, 16, 17, 18)]. As shown in Table I, the good response group included 10 cases, and these cases showed a relatively good clinical course even after the completion of the present study.

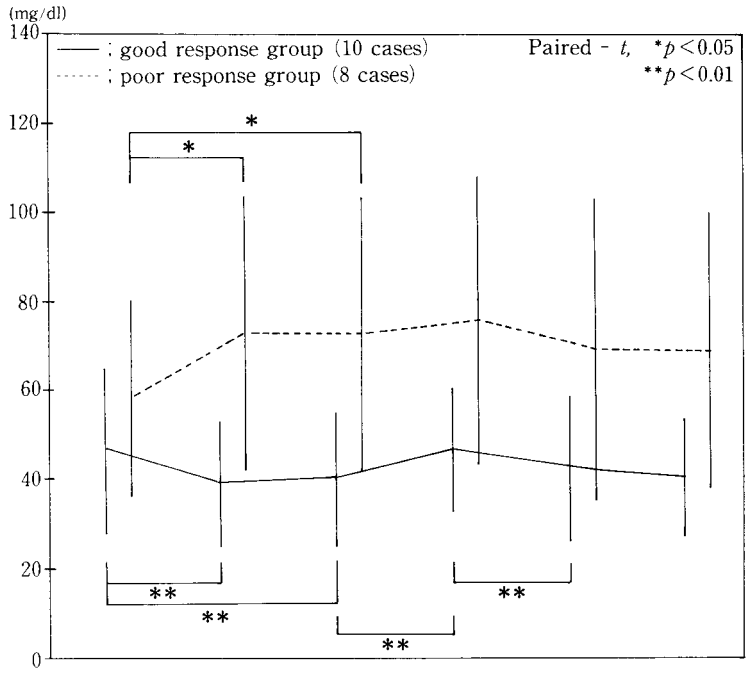
Study on good response group and poor response group

In the good response group, a decrease in the BUN level in Stages I and II was significant in comparison with that in Stage 0. In addition, as was seen for the study on all patient groups, suspension of administration of Daiô-kanzô-tô resulted in a significant increase in the BUN level. A significant decrease in the BUN level was seen in Stage IV (the second administration period) in comparison with Stage III, but the difference between Stage III and Stage V was not significant (Fig. 2). Regarding the poor response group, the BUN level tended to increase in all Stages but no significant difference was seen (Fig. 2).

Table IV-2 Albumin (18 cases).

Stage	0	I	II	III	IV	V
m±S.D. (g/dl)	3.8±0.5	3.9±0.4	3.9±0.4	3.8±0.4	3.9±0.5	4.0±0.5

paired-t, $^*p<0.05$.



Stage	0	I	II	III	IV	V
Good response group	46.8±18.7	39.2±14.4	40.0±15.7	46.5±15.7	42.6±16.3	40.4±13.5
Poor response group	57.9±23.2	73.0±35.3	72.6±31.6	75.6±33.2	69.2±36.2	69.0±32.6

m±S.D. (mg/dl)

Fig. 2 Study on BUN level in each Stage in each of the two group, good response group and poor response group : see text. * : $p<0.05$, ** : $p<0.01$.

With regard to the Cr level, there was a significant decrease in Stage I in comparison with Stage 0, but no significant decrease was seen in Stage II. In addition, as was the case for the BUN level, suspension of administration of the drug resulted in a significant increase in the BUN level. Comparison of the Cr level between Stage III and Stages IV and V (the second administration period) revealed a significant decrease in Stage IV and Stage V (Fig. 3). In the poor response group, the Cr level tended to increase, but there was no significant difference between any of the Stages (Fig. 3).

In the case of uric acid and serum electrolytes, there was no significant differece between any of the Stages in either groups (Fig. 3).

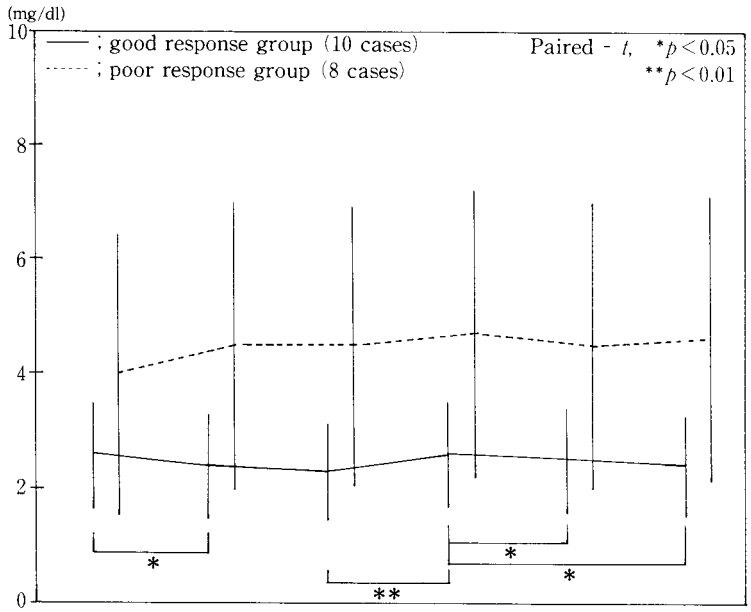
Regarding the Ccr level, in a comparison between Stage 0 and Stage II of the good response group, there was a tendency for the Ccr level to be improved ($p<0.1$), but the difference was not significant. No particular significant difference was also seen in the poor response group (Table V-1).

In the study of the serum total protein level and the serum albumin level, there was a significant increase in the two test items in Stage V in comparison with Stage III of the good response group, but no other differences were significant (Tables V-2 and V-3). There was no particular siginificant difference in these levels in the poor response group.

With the purpose of elucidating what factors are involved in the observed differences between the two groups, a study was made as a function of the following parameters.

Study on two groups and function of various parameters

Regarding the mean age, it was 59.1 ± 17.1



Stage	0	I	II	III	IV	V
Good response group	2.6±0.9	2.4±0.8	2.3±0.6	2.6±0.8	2.5±0.8	2.4±0.8
Poor response group	4.0±2.2	4.5±2.5	4.5±2.5	4.7±2.4	4.5±2.4	4.6±2.5

m±S.D. (mg/dl)

Fig. 3 Study on Cr level in each Stage in each of the two groups, good response group and poor response group : see text. * : $p<0.05$, ** : $p<0.01$.

Table V Study on Ccr, total protein and albumin in each Stage in each of two group.

Table V-1 Ccr [m±S.D. (l/day)].

Stage	0	II	V
Good response group (10 cases)	32.0± 8.0	34.2± 8.4	32.5± 9.2
Poor response group (8 cases)	24.6±11.4	23.0±11.4	21.3±10.5

Table V-2 Total protein [m±S.D. (g/dl)].

Stage	0	I	II	III	IV	V
Good response group (10 cases)	7.5±1.1	7.4±0.9	7.4±0.8	7.3±0.4	7.5±0.9	7.6±1.0
Poor response group (8 cases)	7.4±0.7	7.4±0.5	7.4±0.5	7.4±0.6	7.5±0.6	7.5±0.7

paired-t *$p<0.05$.

Table V-3 Albumin [m±S.D. (g/dl)].

Stage	0	I	II	III	IV	V
Good response group (10 cases)	3.8±0.6	3.9±0.5	3.9±0.5	3.8±0.5	3.9±0.5	4.0±0.5
Poor response group (8 cases)	3.9±0.4	3.8±0.3	3.9±0.3	3.9±0.4	4.0±0.4	4.0±0.4

paired-t *$p<0.05$.

(S.D.) in the good response group, while it was 54.8 ± 21.3 (S.D.) in the poor response group. The mean age thus tended to be higher in the good response group, but the difference was not significant.

With regard to the dietary prescription (calorie, amount of protein and amount of salt), they were respectively : 32.2±6.0 (S.D.) kcal/kg/day, 0.72±0.14 (S.D.) g/kg/day and 0.15±0.03 (S.D.) g/kg/day for the good response group, while they were 34.5 ± 7.3 (S.D.) kcal/kg/day, 0.84 ± 0.16 (S.D.) g/kg/day and 0.15±0.04 (S.D.) g/kg/day for the poor response group, respectively. There were no significant differences in any of the parameters between the two groups.

With respect to the BUN level in Stage 0, the level in the poor response group [57.9±23.2 (S.D.) mg/dl] tended to be higher than that in the good response group [46.8±18.7 (S.D.) mg/dl], but the difference was not statistically significant. However, in Stage III (no-administration period), the BUN level in the poor response group [75.6±33.2 (S.D.) mg/dl] was significantly higher than that in the good response group [46.5±15.7 (S.D.) mg/dl].

An almost similar pattern was seen for the Cr level. That is, in Stage 0, there was no significant difference between the good response group [2.6±0.9 (S.D.) mg/dl] and the poor response group [4.0±2.2 (S.D.) mg/dl], while in Stage III, the level in the poor response group [4.7 ± 2.4 (S.D.) mg/dl] was significantly higher than that in the good response group [2.6±0.8 (S.D.) mg/dl].

In the case of Ccr leval, its level in Stage 0 was 32.0±8.0 (S.D.) l/day in the good response group, and 24.6±11.4 (S.D.) l/day in the poor response group. Thus, the renal function tended to be worse in the poor response group, but the difference was not significant.

On the basis of the above findings, it was suggested that, in the poor response group, the renal function tended to be lower than that in the good response group from before initiation of administration of Daiô-kanzô-tô, although the difference between the two groups was insignificant. With regard to the laboratory tests performed before administration of Daiô-kanzô-tô and after completion of the study, a study was made on the test items shown in Clinical tests A, Fig. 1. In all patient groups, a significant difference was seen only in the serum total cholesterol level. That is, the level was 219.4±55.6 (S.D.) mg/dl before initiation of administration, while it was 201.2±43.9 (S.D.) mg/dl after completion of the study.

Discussion

Chronic renal failure is a disease entity characterized by progressiveness and irreversibility.[1] Therefore, in the treatment of this disease, effort is concentrated on how the progress of the disease can be slowed down. The main objective of the treatment is thus to suppress the activity of renal disorder factors[9] as completely as possible, or elimination thereof. From earlier times, a diet factor[10] as one of various factors of renal disorder had been considered to be important.

In particular, protein has a close relationship[11] with physiological factors related to the progression of renal disorder to which attention is being paid recently.

This knowledge is now being applied as so-called renal disorder diet in clinical medicine, and it is widely known that the diet results in a decrease in the BUN level[12] and improvement in the state of renal failure.[3] However, there are reports which claim that, if an extremely low-protein diet is administered for a long period with expectation of a decrease in the BUN level, hypoalimentation[13] or disorder of the cardiac function[14] may develop. Practically, it is quite difficult to perform strict diet therapy for a long period, and in the case of aged patients, it is often virtually impossible to change diet habits and successfully administer this therapeutic diet. Therefore, if it is possible to limit the degree of diet control at a certain level and compensate for the remaining necessary control by some other means, such therapy would be a more realistic therapy. From such a viewpoint, a pharmacotherapy is hoped for.

Drug therapy employing essential amino acids,[3] keto acids therapy[4] or lactulose[15] has already

been tried and a good effect has been achieved in some cases. However, regarding essential amino acids therapy and keto acids therapy, these agents have become fairly easy to ingest recently. However, these agents taste too badly to follow a long-term ingestion. Lactulose is widely employed in the treatment of hepatic failure. The efficacy of this agent is thought to be hopeful since its action mechanism[16] such as inhibition of entero-hepatic circulation of urea and as a scavenger of hydroxyl radicals is surmised. On the other hand, it has also been suggested that lactulose administration causes hypoalimentation, such as acceleration of anemia and a tendency for the serum total protein to decrease.[15] Thus, further study is thought to be necessary on the long-term administration of lactulose.

With regard to rhubarb employed in the present study, attention is being paid to this oriental drug since the presence of protein-resynthesizing mechanism from BUN is surmised in this drug in addition to an activity similar to that of lactulose.

In all patients, suspension of Daiô-kanzô-tô administration caused a significant increase in the BUN and Cr levels and re-administration of the drug caused a significant decrease in the BUN level. Therefore, the results of the present study seemed to indicate that it is desirable to administer Daiô-kanzô-tô for a long period.

In the study on the good response group that patients with a significant decrease in BUN levels place in and the other in the poor response group, administration of Daiô-kanzô-tô caused a significant decrease in the BUN level in the good response group, and a similar decrease was seen in the Cr levels. These results indicate that Daiô-kanzô-tô has a substantial improvement effect on the BUN metabolism in chronic renal failure. Furthermore, it was noticeable that, in comparison with the suspended administration period, a significant increase in the serum total protein and the serum albumin levels, and a finding indicating an improvement in the general nutritional state was seen in the 20th week, when the re-administration period was completed. In addition, these results were thought to clinically support a theory[5,6,8] that administration of rhubarb results in a decrease in the serum BUN level by promoting resynthesis of protein from BUN, which is thought to be one of the activity of rhubarb.

In the study as a function of various background factors on the good and poor response groups, there were no significant differences between the two groups but the renal function tended to be comparatively better to begin with, in the good response group than in the poor response group. This fact seemed to suggest that, in administration of Daiô-kanzô-tô in the treatment of chronic renal failure, a better effect may be obtained when administration of Daiô-kanzô-tô is initiated while the renal function is maintained at a high level. It was also interesting that the mean age tended to be higher in the good response group than the poor response group.

With regard to a long-term effect of slowing down the progression of chronic renal failure—which is expected from rhubarb—it is necessary to study more cases for a longer period, and it is difficult to draw any conclusion only from the present study. However, administration of Daiô-kanzô-tô was able to be continued until January of 1987 in 8 cases (Cases 3, 4, 6, 7, 11, 12, 14 and 17); one year and 6 months have passed in the longest administration cases. Although no stochastic analysis was possible to perform in the present study, when some cases were estimated for the prognosis[17,18] by the reciprocal number of the serum creatinine concentration, Daiô-kanzô-tô therapy was surmised to have resulted in sufficient prolongation in the prognosis regarding life and prolongation of the time until intiation of hemodialysis. Also, no serious adverse effects were seen to date on the continuous administration of Daiô-kanzô-tô. However, with licorice which is contained in Daiô-kanzô-tô, although it is widely used in the treatment for many diseases, it is also well known that massive and long-term administration of licorice induces pseudo-aldosteronism[19] and myopathy.[20] It is considered to be necessary to be cautious regarding the long-term administration of Daiô-kanzô-tô.

Conclusion

The above results suggested that administration of Daiô-kanzô-tô in the treatment of chronic renal failure may alleviate diet limitation to a certain extent and can eventually be conservative therapy which can maintain a relatively good nutritional state for a long period. It was considered necessary to conduct further study on the optimum dose of Daiô-kanzô-tô and time of initiation of Daiô-kanzô-tô therapy observing many cases.

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和文抄録

慢性腎不全患者18名に大黄甘草湯を投与し，臨床的にBUN値の低下作用もしくは，腎不全改善作用があるかについて検討した。全症例の検討において，大黄甘草湯の8週間投与では有意のBUN値の低下は認められなかった。しかしながら，大黄甘草湯の休薬により有意のBUN，クレアチニン値の上昇を，更に，再投与によりBUN値の低下を認めた。大黄甘草湯とBUN，クレアチニン等との関係をより明確にする目的で，全症例を2群に分類した。すなわち，有意のBUN低下を示した良反応群と，それ以外の不良反応群である。腎機能は，良反応群において比較的良い傾向にあった。また，良反応群に高齢化の傾向もあった。更に休薬期との比較で，大黄甘草湯再投与期においては，血清総蛋白質および血清アルブミン値は有意な増加を示した。これらの結果は，慢性腎不全患者における大黄甘草湯投与が，食事療法をある程度緩め，ひいては，長期に比較的良好な栄養状態に保てる可能性があり，慢性腎不全の保存的療法として有用であることを示唆していると考えられた。

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