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Objekttyp: **Article**

Zeitschrift: **Acta Tropica**

Band (Jahr): **23 (1966)**

Heft (9): **Thérapeutique nouvelle de la Bilharziose et de l'amibiase : Symposium de Lisbonne 2 au 4 Juin 1965**

PDF erstellt am: **09.08.2024**

Persistenter Link: https://doi.org/10.5169/seals-311382

Preliminary Report of Clinical Observations on the Treatment of *Schistosomiasis japonica* with the nitrothiazole Derivative CIBA 32644-Ba

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Introduction

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

Recently, LAMBERT (1964) reported that a newly synthesised nitrothiazole derivative (CIBA 32644-Ba), which is a non-antimonial schistosomicide, has an extremely strong vermicidal effect against *Schistosoma mansoni*.

The authors have tried this drug for the 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. Preliminary results are presented in this paper.

Materials and Methods

The clinical trials with preparation CIBA 32644-Ba–1-(5-nitro-2-thiazolyl)-2-imidazolidinone were carried out in Shikishima machi, Kofu City, Yamanashi Prefecture, which is one of the heavy

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TABLE 1

History and present conditions of the schistosomiasis cases

Case No.	Age	Sex	Years after last infection and treatment	Physical signs in abdomen
1	54	M.	20 years, Stibnal	
2	64	M.	—	
3	36	M.	—	
4	52	F.	10 years, Stibnal	
5	54	M.	2 years, Stibnal	liver palpable
6	51	F.	6 years, Stibnal	
7	43	F.	—	
8	45	M.	2 years	liver palpable
9	24	F.	5 years, Stibnal	liver palpable
10	53	F.	8 years, Stibnal	
11	30	F.	2 years	liver palpable
12	41	F.	10 years, 2 years } Stibnal	liver palpable
13	42	M.	3 years, Stibnal	liver palpable
14	39	F.	—	
15	26	F.	—	
16	49	F.	15 years	
17	36	F.	2 years, Stibnal	
18	32	F.	7 years, Stibnal	liver palpable
19	34	F.	2 years, Stibnal	

Stibnal: 0.3% sodium antimony tartrate (20-26 injections).

endemic areas of schistosomiasis in Japan. Nineteen patients who showed no abnormal findings in their electrocardiograms were selected for this trial. There were 6 males and 13 females, ranging from 24 to 61 years old, all of whom were farm-workers. Thirteen cases had been suffering from *schistosomiasis japonica* for 20 years and had been treated with an antimony preparation, as shown in Table 1. The daily dosage was 15 mg/kg, given orally in 2 divided doses, after breakfast and after supper, for periods ranging from 5 to 7 days. The patients were asked to come every day to the appointed place to receive the drug, and the authors gave them two divided doses to take by themselves in the evening and on the following morning. On each visit, they were questioned about side effects due to the drug. Urinalysis for albumin, sugar and urobilinogen, blood-pressure recording, and liver function tests (see below) were carried out in all patients before treatment, immediately after, one week after and three weeks after the first day of treatment. Stool examinations with the MICF centrifugation technique and the hatching method for miracidium were simultaneously performed twice a week from the completion of the treatment.

TABLE 2

Results of stool examinations before, during and after treatment with CIBA 32644-Ba

Case No.	Age	Sex	Total dosage (g)	Daily dose (15 mg/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 g	7	+	+	+	−	−	−	−
2	61	M.	5.32	0.76 g	7	+	+	+	−	−	(2)[1]	(2)[1]
3	36	M.	5.95	0.85 g	7	+++	+++	++		(1)[1]	−	(1)[1]
4	52	F.	4.41	0.63 g	7	+	+	+	−	−	−	
5	54	M.	5.39	0.77 g	7	+	+	+	+	(4)[1]	(1)[1]	−
6	51	F.	5.81	0.83 g	7	+	++	+	+	−	−	−
7	43	F.	5.25	0.75 g	7	+	++	+	+	−	−	−
8	45	M.	5.25	0.75 g	7	+	+	+	+	−	−	
9	24	F.	7.00	1.00 g	7	+	++	+	−	−	−	−
10	53	F.	4.76	0.68 g	7	+	+	+	−	(2)[1]	−	−
11	30	F.	4.69	0.67 g	7	+	++	+	+	(2)[1]	(1)[1]	−
12	41	F.	4.69	0.67 g	7	+	+	+	+	−	−	−
13	42	M.	5.28	0.88 g	6	+	+	−	−	(2)[1]	−	
14	39	F.	4.32	0.72 g	6	+	−	+	+	(1)[1]	−	
15	26	F.	4.32	0.72 g	6	++	++	++	+	−	−	−
16	49	F.	4.20	0.70 g	6	+	+	+	+	−	−	−
17	36	F.	4.50	0.75 g	6	+	+	++	+	−	−	(1)[1]
18	32	F.	3.65	0.73 g	5	++	++	++	+	−	−	−
19	34	F.	4.30	0.86 g	5	+	+	−	−	−	−	(1)[1]

+ = EPG 1–9; ++ = EPG 10–49; +++ = EPG 50–99.
( ) = No. of degenerated eggs; [1] living eggs were not found.

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 7 days after the first day of treatment, and 7 out of 19 cases became negative for eggs after 14 days. No living eggs (except degenerated eggs) were found in any of the patients 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.

a) Subjective Symptoms

All the patients were asked individually about subjective symptoms due to the drug from the day following the first administration until the symptoms subsided after the end of treatment. The main symptoms were headache, general dullness, anorexia, nausea, vomiting and a heavy feeling in the stomach (see Table 3). In 2 cases, urticaria-like exanthema was observed on the whole body on the second day after the end of treatment. The exanthema was characterised by red papula without itchiness, which subsided 3 days later. A direct relationship between the exanthema and the drug was not established.

The incidence and severity of the above-mentioned symptoms, except the exanthema seemed to increase in proportion to the number of doses administered. There were only two patients who had to stay in bed owing to the side effects, such as vomiting, nausea and anorexia. However, other patients also seemed to be considerably fatigued on the fifth to the seventh day of administration. These symptoms, however, subsided within a very short period 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 symptoms during and after the treatment.

b) Liver Function Tests

The following liver function tests were carried out: total protein (TP), A/G ratio, thymol turbidity test (TTT), Kunkel's test (ZST), total cholesterol (T.Ch.), glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT). Before treatment, total protein values were found to be abnormally high (more than

TABLE 3

Number of patients with given side effects during treatment with CIBA 32644-Ba

Side effects	0	1	Days after the first day of treatment									
			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					
Vomiting		1		2	1		2					
Fatigue		4	4	6	6	7	11	10	9	5	2	
Heavy feeling in the stomach			2		1	1		1	1	1		
Anorexia			3	8	8	7	7	7	3	2		
Loose stools				1	1							
Urticaria									2	2	2	
Number of persons complaining	0	11	11	16	16	16	16	14	9	5	2	0
Number examined	19	19	19	19	19	19	19	19	19	19	19	19

9.0 g/ml) in 2 patients, and abnormally low (less than 6.0 g/ml) in 5 patients; immediately after the completion of 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 cases 2 weeks after the completion of the treatment. Abnormal values of 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 cholesterol and GPT throughout the examinations.

It is interesting to note from the above-mentioned results that there was no evidence of liver damage induced by this drug. On the contrary, those patients who showed abnormal values before treatment all showed normal values 2 weeks after treatment. It was also quite interesting to find out that although almost all of the treated patients had chronic infections, there were not many patients with damaged liver function due to schistosomiasis.

c) Body Weight, Blood, and Urine Tests

Body weight, haemoglobin index and red and white cell counts were obtained. There were no abnormal findings in these tests, except that a slight decrease in body weight was noted in some patients 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) Electrocardiographic Examination

The main changes found in the ECG immediately after the end of treatment were a slight flattening of the T wave in 10 cases, a slight depression of the ST segment in 2 cases (one of which showed the same change before treatment), and a decrease in the amplitude of the R wave in one case (see figures). Six of the 10 cases which showed flattening of the T wave and the case which showed a slight decrease of R amplitude had not yet completely returned to normal two 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 32644-Ba every day for 7 days, 5 patients for 6 days and

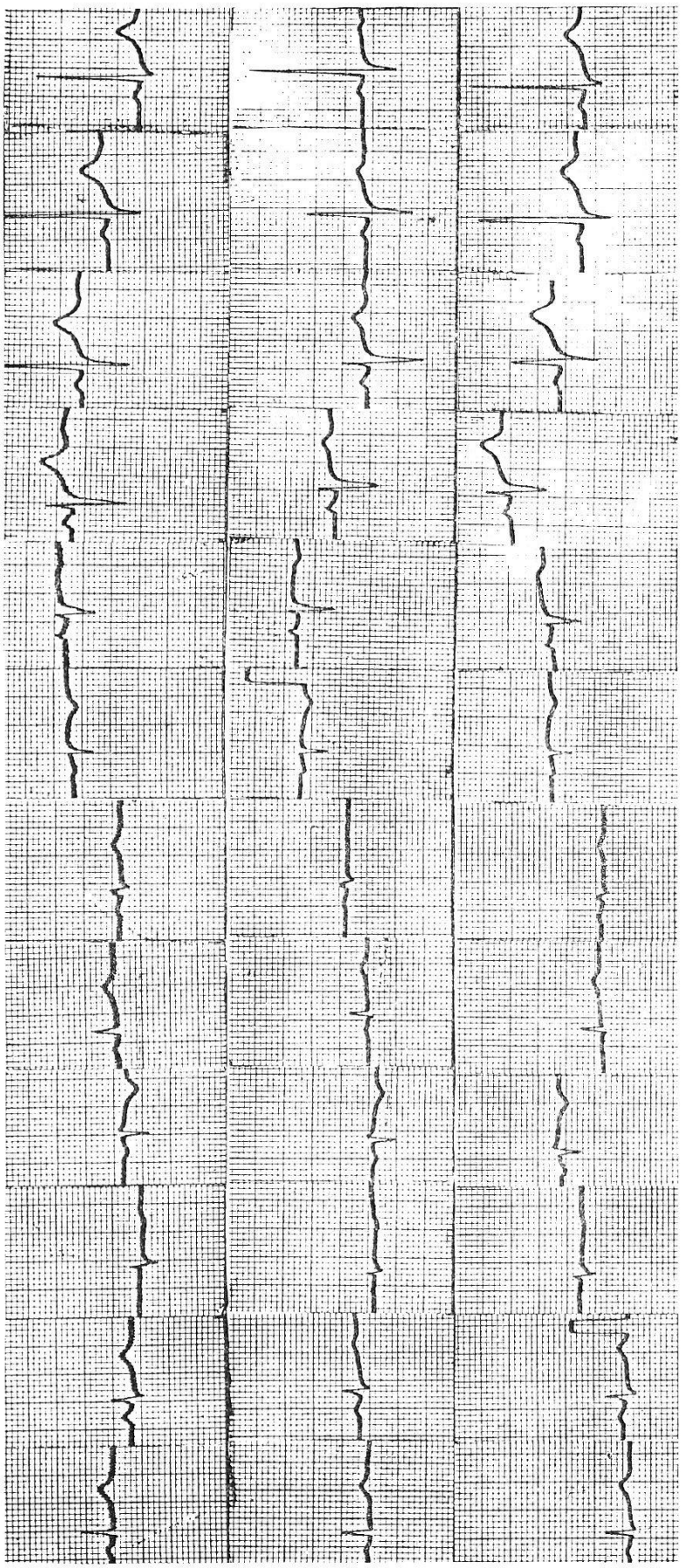

Fig. 1. Slight flattening of T wave was seen immediately after treatment but it returned to normal 2 weeks after the end of treatment.
(Case No. 6)

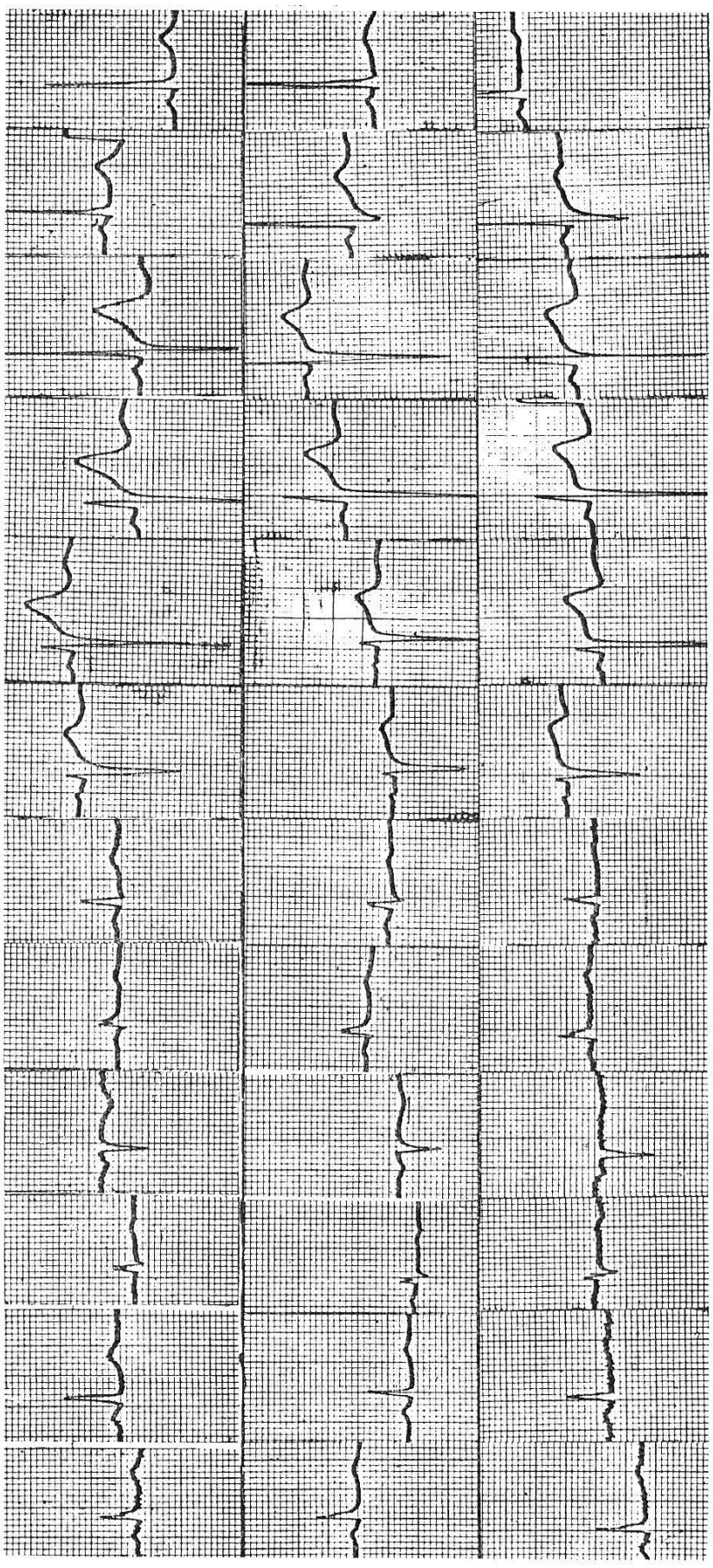

Fig. 2. Slight flattening of T wave was seen immediately after treatment and it had not completely returned to normal 2 weeks after the end of treatment. (Case No. 2)

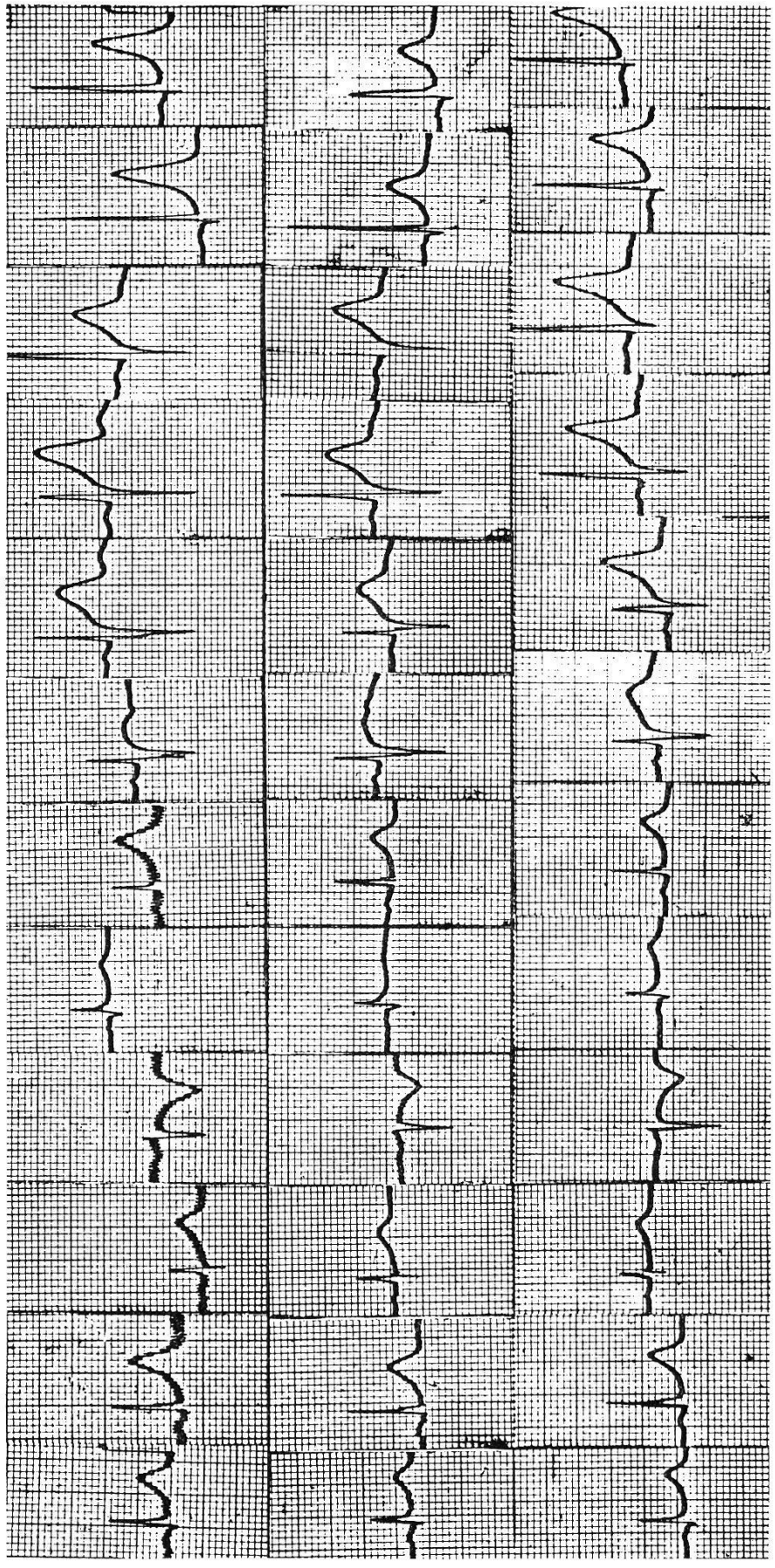

Fig. 3. Slight flattening of T wave was seen immediately after and it returned almost to normal 2 weeks after the end of treatment. (Case No. 8)

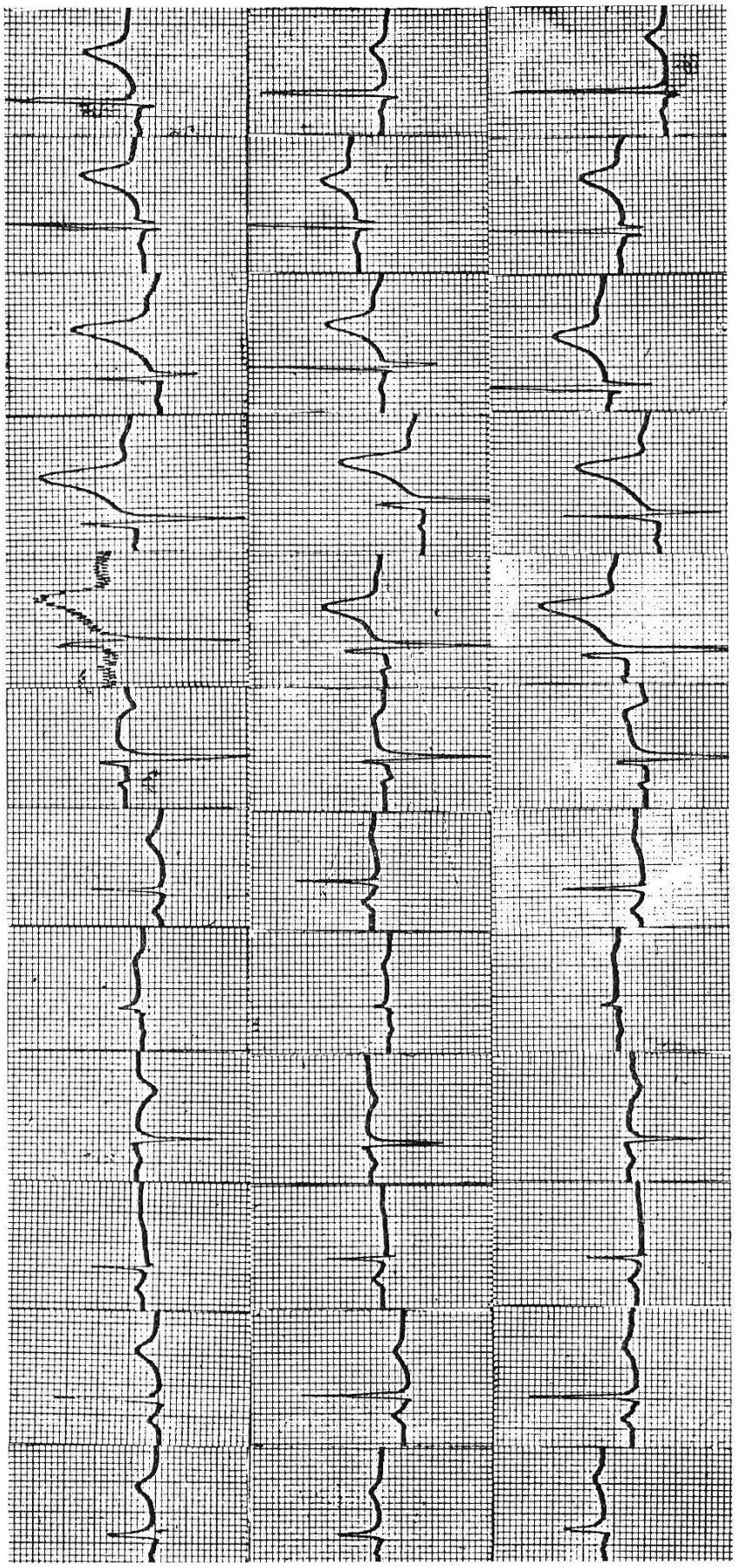

Fig. 4. Slight flattening of T wave and slight depression of ST (in aVF) were seen immediately after treatment. ST returned to normal but the change in T wave was still seen 2 weeks after the end of treatment. (Case No. 5)

2 patients for 5 days. Those 7 patients who did not receive the drug for 7 days were advised to discontinue it because of vomiting. No living *Schistosoma* eggs were found in the faeces in any case, regardless of the dose administered, during the period from 21 days to 35 days after 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 for how long follow-up is necessary after treatment.

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

The patients treated with CIBA 32644-Ba said that the side effects of the drug were much milder than those of an antimony preparation which they had experienced previously. Perhaps because of this, the patients bore their discomfort due to CIBA 32644-Ba patiently. But close attention must, nevertheless, be paid to the side effects when administering this drug. Urticaria-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 sure whether this side effect is due to the 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, but 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 results, although follow-up observations after treatment have not been continued for long enough, we can say that the effect of this drug up to now may be considered excellent compared with the results hitherto obtained with 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.

Conclusions and Summary

In the form of mass-treatment, the nitrothiazole derivative, CIBA 32644-Ba, was given orally to 19 cases of *schistosomiasis japonica* in Shikishima machi in Yamanashi Prefecture. A daily dosage of 15 mg/kg was administered consecutively for 7 days in 12 cases, for 6 days in 5 cases, and for 5 days in 2 cases. The results of stool examinations 5 weeks after the beginning of the treatment showed a markedly good effect in all patients. That is to say that,

in stool examinations 21 to 35 days after the beginning of treatment, the *Schistosoma* eggs with living miracidia could not be detected 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 hatching test. Follow-up studies are still going on. The side effects due to this drug have been especially carefully studied and in no case have such severe symptoms occurred as were hitherto noted with the antimonial preparations. No pathological findings have been noted in the various clinical and laboratory examinations, except for slight changes in the electrocardiogram.

Though the follow-up examinations are not completed, it seems that a great advance in the treatment of *Schistosomiasis japonica* can be expected as a result of the development of this drug.

Conclusions et Résumé

Sous forme de traitement de masse, le CIBA 32644-Ba fut donné par voie orale à 19 malades infestés par *S. japonicum*. Une dose journalière de 15 mg/kg fut administrée pendant 7 jours chez 12 malades, pendant 6 jours chez 5 malades et pendant 5 jours chez 2 malades. Le résultat de l'examen coprologique 5 semaines après le début du traitement a montré un effet très appréciable chez tous les malades ; 21 à 35 jours après le début du traitement, aucun cas ne montrait d'œufs à miracidia vivants, et seuls quelques œufs morts ou dégénérés furent observés dans quelques cas. Aucun miracidium ne fut trouvé au test d'éclosion. La poursuite des examens parasitologiques continue.

Les effets secondaires dus au traitement ont été étudiés de façon particulièrement attentive et dans aucun cas ne furent observés des symptômes sévères, tels qu'ils se produisent lors du traitement aux dérivés stibiés. Les examens cliniques et de laboratoire n'ont révélé aucune trouvaille pathologique, sauf de légères modifications du tracé électrocardiographique.

Quoique les examens parasitologiques n'aient pas encore été poursuivis suffisamment longtemps, il apparaît que le développement du CIBA 32644-Ba représentera un gros pas en avant dans le traitement de la schistosomiase à *S. japonicum*.

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