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TRAPIDIL AND METHYLPREDNISOLONE PULSE THERAPY ARE EFFECTIVE DRUGS FOR TREATING POSTPARTUM PATIENTS WITH TOXEMIA

(toxemia of pregnancy/trapidil/methylprednisolone pulse therapy)

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Trapidil was prescribed for 7 women with severe urinary protein and toxemia of pregnancy and Methylprednisolone pulse therapy (MPT) was prescribed for 3. Reduction of urinary protein, a trend toward increase in total serum protein and serum albumin and a trend toward decrease in total serum cholesterol and urinary FDP (fibrinogen and fibrin degradation products) immediately followed this treatment.

As the chemotherapy for patients with toxemia of pregnancy remains to be established, we prescribed Trapidil or Methylprednisolone for puerperal patients with severe urinary protein. This therapy has considerable and immediate effect.

MATERIALS AND METHODS

The Japanese subjects were 8 primigravida women and 2 multigravida women ranging in age from 23 to 34 years. All were diagnosed as cases of pure toxemia in pregnancy (Table I). Seven (Casel-7) were treated with oral Trapidil (Rocornal), in a dose of 600 mg/day from the 2nd or 7th day postpartum. Three

(Case8-10) were treated with an intravenous injection of a high-dosage- methylprednisolone (Solu-Medrol), so-called methylprednisolone pulse therapy (MPT), 1,000 mg given over a 1 to 2 hour period for 3 consecutive days, three times at one week intervals.

Laboratory findings, including urinalysis and blood chemistry were compared before and after the treatment.

Table I. CLINICAL DATA ON PATIENTS PRESCRIBED TRAPIDIL OR METHYLPREDNISOLONE PULSE THERAPY

Case No.	Name	Age	para.	Toxemia of pregnancy*	Pre-treatment		
					Urinary protein (g/day)	Edema	B.P. (mmHg)
1	M.H	29	primi	severe	5.8	whole body	150/100
2	M.A	26	primi	mild	2.0	pretibial	150/100
3	S.Y	28	primi	severe	9.3	pretibial	150/ 80
4	K.S	25	primi	severe	3.2	whole body	193/130
5	S.H	23	primi	severe	4.3	pretibial	170/100
6	Y.H	31	multi	mild	3.2	pretibial	158/ 98
7	S.M	34	primi	severe	5.4	pretibial	170/ 94
8	N.M	27	primi	severe	16.8	whole body	150/104
9	Y.Y	23	primi	severe	8.0	whole body	160/106
10	K.E	29	multi	severe	17.8	whole body	210/140

* Using the classification of the Japan Society of Obstetrics and Gynecology (11)

RESULTS

I. Trapidil Therapy

1. Changes in urinary protein before and after the treatment (Fig.1)

The amount of urinary protein before the treatment was from 2.0 to 9.3 g/day (mean 4.5 $\pm$ 2.2 g/day) and rapidly decreased within one week after trapidil therapy, that is 2.3 $\pm$ 1.2 g/day, and 2 weeks after the treatment was 1.1 $\pm$ 0.5 g/day. Comparison of the findings before the treatment and one week after the treatment revealed a significant trend toward decrease in urinary protein.

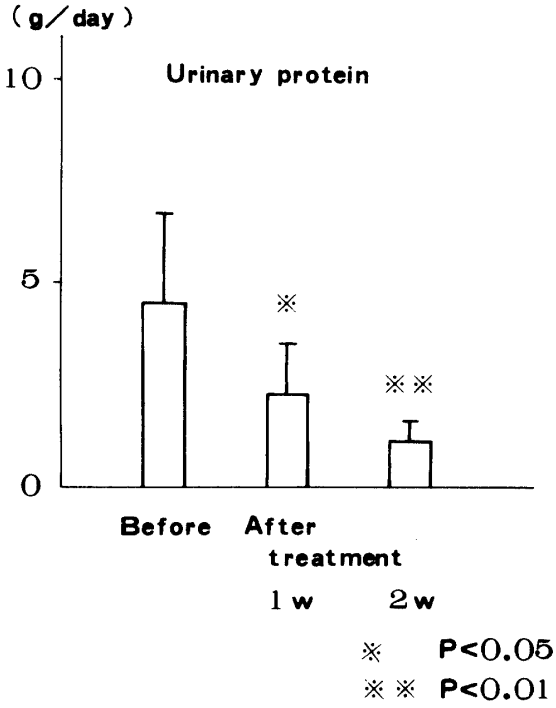

Fig.1. Changes in urinary protein before and after trapidil therapy.

2. Changes in urinary fibrinogen and fibrin degradation products (FDP)

The changes in urinary FDP before and after the treatment are shown in Fig.2. Urinary FDP registered abnormally high values from 0.5 to 2 μg/ml (mean 1.3 ± 0.6 μg/ml). Two weeks after the treatment, urinary FDP was reduced to normal (below 0.1 μg/ml) in 3 and was remarkably decreased from 0.2 to 0.5 μg/ml in the other 4. Comparison of mean values before and after the treatment showed a significant difference ($0.01<p<0.02$).

3. Changes in laboratory data

Changes of total protein, albumin, total cholesterol, BUN and creatinine in the serum are shown in Fig.3. After the treatment, total protein and albumin in the serum had significantly decreased, but BUN and creatinine levels remained unchanged.

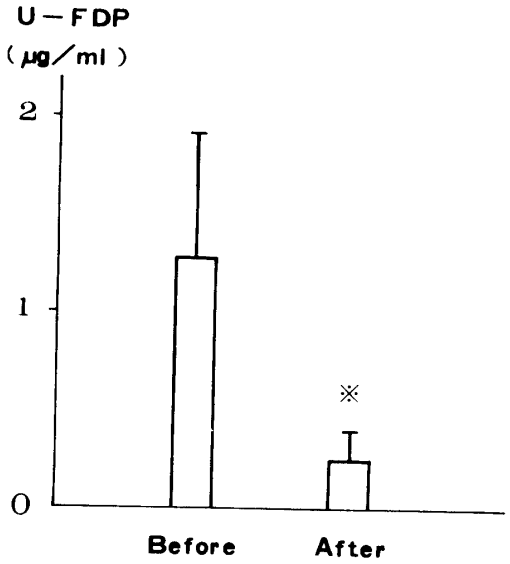

Fig.2. Changes in urinary FDP before and after trapidil therapy.

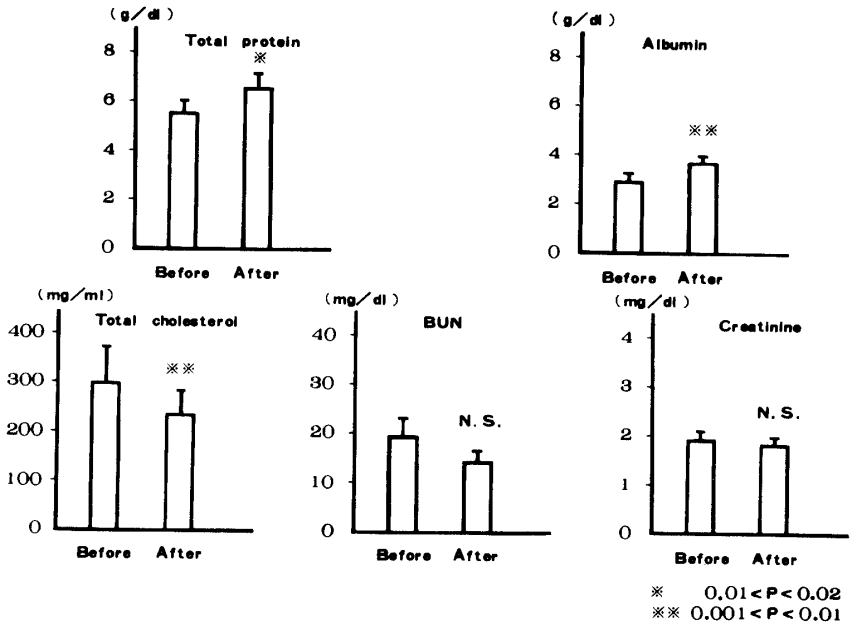

Fig.3. Changes in laboratory data before and after trapidil.

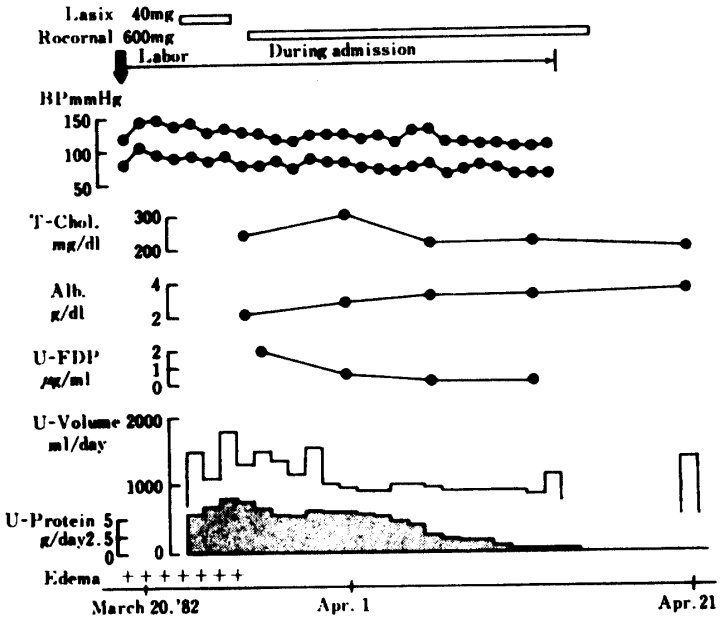

Fig.4. Clinical course of case 7.

4. Clinical course of a patient for Trapidil treatment

This patient was case 7 in Table I. Pretibial edema appeared at 38 weeks of gestation. At 39 weeks of gestation 2.0 g/day of urinary protein was evident together with severe pretibial edema. A male infant was delivered at 39 weeks and 4 days of gestation. The pretibial edema, slight hypertension and urinary protein remained at postpartum. Immediately dietary treatment and administration of Lasix 40 mg/day were prescribed. The pretibial edema and hypertension disappeared, but the severe urinary protein (5.4 g/day) remained.

From the 7th postpartum day Trapidil (600 mg/day) was administrated. Eleven days after this therapy, the urinary protein had decreased to 1.9 g/day, a trend toward increase in total serum protein and serum albumin was observed and a trend toward decrease in total serum cholesterol and urinary FDP was apparent.

The clinical course is summarized in Fig.4.

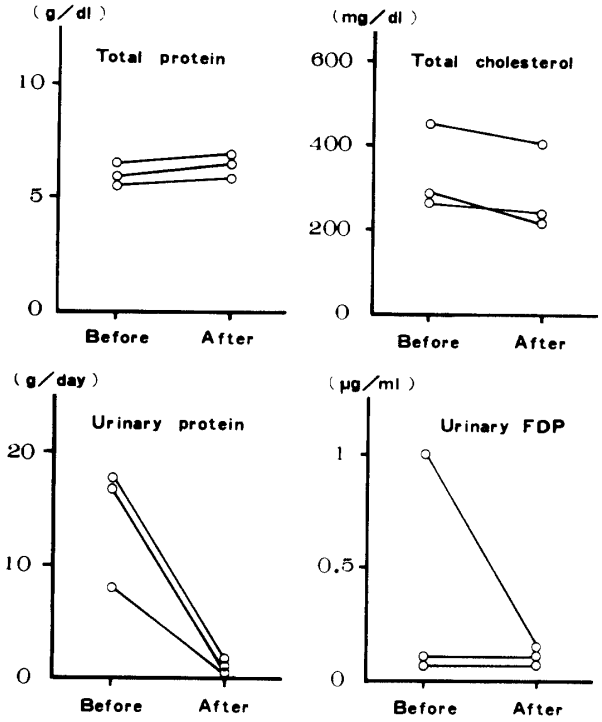

Fig.5. Changes in laboratory data before and after MPT.

II. Methylprednisolone Pulse Therapy (MPT)

1. Changes in biochemical data

Changes in 3 patients are shown in Fig.5. Urinary protein was markedly reduced in 3 after MPT and was below 0.5 g/day, in all the patients. Only one patient had a high value (1.0 μg/ml) of urinary FDP before MPT. After MPT, the urinary FDP was reduced to a normal range (below 0.1 μg/ml). The other 2 had normal values of urinary FDP, before and after MPT. In all, there was a trend toward increase in serum total protein and a trend toward decrease in serum total cholesterol.

2. Clinical course of a patient for MPT

This patient was case 10 in Table I. At 32 weeks and 3 days

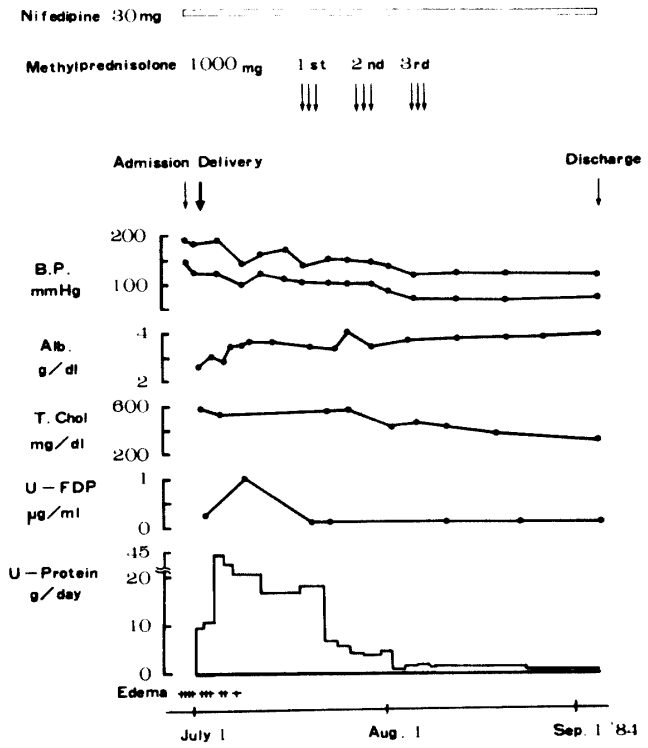

Fig.6. Clinical course of case 10.

of gestation, she was sent to us for examination, as whole body edema, severe hypertension, hydrothorax, ascitic fluid, severe urinary protein and intra-uterine fetal death (IUFD) were evident. She delivered a dead male infant on the 2nd day after admission. Following delivery, hydrothorox, ascitic fluid and edema were immediately reduced, but hypertension and urinary protein remained. The hypertension showed a trend toward decrease following administration of Nifedipine.

MPT was started from the 17th postpartum day. After one course of MTP, the urinary protein was remarkably decreased from 17.8 to 6.0 g/day. After 3 courses of MPT, the urinary protein was about 1.5 g/day, and was negative at 12 weeks after MTP. After MPT, there was a trend toward increase in serum albumin and toward decrease in total serum cholesterol.

The clinical course is summarized in Fig.6.

DISCUSSION

The treatment of urinary protein in toxemia of pregnancy has involved administraion of Steroid, Indomethacin, Aspirin Dipyridamole and Vit.K.

Fukuda (1) reported that pathologic findings of toxemia of pregnancy were 1 swelling and proliferation of the glomerular capillary endothelium, 2 sclerosis of afferent arterioles, 3 adherence of fibrin-like substance under the glomerular capillary basement membrane. Causes of urinary protein have been linked to disorders of the renal glomerulus related to antigen, antibody and its immune complex.

In toxemia of pregnancy, there is platelet aggregation and thrombus formation and a trend toward increase in β-thromboglobulin (2). Decline in platelet function, fibrillation of renal arterioles and thrombus formation in renal arterioles sometimes occur (2). These events lead to a urinary protein (2). Furthermore, renal disorders are enhanced by thromboxane A_2 (TXA_2) production due to an abnormality in lipid metabolism (3).

Trapidil is a drug which dilates the coronary artery, inhibits production of TXA_2 (4) and inhibits platelet aggregation (5).

MPT is a treatment for rejection after renal transplantation as reported by Kounts and Cohn (6). MPT was prescribed for clinical lupus nephritis, by Cathcart et al. (7), and for severe glomerulonephritis, by Cole et al. (8). All reported that MPT was effective therapy for diseases of the renal glomeruli. Methylprednisolone can be given in large quantities at one time. Therefore, Methylprednisonone pulse therapy (MPT) can be expected to produce beneficial effects for inflammation in a short term and provide an anti-immune action (9, 10).

In expectation of the above-stated pharmacological effects, we prescribed Trapidil or Methylprednisolone for puerperal patients with severe urinary protein. In both therapies, reduction of urinary protein, a trend toward increase in total serum protein and serum albumin and a trend toward decrease in total serum Cholesterol and urinary FDP were observed. No definite side effects attributable to the treatment were observed in any of our patients.

Therefore, prescription of Trapidil and MPT for puerperal patients with severe urinary protein are effective. In the

treatment of puerperal patients with a high value (>10 g/day) of urinary protein, MPT is better than prescription of Trapidil. On the contrary, in the treatment of patients with a high value (>1.0 μg/ml) of urinary FDP and a relative high value (<10 g/day) of urinary protein, prescription of Trapidil is better.

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