

Failure of Jonit (phenylene-diisothiocyanate-1, 4) in the Treatment of Clonorchiasis

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No satisfactory chemotherapeutic measures have been yet established in the treatment of infection with *Clonorchis sinensis*, though many drugs have been tested clinically on the patients or experimentally on the infected animals.

It has been reported that "Hetol" of Hoechst Co, -1, 4-bistrichloromethylbenzol- which was proven effective against fascioliasis of sheep and cattle¹ has shown the definite therapeutic response of the patients infected with *C. sinensis*. However, the toxic effects of the drug have never been yet completely ruled out^{2, 3, 4}. Later, the clinical trials of this drug in humans was prohibited by the Farbwerke Hoechst AG. from the toxicological point of view.

Clonorchiasis constituted one of the most important national public health problems in Korea. In this connection, the effective chemotherapeutic agent against the liver fluke disease is urgently needed for conducting the control programme on this trematode infection.

Jonit (phenylene-diisothiocyanate-1, 4) was already known as effective against hookworm infections^{5, 6}. However there is no information available whether this is also effective for clonorchiasis.

Prof. Mohr von Bernhard Nocht-Institut suggested that Jonit does appear to act also on *Clonorchis* from his own experience, in which

he treated three cases in Hamburg, West Germany (cited from the communication to Han-Dok Remedia in Seoul).

In view of the above information, it appeared of interest to know the effect of Jonit in *Clonorchis* infections.

Materials and Methods

Selection of cases for treatment with Jonit: Sixty-seven egg-positive cases of *Clonorchis* screened by fecal examination were selected mostly from the inhabitants who live in the vicinity of Kimhae and Pusan, South Kyungsang Do (=province) and included with some of additional cases from Seoul. Kimhae County is one of the most endemic areas of clonorchiasis in Korea showing over 50 percent of rate of infection among general population. The cases consist of 57 male and 10 female patients, ranging from 11 to 68 years of age, and divided into four groups; the groups indicating E. P. G. (Eggs per Gram of feces) less than 1,000; 1,100 to 5,000; 5,100 to 10,000; and over 11,000.

All of these patients were administered with Jonit. Only 43 out of 67 cases given drug were completed with the post-treatment follow-ups. The additional drug administration was also conducted twice to four times for some of patients (Table 1).

Dosage schedule: The dosage for the patients

Table 1. Cases of drug administration and follow-up study.

Total number of specimens examined for the case detection (by direct smear).....	125
No. of the egg-positives found.....	80
No. of cases selected for the first medication.....	67
No. of cases to whom the follow-ups were made	43

was the same as that employed in the treatment of hookworm; 100 mg, every 12 hours for 3 doses; i. e., 3 x 100 mg, every 12 hours for 67 cases. The total doses received of each patient are varied from 300 mg to 1,200 mg with different intervals.

Evaluation: In a chronic infection of *Clonorchis*, a favorable therapeutic response is usually detected by rapid, remarkable reduction of egg-outputs and gradual disappearance of eggs in the feces. These criteria have long been used in attempting to evaluate the chemotherapeutic response. In this study, the direct smear technique was applied for the detection of the

egg-positives and among them, the egg counting technique due to Stoll and Hausherr (1926) was employed for the selection of cases according to the intensity of infection.

Prior to treatment, one to three egg counts were obtained within a week on the 67 patients. The follow-up was mostly carried out over a period of four weeks after the medication. However, in some instances, the follow-up egg counts were also made with in one to three weeks. The negative conversion in egg-counting technique after treatment was ascertained by the formalin-ether sedimentation technique.

Main subjective symptoms and side effects were checked by careful inquiry during and after treatment. The examinations of vital signs and other laboratory findings; blood and urine analysis etc. were also carried out on the some of patients.

Results

Table 2, 3, and 4 present the changes of

Table 2. Egg-Counts(E. P. G.) in Jonit-treated Patients. Group I (Initial E. P. G. :Less than 1,000).

Pt. No.	Dosage Time & Date	Pretreatment (in average)	During and Post-Treatment (D+n)*
25	1:21/Apr.	100	100(D+30)
21	4:21/Apr. 17, 25/May 10/June	400	400(D+30)
22	1:21/Apr.	400	500(D+30), 400(D+63)
28	1:26/Jan.	400	400(D+7)
53	2:30/Jan. 22/Feb.	500	2,900(D+270)
13	1:21/Apr.	600	800(D+30)
11	4:21/Apr. 17, 25/May 10/June	700	6,000(D+270)
10	1:21/Apr.	900	800(D+30), 500(D+63)
32	1:26/Jan.	900	900(D+7)
34	1:3/Jan.	900	1,200(D+9), 2,300(D+34), 2,100(D+64), 1,400(D+89), 1,400(D+103).
37	1:21/Apr.	900	900(D+8), 200(D+14), 200(D+25), 900(D+32), 200(D+39), 3,500(D+58).
43	2:31/Jan. 22/Feb.	1,000	500(D+38), 700(D+270)
2	1:21/Apr.	500	0(D+30)**

*D+n:n days after treatment

**Positive in formalin-ether technique

Table 3. Egg-Counts(E.P.G.) in Jonit-treated Patients. Group 2 (Initial E.P.G.:1,100-5,000).

Pt. No.	Dosage Time & Date	Pretreatment (in average)	During and Post-Treatment (D+n)*
24	4:21/Apr. 17/May 25/May 10/June	1,100	900(D+30), 1,100(D+63), 1,600(D+187)
4	1:21/Apr.	1,300	900(D+30)
36	1:13/Feb.	1,500	600(D+7), 600(D+12), 200(D+19), 200(D+53), 600(D+60), 500(D+96)
14	1:21/Apr.	1,700	1,700(D+30), 700(D+187)
47	2:31/Jan. 22/Feb.	1,900	300(D+38), 900(D+270)
20	1:21/Apr.	2,000	800(D+30), 600(D+63), 500(D+187)
7	4:21/Apr. 17,25/May 10/June	2,200	4,400(D+30), 2,900(D+63), 1,900(D+187)
46	2:31/Jan. 22/Feb.	2,500	4,300(D+38)
3	4:21/Apr. 17,25/May 10/June	2,700	3,200(D+187)
15	1:21/Apr.	3,100	5,800(D+30), 3,000(D+63)
26	1:26/Jan.	3,200	2,400(D+7), 2,000(D+14), 2,900(D+21)
57	31/Jan. 2:22/Feb.	3,400	900(D+30), 1,700(D+270)
40	1:11/May	3,400	3,300(D+7), 4,500(D+15), 3,000(D+36), 2,600(D+61), 600(D+96)
56	2:31/Jan. 22/Feb.	3,700	1,500(D+38), 0(D+270)**
6	1:21/Apr.	4,300	4,200(D+30)
44	2:31/Jan. 22/Feb.	4,700	6,600(D+38), 4,400(D+270)

*D+n: n days after treatment

**Positive in formalin-ether technique

egg-output in feces of the patients in each four groups before, during and after treatment of Jonit. Most cases were not hospitalized. However, extreme care and repeated health education for the patients were to ensure that none had been exposed to the possible reinfection since the treatment begun. Therefore it is certainly believed that no possibility of reinfection is considered in this period of experiment.

As shown in the above tables, there was none of the case who showed the complete negative conversion of the egg-output in feces. In instances three in the group 1, 2 and 4, egg was not detected in the egg-counting technique, but

it was found positive in formalin-ether concentration technique.

It is apparent, despite the fluctuation of egg-output, that Jonit had little effect on E.P.G, during the course of therapy and it will be clearly seen that Jonit did not cure any of 43 cases in which treatment and follow-ups were completed.

As has been previously reported for Jonit therapy of hookworm, the patients who received drug complained of diarrhea and vertigo, accompanied in certain cases by abdominal pain, nausea and vomiting during the course of treatment. These side effects were in general so moderate in nature that the discontinuation of

Table 4. Egg Counts (E. P. G.) in Jonit-treated Patients. Group 3 (Initial E. P. G. ; 5, 100-10, 000).
Group 4 (Initial E. P. G. ; over 11, 000)

Pt. No.	Dosage Time & Date	Pretreatment (in average)	During and Post-Treatment (D+n)*
39	2:9/May 21/May	5, 400	5, 100(D+7), 5, 500(D+12), 3, 500(D+26), 1, 600(D+40), 5, 5200(D+52)
45	2:31/Jan. 22/Feb.	6, 600	30, 000(D+38), 9, 100(D+270)
5	1:21/Apr.	8, 200	5, 000(D+30)
42	2:31/Jan. 22/Feb.	8, 700	9, 400(D+270)
8	1:21/Apr.	9, 000	7, 100(D+30), 13, 000(D+63)
18	4:21/Apr. 17, 25/May 10/June	9, 700	4, 900(D+30), 4, 000(D+63), 2, 200(D+187)
49	2:31/Jan. 22/Feb.	11, 800	6, 700(D+38), 24, 800(D+270)
48	2:21/Jan. 22/Feb.	12, 800	12, 200(D+38), 6, 300(D+270)
55	2:31/Jan. 22/Feb.	14, 500	24, 100(D+38), 0(D+270)**
50	2:31/Jan. 22/Feb.	15, 500	2, 500(D+38), 7, 500(D+270)
27	1:26/Jan.	20, 900	28, 200(D+7), 26, 400(D+14) 15, 100(D+21)
41	1:13/May	27, 300	28, 400(D+4), 6, 100(D+25), 14, 900(D+32), 15, 100(D+48), 49, 700(D+75), 48, 500(D+149)
30	1:26/Jan.	27, 800	9, 700(D+7)
52	31/Jan. 2:22/Feb.	125, 600	61, 900(D+38), 25, 400(D+270)

*D+n: n days after treatment

**Positive in formalin-ether technique.

treatment was never considered.

The results of hematologic examinations, liver function tests and urinalysis before and after treatment were within normal values and showed nothing considerably abnormal.

Summary

Forty three cases of clonorchiasis were unsuccessfully treated with Jonit in the total received doses ranging from 300 mg to 1,200 mg within various intervals. All patients passed eggs in the feces continuously. Therapeutic response of the patients to Jonit was disappointing.

Jonit did not prove to be an effective chemotherapeutic agent in these groups of patients with clonorchiasis.

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—國文抄錄—

Phenylene-diisothiocyanate-(1, 2) (Jonit)에 의한 肝吸虫症(Clonorchiasis) 治療效果에 對한 檢討

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肝吸虫症은 우리나라 重要 風土病의 하나로서 國內五

大江流域에 濃厚한 流行地를 形成하고 있으며 每年 많은 新患을 내고 있으나 肝吸虫症에 對한 適切한 治療劑가 없어 그 退治가 至難한 實情이다.

따라서 새로운 治療劑의 開發이 時急히 要望되어 왔다. 이에 著者等은 鈎虫(Hookworm)治療劑로서 效果가 크다고 알려진 Jonit (Phenylene-diisothiocyanate-1, 4)로서 肝吸虫症 治療를 試圖하고 그 治療效果를 臨床的으로 檢討하였다.

慶南金海, 釜山 및 서울等지의 肝吸虫症患 67者名에 對하여 投藥前 EPG(便每 gm 當 虫卵數)를 調査한다음 Jonit 를 投與하고 投藥 4週後부터 虫卵減少率 및 虫卵陰轉率을 觀察하였다.

肝吸虫卵 陽性者를 우선 EPG 에 의거 1,000以下, 1,100以上 5,000以下, 5,100以上 10,000以下, 11,000以上の 4群으로 나누고 各群에 對하여 每 12時間 間隔으로 Jonit 100 mg 을 3回 服用시켰다.

總 投藥者 67名中 追跡檢査(Follow-up)에 應한자는 43名뿐이었으며 그中 몇名에 對하여는 同一用量으로 2回 乃至 4回까지 投藥하였으나 虫卵陰轉者를 發見할 수 없었으며 Jonit 에 依하여 虫卵減少를 招來하였다고 생각되는 例는 없는것 같았다.

投藥時의 副作用은 主로 泄瀉, 眩暈, 腹痛, 嘔吐 등이었으나 大體로 輕微한 便이고 投藥을 中止한 境遇는 없었다. 血液學的 檢査, 肝機能檢査, 尿檢査 所見에서는 特히 異常值라고 認定할만한 것을 發見하지 못하였다.

以上の 成績으로 볼때 Jonit 는 肝吸虫症에 有効한 藥劑라고 認定할수 없는것 같다.

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