BLOOD AND URINARY PANTOTHENIC ACID LEVELS IN THE PATIENTS WITH LIVER DISEASES

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(Received March 24, 1962)

A number of investigators (1) have demonstrated that disturbed metabolisms of various vitamins are often encountered in patients with liver injury and also that these vitamins have a protective effect on the injured liver.

However, there have been very few reports on pantothenic acid (PaA) metabolism in liver injury in spite of the possible close relationship of PaA metabolism with liver injury as shown by Nonnenbruch *et al.* (2) who clarified the significance of the vitamin in the living body. One of the reasons for it is that the assay method is more complicated than those for vitamin B complex, thus making the clarification of *in vivo* metabolism of the vitamin difficult. The author at first pursued a proper method for its determination and reported a clinically applicable procedure (3). Using this method, the PaA levels in the blood and urine were determined in the patients with liver diseases, and the metabolism of the vitamin was studied.

EXPERIMENTAL

Materials and Methods

1. Patients

Forty-two patients with various liver diseases admitted to the First Clinic of the Medical Department of Kyoto University Hospital were subjected to the study. They included 15 cases of acute hepatitis (9 cases of infectious hepatitis, 5 of serum hepatitis and 1 of Weil's disease), 14 cases of liver cirrhosis including 2 of hemochromatosis, and 13 of neoplasm of the liver. The diagnoses were confirmed by liver biopsy as well as by laboratory findings.

2. Materials

Blood was drawn from the antecubital vein early in the morning in the fasting state, and a 24-hour urine was collected. The method of preservation of the materials was the same as described elsewhere (3).

3. PaA Determination

The microbiological assay using *Lactobacillus arabinosus* was used (4). Total PaA in the blood was fractionated into free and bound forms by means of Lipmann's enzymatic treatment. For urinary PaA, the enzymatic treatment was

omitted, since the bound form was scarcely detectable in the urine. Details of the procedure have been described in the previous paper (3).

4. Laboratory Study

Serum cobalt reaction (5), serum cadmium reaction (5), icteric index, bromo-sulfalein test (BSP), serum total protein, albumin/globulin ratio, serum cholesterol (6) and its ester quotient were determined.

RESULTS

Blood and urinary PaA levels of normals have been described (3). The mean total PaA level in the blood is 464.2, the mean bound and free forms are 435.5 and 28.7 $\mu\text{g}/\text{ml}$, respectively. The mean PaA level in the urine is 3.2 mg/day (Table I). Blood and urinary PaA levels beyond the range, the above-described mean ± 2 standard were considered abnormal in the present study.

TABLE I
Pantothenic Acid Levels in Normal Controls (30 cases)

	PaA level in blood				PaA in urine
	Free	Bound	Total	B/T	Free
	<i>$\mu\text{g}/\text{ml}$</i>				<i>mg/ml</i>
Mean	28.7	435.5	464.2	0.94	3.23
Range	14—70	351—490	364.5—540.0	0.86—0.97	2.46—4.46
SD	± 15	± 37	± 41	± 0.2	± 0.6
Range of 2SD	58.7—0	509.5—361.5	546.2—382.2	1.0—0.74	4.43—2.03

PaA, pantothenic acid; SD, standard deviation.

TABLE II
Pantothenic Acid Values in Patients with Hepatitis

Subject	Diagnosis	Age	Sex	PaA level in blood				PaA in urine
				Free	Bound	Total	B/T	
				<i>$\mu\text{g}/\text{ml}$</i>				<i>mg/day</i>
M. T.	Inf. Hep.	20	m	103	263	366	0.72	2.0
T. K.	"	33	m	33	277	310	0.89	1.8
T. S.	"	29	m	186	393	579	0.68	3.1
N. T.	"	32	m	288	393	681	0.58	0.4
M. Y.	"	32	m	75	346	421	0.82	0.8
I. K.	"	67	m	252	310	662	0.47	3.4
M. F.	"	28	m	30	250	280	0.89	2.2
K. F.	"	45	f	15	365	380	0.96	1.4
Y. H.	"	47	m	95	350	445	0.79	2.1
O. N.	S. Hep.	56	f	115	432	547	0.79	2.8
I. S.	"	34	m	35	310	345	0.90	1.4
S. Y.	"	59	m	65	398	465	0.86	1.5
O. S.	"	40	m	152	400	552	0.72	4.9
H. K.	"	30	m	132	338	470	0.72	1.8
O. S.	Weil's D.	29	m	225	340	565	0.60	2.7
Mean	—	—	—	120	344	471	0.76	2.2

Inf. Hep., infectious hepatitis; S. Hep., serum hepatitis; Weil's D., Weil's disease; B/T, bound PaA/total PaA.

1. Blood PaA Levels

Acute Hepatitis (Tables II and III, Figs. 1 and 2)—Total PaA: Out of 15 cases, the total PaA levels were low in 4, high in 6 and normal in 5. The mean of 15 cases was 471.2 mμg/ml, not very different from that of normal controls. Free PaA: Out of 15 cases, the free PaA level was normal in 4 but high in the remaining 11. Accordingly, the mean of 15 cases was 120.1 mμg/ml, higher than that of normal controls. Bound PaA: Out of 15 cases, the bound PaA level was normal in 6, while the other 9 had low values. Accordingly the mean of 15 cases was subnormal, 344.3 mμg/ml.

The cases having a low total PaA also had low bound form, and those showing a high total PaA also had markedly high free form. Even in cases showing

TABLE III
Laboratory Findings in Patients with Hepatitis

Subject	Co-R	Cd-R	II	BSP	Total protein	Al/G	Cholesterol	
							Total	Ester Q
				%	g/100 ml		mg/100 ml	%
M. T.	3	6	27	15	6.5	1.3	160	60
T. K.	3	8	20	20	7.4	1.4	150	64
T. S.	3	12	80	20	6.2	0.7	212	31
N. T.	9	5	160	—	5.4	0.9	84	26
M. Y.	5	9	8	15	7.3	0.5	160	55
I. K.	6	8	78	—	7.8	1.3	110	35
M. F.	4	7	20	10	6.8	1.0	147	60
K. F.	—3	8	23	—	7.8	0.8	240	67
Y. H.	—2	18	36	—	6.7	1.0	153	46
O. N.	—1	10	42	40	7.5	1.3	160	61
I. S.	5	7	8	20	6.9	1.2	181	56
S. Y.	7	5	13	20	7.3	0.8	179	50
O. S.	3	5	18	15	7.2	1.4	190	55
H. K.	5	6	16	20	—	—	103	57
O. S.	—2	20	60	—	6.4	0.9	102	19
Mean	3.0	9	41	20	6.9	1.0	156	50

R, reaction; BSP, bromosulfalein; II, icteric index; Al/G, albumin/globulin; Q, quotient. The same are applicable in the following tables.

FIG. 1 *Total Blood Pantothenic Acid Levels in Patients with Liver Diseases*
... ±2×standard deviation of normal values.
The same is applicable in the following figures.

FIG. 2 Bound and Free Pantothenic Acid Levels in the Patients with Liver Diseases

normal total PaA, the bound form showed a tendency to decrease and the free form to increase. Thus the bound to total PaA ratio (B/T) was low in 7 cases, and normal in other 8.

Cirrhosis of the Liver (Tables IV and V, Figs. 1 and 2)—Total PaA: Out of 14 cases studied, the total PaA was low in 7, high in 3, and normal in the remaining 4. Thus the mean of the 14 cases was slightly subnormal, 443.6 $\mu\text{g/ml}$. Free PaA: Free PaA was normal in 4, while high in other 10. Thus the mean was high, 113.9 $\mu\text{g/ml}$. Bound PaA: Bound PaA was normal in 6, but low in other 8. The mean was subnormal, 315.6 $\mu\text{g/ml}$.

In most of the patients of this group, bound form was even lower than that in the patients with acute hepatitis, and there was also a tendency for total PaA to decrease further. The ratio, B/T, was low in 5 out of 14, and in other 9 it

TABLE IV
PaA Values in Patients with Liver Cirrhosis

Subject	Diagnosis	Age	Sex	PaA level in blood				PaA in urine
				Free	Bound	Total	B/T	
				μg/ml				mg/day
I. S.	PLC	49	m	370	430	800	0.54	2.1
Y. K.	"	51	f	240	240	480	0.50	2.9
K. T.	"	71	m	70	250	320	0.78	0.9
K. K.	"	42	m	45	375	420	0.89	1.9
M. K.	"	47	m	95	210	305	0.69	1.2
N. M.	"	45	m	120	370	490	0.76	2.3
F. S.	"	50	m	80	270	350	0.77	1.3
O. K.	"	44	m	50	305	355	0.86	1.5
N. H.	"	41	f	15	227	242	0.94	3.9
T. S.	"	37	m	107	450	555	0.81	3.2
M. M.	"	31	m	43	237	280	0.85	2.4
Y. O.	"	49	f	81	403	484	0.83	2.1
S. S.	Hchr	68	f	250	200	450	0.44	2.1
F. T.	"	53	m	228	452	680	0.66	2.5
Mean	—	—	—	114	316	444	0.74	2.2

PLC, portal liver cirrhosis; Hchr, hemochromatosis.

TABLE V
Laboratory Findings in Patients with Cirrhosis

Subject	Co-R	Cd-R	II	BSP	Total protein	Al/G	Cholesterol	
							Total	Ester Q
					<i>g/100 ml</i>		<i>mg/100 ml</i>	
I. S.	8	6	13	30	6.3	0.7	160	47
Y. K.	8	7	20	20	6.1	0.6	135	48
K. T.	8	8	8	—	6.5	0.2	218	57
K. K.	8	5	12	30	5.1	0.5	200	78
M. K.	8	5	18	30	7.6	0.6	140	51
N. M.	9	4	10	20	5.5	0.6	97	46
F. S.	9	4	6	20	6.1	0.3	155	39
O. K.	8	5	11	30	6.7	0.8	189	60
N. H.	6	6	8	30	7.1	0.7	160	49
T. S.	6	5	8	25	7.0	0.9	150	58
M. M.	8	5	8	—	8.0	0.8	109	50
Y. O.	3	20	132	—	7.0	0.7	140	67
S. S.	9	6	26	—	6.4	0.5	97	54
F. T.	9	6	12	15	5.2	0.2	130	26
Mean	7.6	6.6	20.9	25	6.5	0.6	149	52

was almost normal, since both total and bound PaA values were low. The mean value of B/T was 0.737, lower than 0.94 in normal adults.

Neoplasm of the Liver (carcinoma of the liver) (Table VI and VII, Figs. 1 and 2).—Total PaA: Total PaA was high in 8 cases out of 13 and was normal in other 5. Thus the mean was 542.9 $\mu\text{g/ml}$, higher than normal. Free PaA: Free PaA was high in all of 13 cases. The mean was 173.9 $\mu\text{g/ml}$, higher than normal. Bound PaA: Bound PaA was low in 7 out of 13 cases, and normal in other 6. The mean was 369.4 $\mu\text{g/ml}$, lower than that in normal controls.

B/T was low in 9 and its mean in this group of patients was 0.71 lower than that in normal controls.

TABLE VI
Pantothenic Acid Levels in Patients with Liver Neoplasm

Subject	Diagnosis	Age	Sex	PaA level in blood				PaA in urine
				Free	Bound	Total	B/T	
					<i>$\mu\text{g/ml}$</i>			<i>mg/day</i>
H. M.	Prim. L. N.	56	m	160	420	585	0.72	3.3
Y. S.	"	56	m	113	275	388	0.71	2.4
H. A.	"	62	m	120	430	550	0.78	2.5
T. E.	"	63	m	270	290	560	0.52	2.6
N. Y.	"	60	m	150	320	470	0.68	2.9
Y. S.	"	55	m	225	390	615	0.63	2.8
O. Y.	Met. L. N.	70	m	290	280	560	0.50	3.4
H. M.	"	52	m	180	435	615	0.71	3.4
K. A.	"	60	f	228	502	730	0.69	4.8
Y. T.	"	60	m	230	360	590	0.61	2.1
I. S.	"	73	m	105	350	455	0.77	4.0
N. A.	"	28	m	90	390	480	0.81	3.5
K. H.	"	39	m	100	360	460	0.78	3.0
Mean	—	—	—	174	369	543	0.71	3.1

Prim. L. N., primary liver neoplasm; Met. L. N., metastatic liver neoplasm.

TABLE VIII
Influence of Vitamins on Pantothenic Acid Values in Patients with Liver Diseases

Subject	Diagnosis	Age	Sex	PaA level in blood				PaA in urine
				Free	Bound	Total	B/T	
					<i>mcg/ml</i>			<i>mg/day</i>
M. F.	Inf. H.	28	m	{B 30	250	280	0.89	2.2
				{A 50	460	510	0.90	3.1
M. T.	"	20	m	{B 103	263	366	0.72	2.0
				{A 27	399	426	0.94	3.6
T. K.	"	33	m	{B 33	277	310	0.89	1.8
				{A 17.5	405	422.5	0.96	2.1
K. F.	"	45	f	{B 15	365	380	0.96	1.4
				{A 20	390	410	0.95	1.8
H. K.	S. H.	30	m	{B 132	338	470	0.72	1.8
				{A 35	460	495	0.93	3.6
O. S.	"	48	m	{B 152	400	552	0.72	4.9
				{A 28	452	480	0.94	5.6
I. S.	"	34	m	{B 35	310	345	0.90	1.4
				{A 20	360	380	0.95	2.0
N. H.	Portal Cirrh.	41	f	{B 15	227	242	0.94	3.9
				{A 40	386	426	0.91	3.8
K. K.	"	42	m	{B 45	375	420	0.89	1.9
				{A 30	380	410	0.93	3.5
Y. K.	"	51	f	{B 240	240	480	0.55	2.9
				{A 200	220	420	0.50	4.5
Y. O.	"	49	m	{B 81	403	484	0.83	2.1
				{A 90	350	440	0.80	2.2
I. S.	"	49	m	{B 370	430	800	0.54	2.1
				{A 320	390	710	0.55	2.4
F. S.	"	50	m	{B 80	270	350	0.77	1.3
				{A 65	280	345	0.81	2.5
F. T.	Hchr	53	m	{B 228	452	680	0.66	2.5
				{A 205	420	625	0.67	2.1
Y. S.	Prim. L. N.	56	m	{B 228	502	730	0.69	4.8
				{A 210	400	610	0.66	1.9
K. A.	Met. L. N.	60	f	{B 228	502	730	0.69	4.8
				{A 210	400	610	0.66	1.9

As a basic treatment 20 ml of 20 % glucose was given intravenously. Treatment was continued for approximately a month.

B, before; A, after; Inf. H., infectious hepatitis; S. H., serum hepatitis; Cirrh., cirrhosis; Hchr., hemochromatosis; Prim., primary; L. N., liver neoplasm; Met., metastatic.

IX for a month and the changes in blood and urinary PaA levels as well as liver function were studied (Table VIII). In all of the 8 patients (7 of acute hepatitis and 1 of cirrhosis of the liver) whose clinical symptoms and laboratory findings had been improved, lowered total and bound PaA almost returned to normal. Raised PaA values of 3 cases were brought down to normal and a low B/T ratio fell to normal. In 8 patients, having shown no clinical improvement, abnormal liver function and PaA levels did not return to normal.

4. Correlation between Blood PaA Levels and Various Liver Function Tests (Figs. 4 and 5)

Total PaA and Liver Function—No significant correlation could be found between total PaA and the results of various liver function tests.

Free PaA—There was a slightly positive correlation between free PaA and

TABLE IX
Influence of Vitamins on Laboratory Findings in Patients with Liver Diseases

Subject	Co-R	Cd-R	II	BSP	Total protein	Al/G	Cholesterol		Course	Treatment
							Total	Ester Q		
					g/100 ml		mg/100 mg			
M. F.	{B 4	7	20	10	6.8	1.0	147	60	much imp.	PaA 40 mg
	{A 4	5	7	5	7.6	0.8	—	—		
M. T.	{B 3	6	27	15	6.5	1.3	160	60	much imp.	TiA 25 mg
	{A 3	7	6	5	7.2	1.3	170	65		
T. K.	{B 3	8	20	20	7.4	1.4	150	64	much imp.	PaA 40 mg
	{A 3	8	5	5	6.9	1.3	160	60		
K. F.	{B -3	8	23	—	7.8	0.8	240	67	much imp.	OrA 20 mg
	{A 2	9	9	15	7.0	0.6	234	62		
H. K.	{B 5	6	16	20	—	—	108	57	much imp.	PaA 40 mg
	{A 4	7	7	5	6.7	1.0	120	65		
O. S.	{B 3	5	18	15	7.2	1.4	190	55	much imp.	TiA 25 mg
	{A 4	7	5	5	7.5	1.5	178	59		
I. S.	{B 5	7	8	20	6.9	1.2	181	56	imp.	OrA 20 mg
	{A 4	6	6	15	7.5	0.9	196	63		
N. H.	{B 6	6	8	30	7.6	0.7	160	49	imp.	PaA 40 mg
	{A 6	6	7	15	7.1	0.8	—	—		
K. K.	{B 8	5	12	30	5.1	0.5	200	78	no change	PaA 40 mg
	{A 8	6	12	30	6.2	0.5	178	69		
Y. K.	{B 8	7	20	20	6.1	0.6	135	48	no change	TiA 25 mg
	{A 9	7	40	20	6.0	0.6	140	36		
Y. O.	{B 3	20	132	—	7.0	0.7	140	71	no change	TiA 25 mg
	{A 5	16	100	—	6.9	0.7	160	73		
I. S.	{B 8	6	13	30	6.3	0.7	160	47	no change	PaA 40 mg
	{A 9	5	24	30	5.3	0.6	140	51		
F. S.	{B 9	4	6	20	6.1	0.3	155	39	no change	OrA 20 mg
	{A 8	6	8	30	6.0	0.8	123	50		
F. T.	{B 9	6	12	15	5.2	0.2	130	26	no change	TiA 25 mg
	{A 8	6	15	20	6.1	0.3	140	30		
Y. S.	{B 2	5	15	15	7.1	0.8	150	27	no change	PaA 40 mg
	{A 1	7	20	25	6.0	0.6	140	36		
K. A.	{B 2	5	15	15	7.1	0.8	150	27	no change	TiA 25 mg
	{A 1	7	20	25	6.0	0.6	140	36		

B, before; A, after; imp., improvement; TiA, thioctic acid; OrA, orotic acid.

icteric index of hepatitis patients ($r=0.843$, $P<1\%$). Otherwise, no significant correlation was noted.

Bound PaA and Liver Function—There was no significant correlation.

B/T and Liver Function—When B/T was more than 0.55, there was a positive correlation between the ratio and the ester quotient of cholesterol in all the liver diseases tested ($r=0.848$, $P<1\%$).

DISCUSSION

As for blood PaA, an increase of the free form in 34 out of 42 patients (81%) and a decrease of the bound form in 24 (57%) were observed. B/T was reduced in 20 patients (48%). Therefore, the rise of the free form and the fall of the bound, *i.e.*, decrease of blood B/T may be considered specific, to some extent, to liver diseases. In the patients showing improvement of injured liver function by treatment, B/T had a tendency to return to normal.

The importance of PaA in the living body is ascribed, as clarified by Lipmann

FIG. 4 *Correlation between Free or Bound Pantothenic Acid and Liver Functions*
○, hepatitis; ×, cirrhosis; △, tumor.

FIG. 5 *Correlation of Bound Pantothenic Acid/Total Pantothenic Acid with Liver Functions*

(7), to the important role played by the vitamin as an essential constituent of coenzyme A (CoA). It is well known that CoA and bound PaA act mainly in the liver, a fact of physiological and biochemical importance. The synthesis of CoA from free PaA is assumed to be disturbed in liver injury. Changes in blood PaA levels in the patients with liver diseases as shown in the present study might strongly support the assumption described above. Concerning the

relationship between the PaA content in a living body and liver function, Ueshima (8) noticed some correlations between urinary free PaA and some liver functions. In the present experiment the correlation of blood PaA levels with liver function was investigated. It was observed that the free form of the vitamin in the blood a positive correlation with the icteric index in the patients with actue hepatitis. In the patients with neoplasm of the liver, having severe icterus, increase of the free form of the vitamin in the blood seemed to be higher in grade than that in the patients with cirrhosis of the liver, having slight icterus. Thus the author was led to the conclusion that the rise of free PaA in the blood due to the degradation of the bound form might run parallel with that of blood bilirubin content.

Of interest is the fact that there is a positive correlation in all the patients with liver diseases between the ester quotient of cholesterol and B/T when the latter is above 0.55. It suggests a possible existence of an enzyme in the liver which participates in activating both PaA and cholesterol. Concerning this problem, further studies are needed.

However, the changes in each form of blood PaA did not always correlate well with those of liver function, and therefore it seems difficult to conclude that the changes of blood PaA values are regarded as a criterion for liver injury.

Although renal function should not be neglected in the evaluation of urinary PaA, no correlative study was made in the present investigation. Apart from renal function, it seems reasonable to think that the urinary PaA is reduced due to the decrease of dietary PaA intake in the patients with liver diseases. In order to clarify the result that in the patients with hepatitis and cirrhosis of the liver blood free PaA increased, while urinary PaA was decreased, the PaA loading test may be essential.

SUMMARY

In order to study the pantothenic acid metabolism in liver diseases, blood and urinary levels of the vitamin were determined in the patients with various liver diseases and found the following results.

1. The total level of the vitamin in the blood fractionated into free and bound form according to Lipmann's enzymatic treatment.

In 24 patients with liver diseases, there was an increase of the free form and a decrease of the bound form in 34 and 24 cases, respectively; the ratio of the bound form to the total, B/T, was low in 20 cases.

In the patients, whose impaired liver function was improved by treatment, the B/T ratio tended to return to normal.

The level of the free form in the blood had a positive correlation, to some degree, with the icteric index in hepatitis. The ester quotient of cholesterol had a positive correlation with B/T in all the cases having B/T above 0.55.

2. The urinary elimination of the vitamin was low in hepatitis and cirrhosis, whereas it was almost normal in neoplasm.

ACKNOWLEDGEMENT

The author wishes to express his gratitude to Professor Gyoichi Wakisaka, and to Drs. Akima Miyoshi, and Haruto Uchino of the First Division, Department of Internal Medicine, Kyoto University, for their kind suggestions and advice. Thanks are also extended to the Daiichi Drug Co., Ltd. for their generous supply of calcium pantothenate.

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