2) PRELIMINARY REPORT ON THE CLINICAL OBSERVATIONS ON THE TREATMENT OF *SCHISTOSOMA JAPONICUM* WITH NITRO-THIAZOLE, CIBA 32'644-Ba.

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Introduction

Schistosomiasis japonica in man has been mainly treated with intravenous injection of a trivalent antimony preparation (Sodium antimony tartrate) in Japan. This drug, however, is not always effective even when used intersively and also it has severe side-effects. A new drug, less toxic and more effective in a relatively short period by oral administration has been looked for.

Resently, Lambert (1964) reported that a newly synthesized nitro-thiazole derivative, 1- (5-nitro-2-thiazole) imidazolimdinone (CIBA 32'644-Ba), which is a nonantimonial schistosomicide, has an extremely strong vermicidal effect against

Schistosoma mansoni.

The authors have tried this drug for treatment of patients with *Schistosoma japonicum* in the endemic area of schistosomiasis in Japan. At present the follow-up studies were made only one month after the treatment. A preliminary results presented in this paper.

Mateials and Methods

The clinical trials with this agent were carried out in Shikishima machi, Yamanashi Prefecture which is one of the heavy endemic areas of schistosomiasis in Japan. Nineteen cases which showed no abnormal findings in electrocardiogram examination were selected for this trial. There were 6 males and 13 females, ranging 24 to 61 years old, and all were farmers. Thirteen cases had been suffering from schistosomiasis japonica for 20 years and had been treated with an antimony preparation as show in Table 1.

The drug used was CIBA 32'644-Ba, a nitro-thiazole derivative, 1-(5-nitro-2-thiazole)-2-imidazolimdinone, supplied by CIBA Limited. The daily dosage was 15 mg/kg, divided into 2 doses and administered orally after breakfast and supper, every for from 5 to 7 days. The patients were asked to come every day to the appointed place to receive the drug when the suthors gave them two divided doses to take by themselves in the evening and following morning. On this occasion, each patient was asked about side-effects due to the drug. Urinalysis for albmin, sugar and urobilinogen, blood pressure and liver function tests were given to all of the patients before the treatment, immediately after, one week after and three weeks after the first day of treatment. Stool examination with MIFC centrifugation technique and hatching methnd for miracidium were simultoneously performed twice a week from the completion of the treatment,

Table 1. History and present conditions of the schistosomiasis cases.

No. Cases	Age	Sex	Years after last infection and treatment	Physical signs in Abdomen
1	54	M.	20 years, Stibnal (20 inj.)	
2	64	M.	—	
3	36	M.	—	
4	52	F.	10 years, Stibnal (20 inj.)	
5	54	M.	2 years, Stibnal (26 inj.)	Liver palpable 2 f. b.
6	51	F.	6 years, Stibnal (20 inj.)	
7	43	F.	—	
8	45	M.	2 years,	Liver palpable 1/2 f. b.
9	24	F.	5 years, Stibnal (20 inj.)	Liver palpable 2 f. b.
10	53	F.	8 years, Stibnal (22 inj.)	
11	30	F.	2 years,	Liver palpable 2 f. b.
12	41	F.	(10 years, 2 years, Stibnal (23 inj.)	Liver palpable 1/2 f. b.
13	42	M.	3 years, Stibnal (20 inj.)	Liver palpable 1 f. b.
14	39	F.	—	
15	26	F.	—	
16	49	F.	15 years,	
17	36	F.	2 years, Stibnal (23 inj,)	
18	32	F.	7 years, Stibnal (25 inj,)	Liver palpable 1/2 f. b.
19	34	F.	2 years, Stibnal (22 inj.)	

f. b. ····· finger-breadths.

Stibnal ····· 0.3% Sodium antimony tartrate.

inj. ····· intravenous injections of 20 cc of Stibnal.

Results

1. *Therapeutic effects*

The results of stool examinations made twice a week until 35 days after the first day of treatment are shown in Table 2. A gradual decrease in the number of *Schistosoma* eggs was observed at 7 days after the first day of treatment, and 7 cases out of 19 cases became negative for eggs at 14 days. No living eggs (except degenerated eggs) were found in any of the cases, thereafter, at 21, 28 and 35 days after the first day of treatment. Degenerated eggs were found in 6 cases at 21 days, in 3 cases at 28 days and in 4 cases at 35 days.

2. *Side effects*

a. Subjective symptoms.

All the patients were asked individually about subjective symptoms due to this drug from the following day of the first administration until the symptoms subsided after the end of treatment. The main symptoms were headache, general dullness, anorexia, nausea, vomiting and heavy feeling in the stomach as shown in Table 3. In 2 cases exanthema like urticaria were observed on the whole body on the second day after the end of treatment. The exanthema were red papula without itchiness, which subsided 3 days later. Direct relation between the exanthema and this drug was not cleared.

The above mentioned symptoms except exanthema seemed to be more frequent and more sever with the number of doses administered. There were only two patients who had to lie in bed due to the side effects,

Table 2. Results of stool examinations before, during, and after treatment with nitro-thiazole derivative, CIBA 32' 644-Ba.

No. cases	Age	Sex	Total dosage (gr.)	Daily dose (15mg/kg)	Days of treatment	Before treatment	Days after the first day of treatment					
							3	7	14	21	28	35
1	54	M.	5.04	0.72 gr.	7	+	+	+	−	−	−	−
2	61	M.	5.32	0.76 gr.	〃	+	+	+	−	−	(2)*	(2)*
3	36	M.	5.95	0.85 gr.	〃	+++	+++	++		(1)*	−	(1)*
4	52	F.	4.41	0.63 gr.	〃	+	+	+	−	−	−	
5	54	M.	5.39	0.77 gr.	〃	+	+	+	+	(4)*	(1)*	−
6	51	F.	5.81	0.83 gr.	〃	+	++	+	+	−	−	−
7	43	F.	5.25	0.75 gr.	〃	+	++	+	+	−	−	−
8	45	M.	5.25	0.75 gr.	〃	+	+	+	+	−	−	−
9	24	F.	7.00	1.00 gr.	〃	+	++	+	−	−	−	−
10	53	F.	4.76	0.68 gr.	〃	+	+	+	−	(2)*	−	−
11	30	F.	4.69	0.67 gr.	〃	+	++	+	+	(2)*	(1)*	−
12	41	F.	4.69	0.67 gr.	〃	+	+	+	+	−	−	−
13	42	M.	5.28	0.88 gr.	6	+	+	−	−	(2)*	−	−
14	39	F.	4.32	0.72 gr.	〃	+	−	+	+	(1)*	−	−
15	26	F.	4.32	0.72 gr.	〃	++	++	++	+	−	−	−
16	49	F.	4.20	0.70 gr.	〃	+	+	+	+	−	−	−
17	36	F.	4.50	0.75 gr.	〃	+	+	++	+	−	−	(1)*
18	32	F.	3.65	0.73 gr.	5	++	++	++	+	−	−	−
19	34	F.	4.30	0.86 rg.	〃	+	+	−	−	−	−	(0)*

\+ EPG 1 − 9.
++ EPG 10 − 49.
+++ EPG 50 − 99.
( ) No. of degenerated Eggs.
* living eggs were not found.

Table 3. Side effects during treatment with CIBA 32' 644-Ba

Side effects	Days after the first day of treatments.											
	0	1	2	3	4	5	6	7	8	9	10	11
Headache		11	9	14	12	11	9	9	6	1	1	
Nausea			4	3	4	3(1)	1					
Vomiting		1		2	1(1)		2(2)					
Fatigue		4	4	6	6	7	11	10	9	5	2	
Feeling heavy in the stomach			2		1	1		1	1	1		
Anorexia			3	8	8	7(1)	7	7(1)	3	2		
Loose stool				1	1							
Urticaria									2	2	2	
No. Persons complained / No. examination	0/19	11/19	11/19	16/19	16/19	16/19	16/19	14/19	9/19	5/19	2/19	0/19

( ) : No. of Lying in bed.

Table 4. Liver function tests before and after treatment with CIBA 32' 644-Ba.

No. cases	Age	Sex	T. P.			A/G			TTT			ZST			MG.			T.Ch.			GOT			GPT		
			a.	b.	c.	a.	b.	c.	a.	b.	c.	a.	b.	c.	a.	b.	c.	a.	b.	c.	a.	b.	c.	a.	b.	c.
1	54	M.	7.7	7.8	6.8	1.8	1.3	1.3	2.8	1.4	1.2	6.7	5.7	5.9	9.2	7.6	4.5	230	200	233	15	18	19	5	8	10
2	64	M.	8.0	7.3	6.2	1.4	1.0	1.2	2.6	2.8	2.8	7.9	7.6	7.8	8.8	4.6	6.0	165	253	238	15	16	15	6	5	6
3	36	M.	7.7	7.4		1.3	1.4		1.8	2.1		9.7	6.8		7.5	8.0		165	158		17	14		8	8	
4	52	F.	8.3	7.1	7.4	1.3	1.1	1.2	5 8	5.7	6.9	11.8	11.6	13.3	9.6	6.4		230	218	245	32	47	18	15	25	8
5	54	M.	7.3	7.6	7.7	1.7	1.5	1.5	3.0	3.7	3.8	7.5	6.7	7.4	7.4	4.8	10.6	200	220	241	16	'5	15	5	6	6
6	51	F.	4.0	6.3	7.3	1.5	1.4	1.4	3.0	3.8	3.8	6.6	6.0	7.6	5.5	6.0	5.0	167	203	218	15	15	19	3	3	10
7	43	F.	5.9	5.4	7.7	1.9	2.3	1.5	3.1	2.8	3.6	7.9	6.8	9.0	9.5	5.8	7.2	154	145	177	15	11	11	4	7	7
8	45	M.	8.4	8.0	7.4	1.3	1.2	1.3	3.5	2.8	1.9	2.6	10.9	13.0	7.2	5.5	5.4	183	192	177	16	19	19	4	5	12
9	24	F.	5.8	5.7	7.6	1.5	1.6	1.5	3.0	2.2	3.7	6.9	6.6	8.9	5.4	2.8	4.8	130	112	165	11	11	11	5	4	6
10	53	F.	6.9	6.5	7.7	1.3	0.9	1.0	7.4	5.5	8.3	17.0	14.2	17.5	7.4	7.8	7.2	233	200	242	24	25	20	6	5	10
11	30	F.	5.5	7.7	6.7	1.3	1.2	1.1	1.6	2.0	2.6	6.8	6.7	8.4	5.8	4.4	5.6	195	195	192	9	9	11	4	4	7
12	41	F.	8.3	6.0	7.0	1.3	1.1	1.3	3.2	0.9	2.1	8.3	6.7	8.4	6.6	7.0	6.4	202	227	210	11	11	14	5	2	7
13	42	M.	8.4	8.1	7.6	1.9		1.3	3.6	3.1	3.9	9.5	6.9	9.5				192		215	41	50	21	21	22	18
14	39	F.	10.0	6.8	6.4	1.5	1.5	1.5	2.8	2.6	2.6	6.6	6.4	8.5	9.0	5.4	6.4	183	153	195	17	15	11	5	4	5
15	26	F.	8.9	8.6	7.2	1.5	1.4	1.6	4.5	3.7	3.7	9.4	8.1	9.3	6.2	5.0	4.8	208	203	163	11	9	10	5	2	5
16	49	F.	10.3	7.7	6.9	1.4	1.5	1.6	1.6	1.1	1.1	7.4	7.2	8.1	6.0	7.2	6.0	200	226	187	16	14	17	6	4	9
17	36	F.	5.2	6.4	6.6	1.2	1.3	1.4	3.1	3.2	3.8	6.0	6.2	7.6	7.6	9.2	4.6	134	158	139	13	10	9	5	5	7
18	32	F.	8.2	7.0	7.0	1.1	1.0	1.1	3.1	2.9	2.8	11.2	8.7	11.2	8.6	3.4	4.8	170	168	145	15	12	11	4	4	6
19	34	F.	6.0	6.9	7.6	1.5	1.4	1.7	2.8	2.2	4.1	6.6	6.7	8.5	7.0	4.8	7.0	204	179	218	12	10	11	7	2	4

a. Before treatment
b. Immediately after treatment
c. 3 weeks after the first day of treatment

such as vomiting, nausea and anorexia. However, other patients also seemed to be considerably fatigued on the fifth to the seventh day of adoministration. These symptoms, however, subsided in a very short priod after the end of the treatment, and the patients all recovered completely on the third or fourth day after the completion of the treatment. There were 2 patients who did not complain of any symptom during and after the treatment.

b. Liver function tests.

The results of the liver function tests; total protein (TP), A/G ratio, thymol turbididy test (TTT), Kunkel's test (ZST), total cholesterol (T. Ch), glutamic oxalatic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were shown in Table 4. Before treatment, total protein values were found to be increased abnormally, more than 9.0 g/dl, in 2 patients and decreased abnormally, less than 6.0 g/dl, in 5 patients, but immediately after the completion of the treatment the decreased values were still noted in 2 of the 5 patients, the rest had returned to normal. No abnormal changes in total protein were found in any of the case 2 weeks after the completion of the treatment. Abnormal values in GOT were noted in 2 patients before and immediately after the treatment but they all showed normal values 2 weeks after the treatment. No abnormal values were found in A/G ratio, TTT, total choresterol and GPT throughout the examinations.

It is interesting to note from the above mentioned results that the findings of liver damage induced by this drug were completely negative and on the contrarary, those patinets who showed abnormal values before treatment all showed normal values 2 weeks after treatment. It was quite interesting to find out that, although almost all of the treated patients were of chronic infections, there were not many patinets

Table 5. Changes in body-weight, blood examinations and urine tests of the patients before and after treatment with CIBA 32' 644-Ba.

No. cases	Age	Sex	Body-weight (kg)			Blood examinations: Hemoglobin (Sahli %)			No. of Erythrocytes (X10)			No. of Leukocytes			Urine teste: Albuminuria			Glycosuria			Urobilinogen		
			a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c
1	59	M.	45.0	43.0	44.5	96	98	94	510	548	499	6,000	4,400	5,600	—	—	—	—	—	—	+	+	+
2	64	M.	48.0	48.0	47.5	73	78	80	476	384	440	7,100	7,200	9,600	—	—	+	—	—	—	+	+	+
3	36	M.	53.0	53.5		75	82		438	398		7,200	7,200		—	—		—	—		+	+	
4	52	F.	39.0	37.5	38.0	73	84	82	436	396	415	6,400	6,600	6,600	—	—	—	—	—	—	+	+	+
5	54	M.	48.0	46.5	46.0	80	90	93	414	412	435	6,600	6,400	6,800	Tr.	—	—	—	—	—	+	+	+
6	51	F.	52.0	50.0	50.5	82	90	80	478	430	452	5,200	4,800	4.800	—	—	—	—	—	—	+	+	+
7	43	F.	47.0	47.0	46.0	83	94	92	462	528	461	6,700	6,200	6,400	—	Tr.	—	—	—	—	+	+	+
8	45	M.	47.0	46.5	47.5	88	82	95	454	426	478	6,800	6,200	6,400	—	—	—	—	—	—	+	+	+
9	24	F.	62.0	59.5	59.5	88	87	78	496	496	486	8,000	8,200	7,200	—	—	—	—	—	—	+	+	+
10	53	F.	43.0	42.5	42.5	88	91	95	418	436	501	7,600	6,800	6,200	—	—	Tr.	—	—	—	+	+	+
11	30	F.	42.0	41.0	42.5	75	80	70	414	392	415	6,800	6,000	6,400	—	—	—	—	—	—	+	+	+
12	41	F.	42.0	41.5	41.5	82	82	85	348	352	404	6,800	6,800	6,200	—	—	—	—	—	—	+	+	+
13	42	M.	55.0	53.0	56.0	85	98	95	398	424	440	6,000	4,600	5,400	—	—	—	—	—	—	+	+	+
14	39	F.	45.0	45.0	45.0	78	85	92	602	418	458	9,600	6,400	6,000	—	—	—	—	—	—	+	+	+
15	26	F.	45.0	43.5	44.5	78	76	75	422	478	429	8,200	6,200	6,000	—	—	—	—	—	—	+	+	+
16	49	F.	44.0	41.0	42.5	75	85	80	444	418	472	5,200	4,200	4,600	—	—	—	—	—	—	+	+	+
17	36	F.	47.0	43.5	45.0	80	86	75	446	512	401	7,500	6,200	6,600	—	—	—	—	—	—	+	+	+
18	32	F.	46.0	46.5	45.5	72	78	82	398	378	400	9,200	8,000	7,000	—	—	—	—	—	—	+	+	+
19	34	F.	54.0	52.5	53.0	83	92	85	578	444	456	5,600	4,400	4,600	—	—	—	—	—	—	+	++	+

a. : Before treatment
b. : Immediately after treatment
c. : 2 weeks after the end of treatment
Tr. : trace

Table 6. Changes in the ECG after treatment with CIBA 32' 644-Ba.

No. cases	Days of treatment	Flattening of T wave			Depression of ST			Increase of R amplitude		
		a	b	c	a	b	c	a	b	c
1	7 days	−	0.2−0.3 mV +	0.2−0.3 mV +						
2	〃	−	0.1−0.2 mV +	0.1−0.2 mV +						
3	〃	−	0.3−0.4 mV +							
4	〃									
5	〃	−	0.2−0.3 mV +	0.2−0.3 mV +	−	+	−			
6	〃	−	0.2−0.3 mV +	−						
7	〃	−	0.2−0.4 mV +	−	+	+	−			
8	〃	−	0.2−0.4 mV +	0.1−0.2 mV +						
9	〃									
10	〃	−	0.2−0.3 mV +	0.2−0.3 mV +						
11	〃									
12	〃									
13	6 dyas									
14	〃									
15	〃	−	0.1 mV +	0.1 mV +				−	0.2mV+	0.2mV+
16	〃									
17	〃									
18	5 days	−	0.2−0.3 mV +	−						
19	〃									

a . : Before treatment
b . : Immediately after treatment
c . : 2 weeks after the end of treatment

\+ : Slight change
( ) : Showing the difference(mV) from the normal level.

with damaged liver function due to schistosomiasis.

c. Body weight, blood and urine tests.

Body weigh, haemoglobin index, blood cell count and blood picture were examined as shown in Table 5. No abnormal findings in these tests except slight decresse in body weight were noted before, immediately after, and two weeks after the treatment, Brown coloured urine was noted during administration and about 24-48 hours after the last administration, but no abnormal findings in urinalysis were noted.

d. Electrocardiogram examination.

The main changes found in ECG immediately after the end of treatment were the slight flattening of T wave in 10 cases, slight depression of ST in 2 cases (one of which showed the same change before treatment), and decrease of R amplitude in one case as shown in Table 6 and Fig. 1−4. Six of the 10 cases which showed flattening of T wave and the case which showed slight decrease of R amplitude had not yet completely returned to normal 2 weeks later. No abnormal findings were noted in the blood pressure.

Discussion

In the present study 12 patients received a daily dose of 15 mg/kg of CIBA 32' 644-Ba every for 7 days, 5 patients for 6 days and 2 patients for 5 days. Those 7 patients who did not receive the drug for 7 days were adviced to stop taking more because of vomiting. No living *Schistosoma* eggs were found in the feces in any case regardless of the doses administered during the period from 21 days to 35 days after

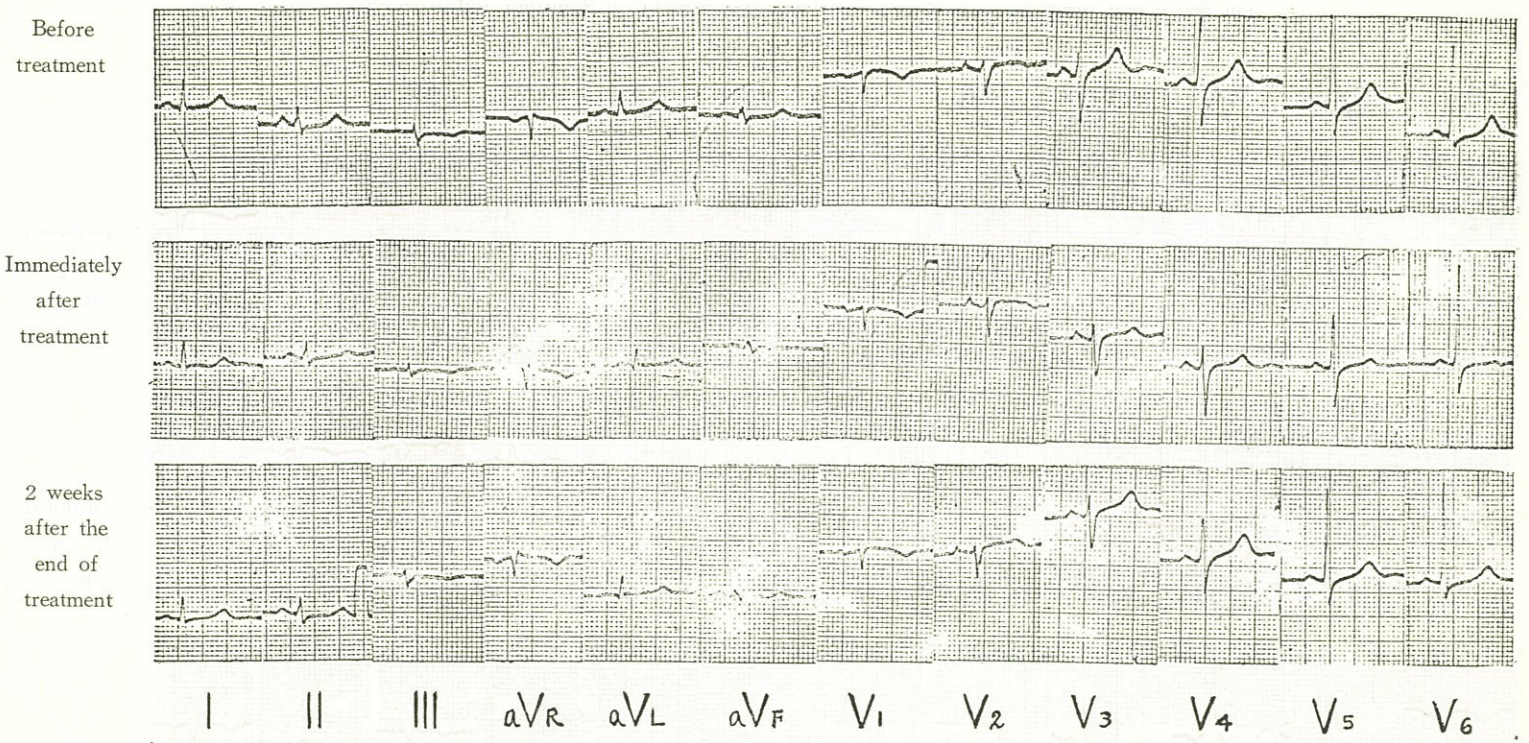

Fig. 1 Slight flattening of T wave was seen immediately after treatment but it returned to normal 2 weeks after the end of treatment. (Case No. 6)

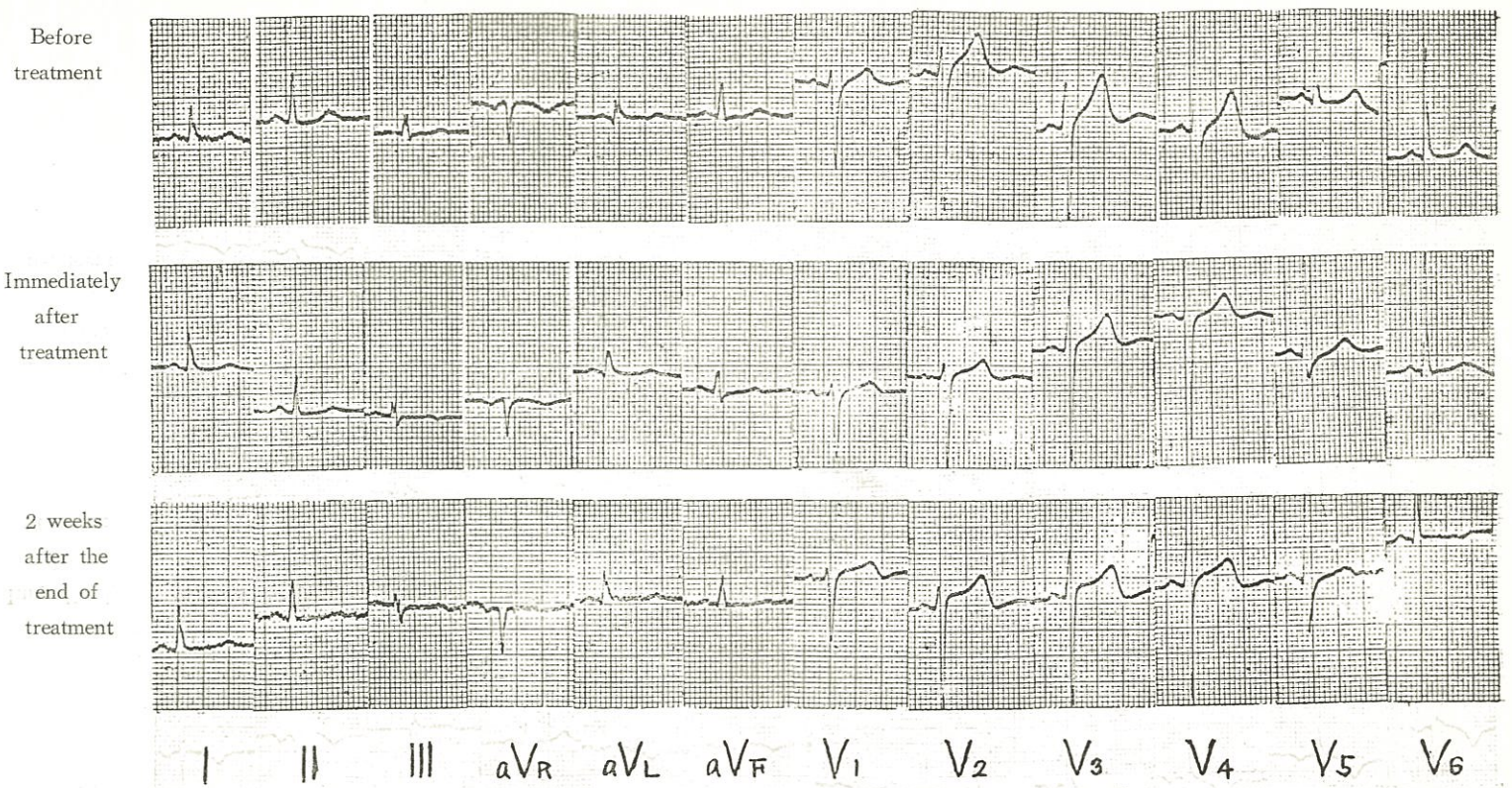

Fig. 2 Slight flattening of T wave was seen immediately after treatment and it had not completely returned to normal 2 weeks after the end of treatment. (Case No. 2)

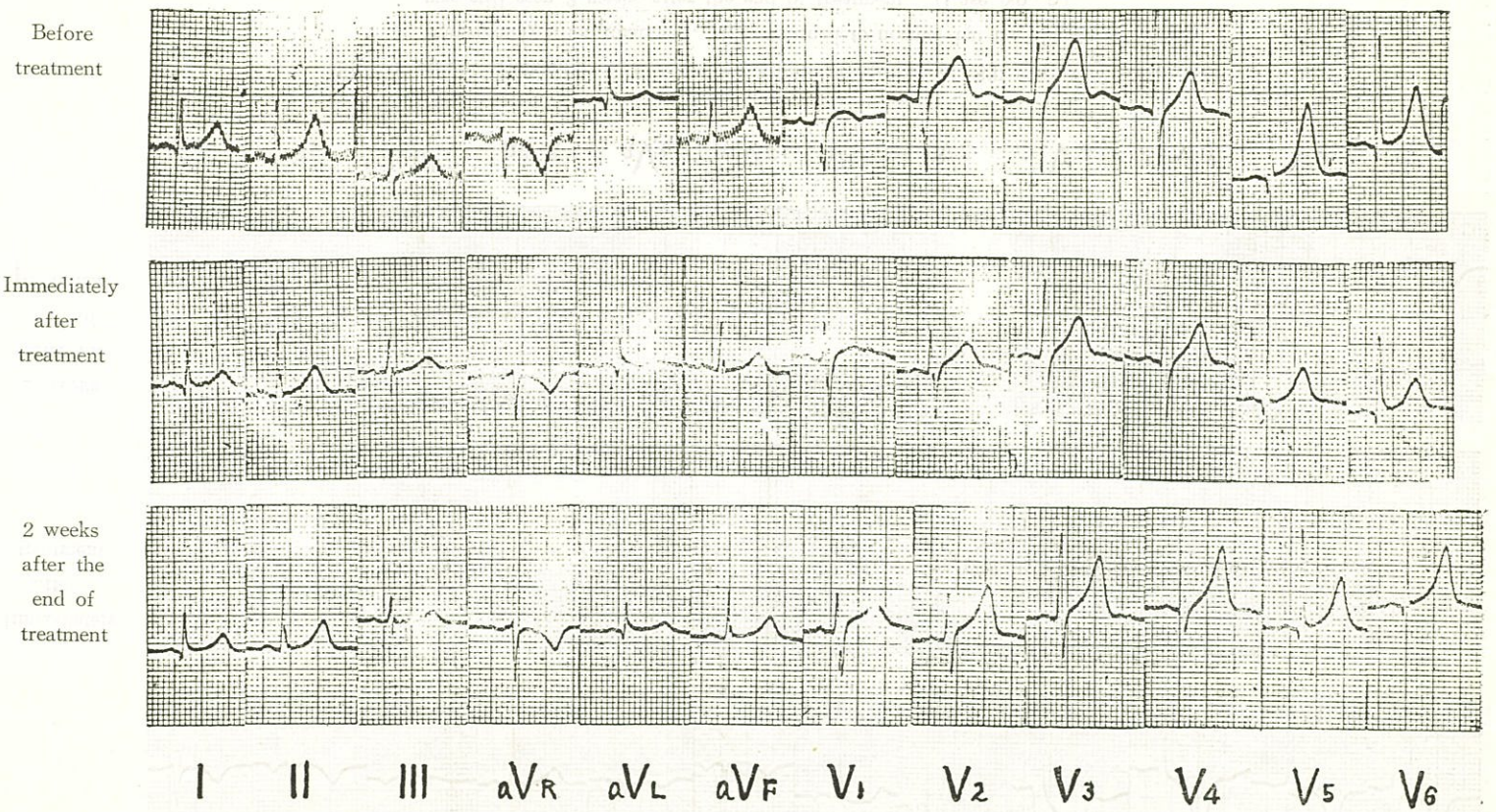

Fig. 3 Slight flattening of T wave was seen immediately after and it returned almost to normal 2 weeks after the end of treatment. (Case No. 8)

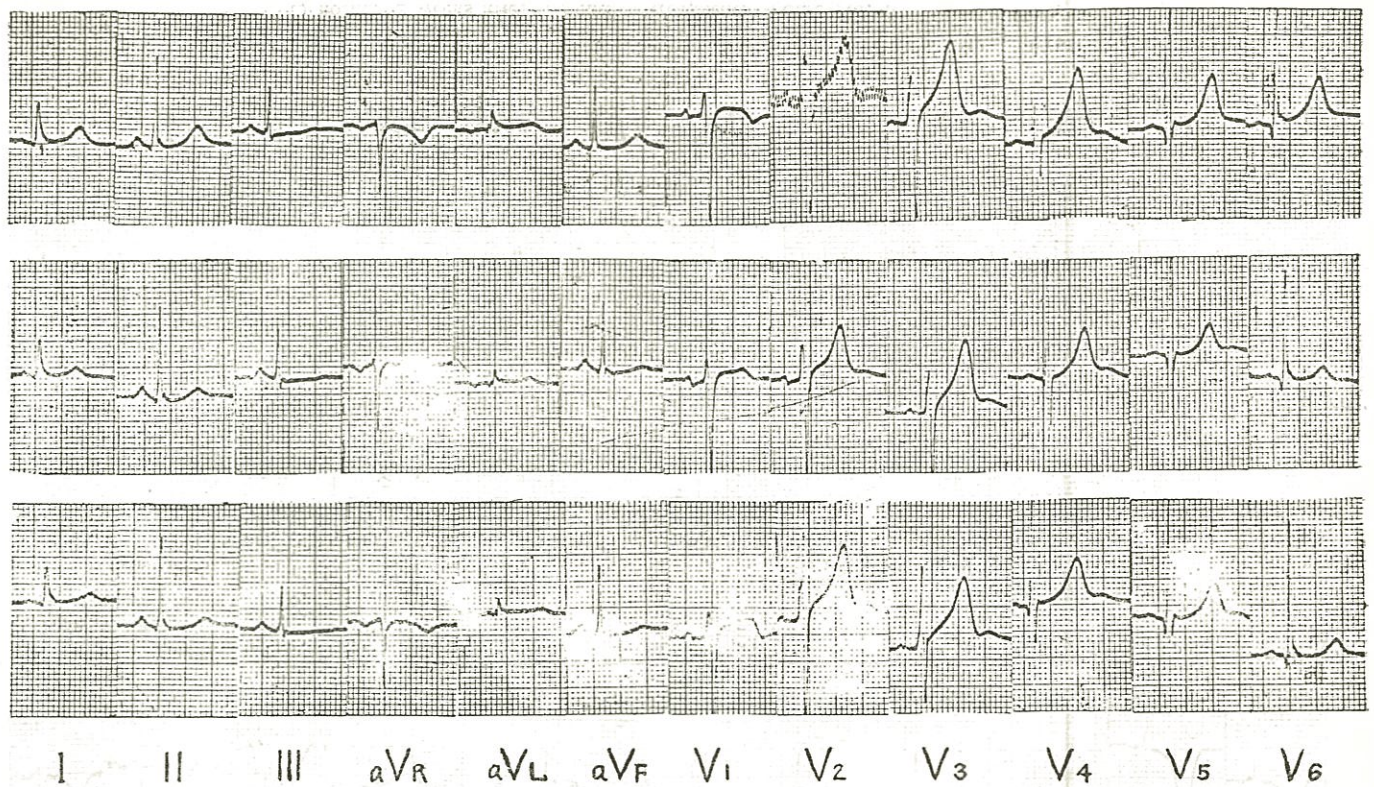

Fig. 4 Slight flattening of T wave and slight depression of ST (in aV_F) were seen immediately after treatment. ST returned to normal but the change in T wave was still seen 2 weeks after the end of treatment. (Case No. 5)

the first day of treatment. It seems to be very difficult to evaluate the effect of this drug against schistosomiasis japonica. It is not yet known how long followed-up examination should be continued after the treatment.

As the side effects, headache, general dullness, anorexia, nause and vomiting were found in 17 (89.4%) out of 19 patients. Most of these side effects seemed to be not so severe that the patients had to lie in bed during the treatment except for 2 patients who were prostrate with vomiting.

The patients treated with CIBA 32'644-Ba said that the side effects of the drug were much milder than those of antimony preparation which they had experience previously, perhaps because of this, the patients bore their discomfort due to CIBA 32'644-Ba patiently, but close attention must, neverthless, be paid to the side effects when administering this drug. Uriicaria-like exanthema appeared on the whole body in 2 patients, 2 to 3 days after completing the administration. A study should be done to make clear whether this side-offect is due to this drug or not.

Some changes in the electrocardiogram were noted in 10 patients on the examination immediately after treatment. 3 of them had returned to normal one week later the changes were still noted 2 weeks later in 7 patients. None of the changes, however, seemed to be associated with any clinical sign or symptom.

From the above mentioned rsults, although the follow-up observations after treatment were not long enough, the effect of this drug obtained until now would be excellent compared with the results higherto available wtih other drugs. The authors think that it is a great advance that the treatment can be completed with oral administration in 5 to 7 days.

Conclusion

In the form of mass treatment, nitro-thiazole derivative, CIBA 32'644-Ba, was given orally in 19 cases of schistosomiasis japonica in Shikisima-machi in Yamanashi Prefecture. Daily dosage of 15 mg/kg was administered consecutively for 7 days in 12 cases, 6 days in 5, 5 days in 2. The results of stool examinations 5 weeks after the beginning of the treatment showed markedly good effect in all. That is, by the stool examinations 21 to 35 days after the beginning of treatment, the *Schistosoma* eggs with living miracidia could not be detected at all in any case and only a few degenerated dead eggs were found in a few cases. No miracidium was found in any case by the haching test. Follow-up studies were still going on. The side-effets due to this drug have been especially carefully studied, and no case have such sever symptoms, which were higherto noted with the antimonial preparations, occurred. No pathological findings have been noted in the various clinical and laboratory examinations except for the slight changes of the electrocardiogram.

Though the follow-up results are not completed, it seems that a great advance in the treatment of schistosomiasis japonica can be expected hereafter by the development of this drug.

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