EFFECTS OF URSODESOXYCHOLIC ACID ON THE AMOUNT OF URINARY THIAMINE AND RIBOFLAVIN FROM PATIENTS WITH PULMONARY TUBERCULOSIS

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Ursodesoxycholic acid (UDCA), $3\alpha,7\beta$ -dioxycholanic acid, has been isolated from the bile of the bear by Shoda (1). Onishi (2) reported that certain kinds of cholic acids were effective to phosphorylate thiamine *in vivo*, the UDCA being most effective. The same author (3) also observed that the UDCA accelerated the absorption of riboflavin through the intestinal canal and phosphorylated the vitamin too. Many authors, on the other hand, have suggested the presence of metabolic anomalies of thiamine and riboflavin in the patients with tuberculosis. This paper is concerned with the study of the effects of UDCA on the metabolism of those vitamins in the patients with pulmonary tuberculosis.

EXPERIMENTAL AND RESULTS

1. Method

Patients—All patients tested were the in-patients patients of Kumamoto City Hospital. Some of them had not been treated with any chemotherapeutic drugs for tuberculosis and the others had not been medicated with the drugs at least for 6 months before this study.

Medication—UDCA and vitamins were administered after collection of urine and before taking breakfast. UDCA, 1 g, was daily orally administered and 10 mg of the vitamins were administered subcutaneously every day.

Estimation of Urinary Thiamine and Riboflavin—Each vitamin was estimated by the method described in “Eisei Shiken-Ho” (An Official Methods of Analysis authorized by Pharmaceutical Association of Japan), *i. e.*, thiamine was estimated by thiochrome method and riboflavin by lumiflavin method.

2. Urinary Thiamine and Riboflavin from the Patients with Pulmonary Tuberculosis

Thirteen patients were tested and the average amounts of urinary thiamine and riboflavin excreted for 24 hours are listed in Table I.

The values given in the tables of this paper were tested statistically and unusual values were omitted from the calculation of mean values.

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TABLE I
Amounts of Urinary Thiamine and Riboflavin Excreted in 24 hr

Patient No.	Vitamins excreted	
	Thiamine	Riboflavin
	μg	μg
1	297.0	1600.0 ^a
2	115.0	766.5
3	253.0	1474.0 ^a
4	60.0	220.0
5	774.0	216.0
6	234.0	120.0
7	116.0	101.5
8	42.0	168.0
9	144.0	288.0
10	1020.0 ^a	260.0
11	684.0	60.0
12	1155.0 ^a	132.0
13	196.0	126.0
Mean	291.5 ± 72.7	223.5 ± 57.2

^a Unusual value omitted from calculation.

3. Effects of UDCA on the Amounts of Urinary Thiamine and Riboflavin

All the patients tested in the preceding experiments were administered with 1.0 g of UDCA, and the urine was collected for 24 hours. Urinary thiamine and riboflavin excreted for 24 hours before and after the administration of UDCA were compared as shown in Table II. Decreases of the excretions of both vitamins were observed statistically ($p < 0.01$).

TABLE II
Amounts of Urinary Thiamine and Riboflavin Excreted
in 24 hr after Administration of UDCA

Patient No.	Thiamine		Riboflavin	
	After administration of UDCA	Difference between before and after	After administration of UDCA	Difference between before and after
	μg	μg	μg	μg
1	162.5	134.5	137.5	1462.5 ^a
2	—	—	260.0	506.5
3	199.5	53.5	57.0	1417.0 ^a
4	72.0	— 12.0	104.0	116.0
5	792.0	— 18.0	198.0	18.0
6	1674.0	— 1440.0 ^a	78.0	42.0
7	63.0	53.0	108.0	— 6.5
8	20.0	22.0	190.0	— 22.0
9	98.0	46.0	140.0	148.0
10	234.0	786.0 ^a	54.0	206.0
11	120.0	564.0	96.0	— 36.0
12	136.5	1018.5 ^a	84.0	68.0
13	130.0	66.0	91.0	35.0
Mean	305.5 ± 137.0		122.9 ± 16.9	

^a Unusual value omitted from calculation.

4. Effects of UDCA on the Urinary Excretions of Thiamine and Riboflavin Following the Administration of Both Vitamins

After subcutaneous injection of each 10 mg of the vitamin, the amounts of the vitamins excreted in urine for 24 hours were estimated, then the next 24-hour urine was collected after administrations of UDCA together with each 10 mg of thiamine or riboflavin. The results are listed in Tables III and IV. In all the cases, the reduction of the excreted amounts of the vitamins was observed.

TABLE III
Urinary Excretion of Thiamine under Administration of Both Vitamins

Patient No.	Urinary thiamine excreted in 24 hr		
	Before administration of UDCA	After administration of UDCA	Difference between before and after
	μg	μg	μg
1	4746.0	4737.5	8.5
2	4074.0	3517.0	556.5
3	2740.0	2030.0	710.4
4	9500.0	6960.0	2540.0
5	6732.0	3528.0	3204.0
6	8122.7	—	—
7	7750.0	3000.0	4750.0
8	5775.0	3562.0	2213.0
9	9000.0	6858.0	2142.0
10	7898.0	5140.0	2758.0
11	2760.0	756.0	2004.0
12	4952.0	2814.0	2138.0
13	6210.0	1027.0	5183.0
Mean	6173.8 ± 621.0	3660.8 ± 575.9	

TABLE IV
Urinary Excretion of Riboflavin under Administration of Both Vitamins

Patient No.	Urinary riboflavin excreted in 24 hr		
	Before administration of UDCA	After administration of UDCA	Difference between before and after
	μg	μg	μg
1	5323.5	1512.5	3811.0
2	3594.0	1170.0	2424.0
3	4450.0	1570.0	2880.0
4	10735.0	5120.0	5615.0
5	5852.0	3852.0	2000.0
6	3891.5	—	—
7	2670.0	732.0	1938.0
8	4609.0	1807.0	2802.0
9	3450.0	1908.0	2542.0
10	3520.0	3460.0	60.0
11	3340.0	1260.0	2080.0
12	5022.5	3248.0	1774.5
13	4358.5	832.0	3526.5
Mean	4678.2 ± 561.7	2206.0 ± 399.1	

5. Effects of the Administration of UDCA for a Long Period of Time

Five patients received thiamine and the excretions of the vitamin for 24 hours were estimated. Then UDCA was administered for the following two weeks,

followed by the administration of thiamine for 4 days. The amounts of urinary thiamine were estimated every 24 hours. The results are shown in Table V.

TABLE V
*Urinary Excretion of Thiamine after Administration
of UDCA for a Long Period of Time*

Patient No.	Date	Urinary thiamine excreted in 24 hr		
		Before (A)	After (B)	(A) - (B)
8	1	3632	3800	
	2	4912	5510	
	3	1003	1159	
	4	7462	3135	
	Mean	4252	3401	851
2	1	4596	4360	
	2	6132	6300	
	3	572	915	
	4	5595	5661	
	Mean	4223	4309	- 85
15	1	6882	5330	
	2	6201	4680	
	3	528	854	
	4	6975	5159	
	Mean	5147	4006	1141
16	1	5148	8800	
	2	2688	7152	
	3	8472	5544	
	4	8320	9000	
	Mean	6157	7557	- 3551
18	1	2700	7632	
	2	2457	7852	
	3	7120	5797	
	4	9480	9196	
	Mean	5439	7619	- 2189
Mean		5043.6 ± 367.8	5378.4 ± 913.8	

Estimation of urinary riboflavin after medication of UDCA was carried out by the same method as described above for three patients, and the results are shown in Table VI.

DISCUSSION

Many authors have reported on the metabolisms of thiamine and riboflavin in the patients with tuberculosis. Arima (4), Iwasaki (5), and Satoyoshi (6) observed the reduction of urinary thiamine from the patients with tuberculosis, and the cause was explained as a large consumption of the vitamin in the patient with such disease as tuberculosis. An increased amount of urinary thiamine being observed by Sugihara (7) in serious cases of the disease, he ascribed the excretion of the vitamin to the disorder of phosphorylation.

TABLE VI
*Urinary Excretion of Riboflavin after Administration
 of UDCA for a Long Period of Time*

Patient No.	Date	Urinary riboflavin excreted in 24 hr		
		Before (A)	After (B)	(A) - (B)
		μg	μg	
17	1	1024	8535	
	2	7000	8016	
	3	7490	6490	
	4	5760		
	Mean	5294	8327	- 3033
19	1	4200	2550	
	2	5315	6798	
	3	8340		
	4	5190		
	Mean	5761	4674	1087
20	1	3400	5586	
	2	8448	7384	
	3	8840	9585	- 745
	4	9828	4640	
	Mean	7629	6799	830
Mean		6228.0 $\pm$ 713.3	6600.0 $\pm$ 1059.2	

Yukisada (8) reported that the normal Japanese excreted on an average 354.5 μg of thiamine a day in February. In our experiments, 4 patients excreted the vitamin more than 354.5 μg , and two of them excreted so much thiamine that the values were to be omitted from calculation. In this experiment the tendency of reduction in urinary thiamine was observed in these patients, if not ascertained.

In relation to the excretion of riboflavin in the patients with tuberculosis, many reports have also been presented, Omori *et al.* (9), Yamaki (10), and Yamamura *et al.* (11) observed lesser amounts of urinary riboflavin in the patients with tuberculosis than in normal subjects. The amounts of excreted riboflavin in normal Japanese were supposed to be 50–150 μg per day after taking 0.4–0.6 mg of the vitamin a day (12). In this experiment, the amounts of the both vitamins taken as a diet was not estimated, so the comparisons of the amounts of the excreted vitamins from the patients with those from normal subjects were not possible.

In the experiment 3, it was observed that UDCA reduced the urinary thiamtne and riboflavin from the patients as shown in Table II. The effect of UDCA on the excretion of the vitamins was studied further after loading both vitamins to the the patients, and more remarkable decreases of the urinary vitamins by UDCA were observed as shown in Tables V and VI.

Those results, however, obtained in the patients with tuberculosis, having supposedly the disorder of the liver function. Thus the improvement of the liver function which might decrease the excretion of the vitamins was attempted by administration of UDCA for a long period of time, but any expected influence of UDCA was not observed.

Those findings suggested that UDCA increased the absorption and phosphorylation of both vitamins as reported by Onishi (2, 3), Mizuhara *et al.* (13), and Kagaya *et al.* (14).

SUMMARY

1. Abnormal excretion of thiamine and riboflavin from the patients with pulmonary tuberculosis was not ascertained in this study.

2. More reduction of urinary thiamine and riboflavin by administration of UDCA was observed after loading the vitamins to the patients than without loading.

3. Administration of UDCA for a long period of time did not improve the liver function of the patients with tuberculosis to absorb the vitamins.

4. Reduction of the amounts of excreted thiamine and riboflavin after administration of UDCA was supposed to be due to the increase of phosphorylation and absorption of both vitamins.

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