

Epidemiology Bulletin

- 55 Epidemiological Survey and Drug Therapy of Clonorchis sinensis in Kuo-Hsing Township, Nantou County, Taiwan
- 64 Cases of Notifiable and Reportable Diseases, Taiwan-Fukien Area
-

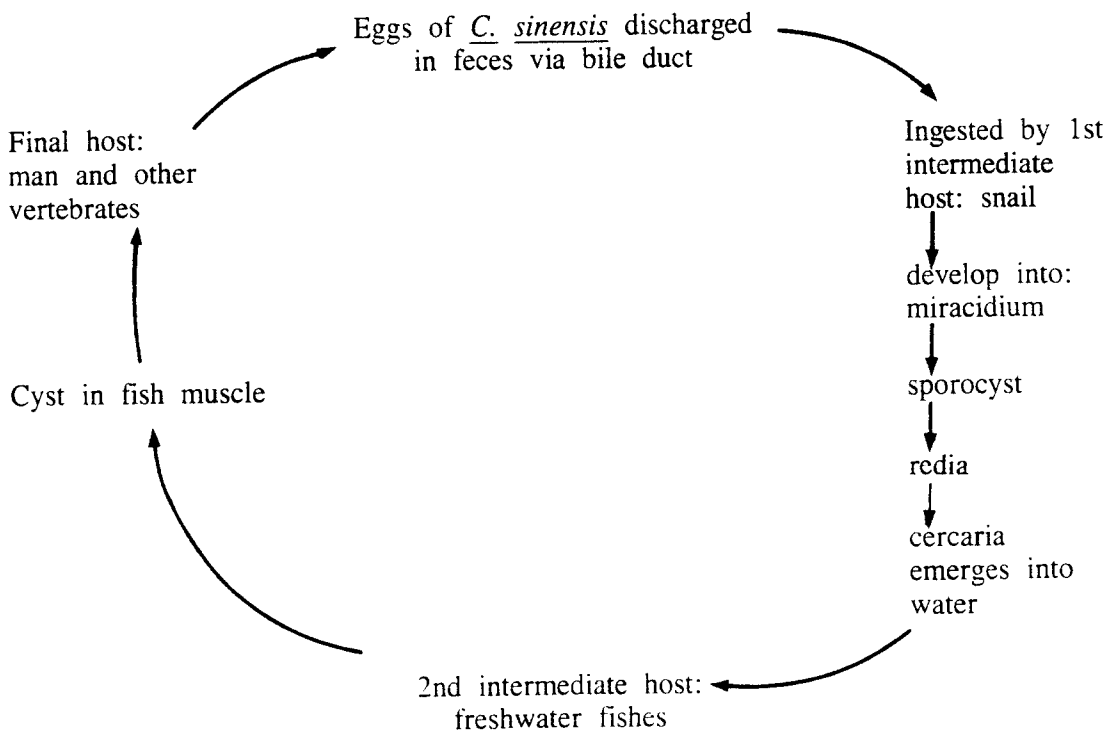
Epidemiological Survey and Drug Therapy of Clonorchis sinensis in Kuo-Hsing Township, Nantou County, Taiwan

1. Introduction

In 1874, while performing a pathological anatomy in Calcutta, India, McConnel, found a never-reported parasite in the bile duct of a Chinese carpenter. Next year, Cobbold, after some important studies of this parasite, named it Clonorchis sinensis⁽¹⁾. In the subsequent years, through the efforts of many researchers, the life cycle of the parasite had been established⁽²⁾. The source and mode of infection are primarily from eating raw freshwater fish containing the cysts of C. sinensis, from which the metacercariae set free and migrate via the digestive tract into the host. They remain in the bile duct of the host, and become adults to lay eggs in about a month. One adult produces around 4,000 eggs a day, and the longevity of adults is 15 to 20 years. Eggs, through the bile duct and duodenum of the host (humans, dogs, cats and pigs), are discharged in feces and ingested by the first intermediate host, a susceptible snail, Parafossarulus manchouricus. They hatch in its intestine and develop into miracidia, sporocysts, redia and cercariae, and then escape into water. On contacting with the second intermediate host (freshwater fishes), cercariae penetrate the host and encyst, usually in muscles, occasionally on the underside of scales. The complete life cycle, from the egg to adult worm, requires at least three months (see Figure 1). Clinical reaction may be slight or absent in light infections. Symptoms include nausea, headache, a sensation of abdominal pressure, enlargement and tenderness of liver, edema and complications such as pancreatitis^(3,4). In severe cases, cirrhosis of liver, hepatocellular carcinoma and bile-duct carcinoma may develop⁽⁵⁻⁹⁾. The disease is highly endemic in southeast China, Japan, Korea, Vietnam and Taiwan. The report by Cross⁽¹⁰⁾ gave an infection rate of C. sinensis in Taiwan between 0.012 and 1.5%. Other reports gave infection rates in endemic areas between 10 and 59%⁽²⁾. Mei-nung of Kaohsiung County, Sun-Moon Lake of Nantou County and Miaoli of Miaoli County were the major endemic areas in Taiwan with infection rates higher than 50%⁽¹¹⁻¹³⁾. In the last 30 years, with the improvement in public health, many parasitic diseases have been well controlled. There are still, however, areas of high infection with C. sinensis, such as Chu-Wei, Tou-Lun and Hsin-Tien villages of Pingtung County, with infection rates of 10.6%, 10.2% and 21.8%

respectively⁽¹⁴⁾. The screenings for *C. sinensis* conducted by the Malaria and Parasitology Division, the National Institute of Preventive Medicine, in Chang-Feng and Chang-Liu villages of Kuo-Hsing Township, Nantou County and Chu-Mu village of Shi-Tan Township, Miaoli County also gave an infection rate as high as 12.75%⁽¹⁵⁾. This parasitic infection can be easily prevented by not eating raw freshwater fishes. More health education, therefore, is needed to improve the understanding of the residents of these areas concerning *C. sinensis* and its prevention. The present study was conducted in Kuo-Hsing Township of Nantou County: to investigate the prevalence rate of *C. sinensis* by finding the characteristic fluke eggs in feces, and to undertake survey with questionnaires of the public's knowledge of the mode of transmission and the sequelae of infecting *C. sinensis*, and their attitudes toward the infection, for the future planning of public health programs. Praziquantel, a highly effective medicine of low toxicity and little side effects for the treatment of *C. sinensis* infection at 25 mg per kg of body weight, three times a day for one or two days, has been reported to be almost 100% effective⁽¹⁶⁻²¹⁾. However, in an endemic area with large numbers of infections, considerations should be taken on the costs, effectiveness and side effects for mass treatment. For cost-effectiveness, for the convenience of medication, and for efficacy of treatment, dosage has to be well defined. The present study, therefore, divided the patients into groups for treatment with Praziquantel at various dosages. Patients were examined for eggs in the second, sixth and twelfth months after medication for cure rates. The purpose was to identify a more convenient and effective way of medication in Taiwan for mass treatment in endemic areas in the future.

Figure 1. Life Cycle of *Clonorchis sinensis*



2: Materials and Methods

(1) Target groups for study

Residents of the 13 villages of Kuo-Hsing Township, Nantou County, were made targets for the study. Two lin's (neighborhoods) were selected from each village using the cluster sampling method. Sixty to 70 persons were then selected from each lin, totaling 1,760 to 1,980 persons for the study. They were interviewed with questionnaires, and examined for eggs in their feces. At an estimated prevalence of 12%, around 200 patients would have been identified for medication study.

(2) The questionnaire

The questionnaire consisted of individual background information, educational attainment, and knowledge of and attitude toward C. sinensis infections.

(3) Prevalence survey

Hydrochloric acid, sodium sulfuric acid and tritone sedimentation method (AMSIII method) were applied to examine feces for positive cases⁽²²⁻²⁴⁾.

(4) At an estimated 12% of infection rate, 200 patients would be sorted out for a medication study with Praziquantel. The procedure was:

1) Selection of patients: for safety reason, individuals allergic to drugs, pregnant women, heart and liver disease patients, and individuals with recent attack of cerebrovascular diseases were excluded from the study.

2) History-taking and physical examination: patients were asked to fill out a form concerning the history of these diseases. They were also told of the possible side effects of the medicine. They were then asked to sign their consent for the study, and given physical examination including testings for vital signs (blood pressure and palpitation) and heart, lung and abdominal functions.

3) Laboratory testings: including blood testings (RBC, WBC, D/C, Hgb, eosinophil), urine testings, liver function testings (total protein, A/G ratio, AST, ALT, total bilirubin, ALK-P), blood sugar, and kidney function (BUN, creatinine), all conducted before medication to exclude any serious illness.

4) Praziquantel treatment: positive cases were randomly divided into three groups: A, B and C, for treatment with Praziquantel at three different dosages: 40 mg/kg st, 20 mg/kg bid, and 25 mg/kg tid. They were asked about the side effects five hours after the medication.

5) Follow-up: feces were examined for eggs again in the second, sixth and twelfth month after medication. The cure rate was calculated as follows:

$$\text{Cure rate (\%)} = \frac{\text{No. of egg positive turning negative}}{\text{No. of } \underline{C. \textit{sinensis}} \text{ egg positive}} \times 100$$

3. Findings

The present study was conducted in 13 villages of Kuo-Hsing Township, Nantou County to: 1) investigate the prevalence rate of C. sinensis, 2) to understand the residents' knowledge of and attitude toward C. sinensis infections, and 3) to determine the dosage-effect relationship of Praziquantel, as well as to understand the clinical symptoms and side effects of C. sinensis infection.

(1) The prevalence rate of C. sinensis

As shown in Table 1, of the 1,758 persons studied, 297 (180 males and 107 females) were identified as C. sinensis patients. The prevalence rate was 16.9%, the man to woman ratio being 1.68:1. Infection increased with age. The age-specific infection rates were less than 5% before the age of 19 years, 11% after 20 years of age, and 29% in the age group 40 to 49 years. The rate declined thereafter, though leveled off at around 20%. The number of patients by village is shown in Table 2.

(2) Questionnaire survey

1) 41% of those studied were at primary education level, followed by the illiterates. By occupation of respondents, 38% were in agriculture and 36% unemployed (see Tables 3 and 4).

2) Knowledge of and attitude toward C. sinensis infections

a. Of the 1,758 persons interviewed, 187 (10.64%) did not know that eating of raw or partly cooked freshwater fish could cause C. sinensis infection, and 31 (1.76%) often fed fishes with feces. Of a total of 931 persons (53%) interested in eating raw fish, 45 (2.56%) had it once every week, 239 (13.59%) once a month, and 647 (36.8%) more than once a year. The infection of C. sinensis of those who had raw fishes in the past was 5.1 times higher (Relative Risk = 5.1) than those who never had raw fish, though 50 persons (17%) of those who never had raw fish were also infected. This could mean that C. sinensis infection may have other routes of transmission, and it requires further studies. Of those interviewed, 126 persons (7.17%) who knew that eating raw fish could cause C. sinensis infection still insisted on having it.

b. As shown in Table 5, when those infected with C. sinensis were compared with those not infected in terms of their knowledge, attitude and habit of eating raw fish, the infected ones seemed to know obviously less about the routes of transmission and were more likely to eat raw fish.

(3) Dosage-effectiveness of Praziquantel

1) Clinical symptoms: primarily nervousness and gastro-intestinal disorders (see Table 6).

2) Treatment with Praziquantel: excluding pregnant women and persons with abnormal functions of liver, heart and lung, 241 out of the 297 patients identified were given Praziquantel for treatment as shown in Table 7. The cure rates in the twelfth month for those treated at 40 mg/kg st or 20 mg/kg bid did not differ, being 76.0% and 77.9% respectively. The one-year cure rate of the 25 mg/kg tid was as high as 90%. Only 21 patients showed some side effects of nervousness or gastro-intestinal disorders such as nausea and abdominal pressure (see Table 8).

4. Discussion

The present survey of 1,758 residents of 13 villages of Kuo-Hsing Township, Nantou County, revealed 297 infected with *C. sinensis*, giving a prevalence rate of 16.9%. The infection rate was 1.68 times more in man than in woman. The infection began early in life and reached a peak around 40 to 49 years of age. The findings were similar to those reported by Ong⁽¹³⁾ and Yen et al.⁽¹⁴⁾ The possible reasons for the high infection are that: Kuo-Hsing County is relatively isolated with poor transportation facilities; fish-pond farming has been popular, and fish used to be fed with feces in the past when economy was poorer; and local residents are fond of raw fish. These conditions and others provide both breeding places and routes of transmission for *C. sinensis*, and the infection has, thus, been relatively high.

Though economic conditions have been improved, feeding fish with feces is still practised, and the eating of raw fish also still prevails. The major tasks of public health workers are to educate the people against feeding fishes with feces, and also against eating raw or partly cooked fishes, and to encourage them to use separate chopping boards. For those who though know eating raw fish could cause infection and yet insist on having it, more efforts should be made to change their behavior.

Elimination of the sources of infection is as important as treatment. Treatment with Praziquantel at three different dosages and examinations of eggs in feces in the second, sixth and twelfth months after medication were tried out during the present study. The effect was the highest in the sixth month with a cure rate of more than 90% for all the three groups. The cure rate declined thereafter one year of follow-up. The cure rates for the 40 mg/kg st and the 20 mg/kg bid had dropped to around 75%, but that for the 25 mg/kg tid had remained at around 90%. Why would the cure rate drop after one year? Could it be that Praziquantel can not kill *C. sinensis* completely and that the surviving parasites continue to produce eggs? Or is it because that the residents continue to take raw fish and are infected again? These have never been reported, and further investigations are thus required. The side effects of the drug are moderate, only temporary nervousness or gastro-intestinal disorders such as nausea, vomiting and headache. Some had developed severe nausea and vomiting but recovered shortly after medication and taking some rest. It seems that the drug is highly effective, and it is, therefore, recommended that Praziquantel at 25 mg/kg tid be administered for mass treatment in endemic areas to eliminate completely the sources of infection.

Prepared by: C.L. Yeh¹, M.Y. Cheng², H.Y. Lee², K.H. Liu², L.P. Chow², C.J. Chien³.

1. FETP, National Institute of Preventive Medicine (NIPM), DOH
2. Malaria and Parasitology Division, NIPM, DOH
3. Kuo-Hsing Health Station, Nantou County

References:

1. Kim DC, Kunz RE. Epidemiology and helminth diseases. *Clonorchis sinensis* (Cobbold, 1875) Looss, 1907 on Taiwan (Formosa). *Chin Med J* 1964; 11:29-47.
2. Fan PC. Medical parasitology, Taipei, Taiwan, ROC, Men-Chin Book Printing Co., 3rd edition: 1977; 242-257.
3. Min HK. *Clonorchis sinensis*. Pathogenesis and clinical features of infection. *Arzneimittelforschung* 1984; 34(9B):1151-1153.
4. Choi TK, Wong J. Severe acute pancreatitis caused by parasites in the common bile duct. *J Trop Med Hyg* 1984; 87:211-214.
5. Kim YI. Liver carcinoma and liver fluke infection. *Arzneimittelforschung* 1984; 34(9B):1121-1126.
6. Flavell DJ. Liver-fluke infection as an aetiological factor in bile-duct carcinoma of man. *Trans Roy Soc Trop Med Hyg* 1981; 75:810-824.
7. Nakashima T, Sakamoto K, Okuda K. A minute hepatocellular carcinoma found in liver with *Clonorchis sinensis* infection. *Cancer* 1977; 39:1306-1311.
8. Baker MS, Baker BH, Woo R. Biliary clonorchiasis. *Arch Surg* 1979; 114:748.
9. Belamaric J. Intrahepatic bile duct carcinoma and *C. sinensis* infection in Hong Kong. *Cancer* 1973; 31:468-473.
10. Cross JH. Clonorchiasis in Taiwan. A Review. In: Proceedings of the 4th Southeast Asian Seminar on Parasitology and Tropical Medicine, Schistosomiasis and other Snail-transmitted Helminthiasis. Manila, 24-27 February 1969, Thai Watana Panich Press, Bangkok, 1969; 231-242.
11. Chow LP. Epidemiological studies of Clonorchiasis at Meinung Township in Southern Taiwan. *Formosan Sci* 1960; 14:135-165.
12. Clarke MD, Khaw OK, Cross JH. Clonorchiasis in Sun Moon Lake Area. *Chinese J Microbiol* 1971; 4:50-60.
13. Ong SJ, Lu SC. Protozoan and helminthic infections among the Government workers and students of Miaoli District in Miaoli County: A highly endemic area of Clonorchiasis in Taiwan. *Chinese J Microbiol* 1979; 2:13-20.
14. Yen CM, Chen ER, Fang AY, Chung TC. Human Clonorchiasis in new endemic areas of Taiwan, an epidemiological survey. *Kaohsiung J Med Sci* 1988; 4:538-546.
15. Cheng MY, Lee SY, Chou CH, Wang K. *C. sinensis* in Taiwan. *Epidemiology Bulletin* 1990; 6:17-20.
16. Chen CY, Hsieh WC. Clinical investigation of Praziquantel in the treatment of *Clonorchiasis sinensis*. *J Formosan Med Assoc* 1982; 81:1434-1442.
17. Wegner DH G. The Profile of the trematocidal compound Praziquantel. *Arzneimittelforschung* 1984; 34(9B):1132-1136.
18. Froberg H. Results of toxicological studies on Praziquantel. *Arzneimittelforschung* 1984; 34(9B):1137-1144.

19. Chen CY, Hsieh WC. *Clonorchis sinensis*: Epidemiology in Taiwan and clinical experience with Praziquantel. *Arzneimittelforschung* 1984; 34(9B):1160-1162.
20. Kuang OH, Zhou YT, Lei SZ, Cao WJ, Zhong HL. Clonorchiasis: Treatment with Praziquantel in 50 Cases. *Arzneimittelforschung* 1984; 34(9B):1162-1163.
21. Lee SH. Large scale treatment of *Clonorchis sinensis* infections with Praziquantel under field condition. *Arzneimittelforschung* 1984; 34(9B):1227-1230.
22. Ritchie LS. An ether sedimentation technique for routine stool examination. *Bull US Army Med Dept* 1984; 8:326.
23. Cross JH, Murrel KD, Tsai SH. An Evaluation of diagnostic techniques in a sample survey for intestinal parasites. *Chinese J Microbiol* 1968; 1:117-124.
24. Stoll NR, Hausheer WC. Concerning two options in dilution egg counting: small drop and displacement. *Am J Hyg* 1926; 6:134-145.

Table 1. Age-Specific Prevalence of *C. sinensis*, Kuo-Hsing Township, Nantou County

Age	-10	10-19	20-29	30-39	40-49	50-59	60+	Total
No. infected	2	5	12	33	66	68	112	297
No surveyed	200	167	112	232	231	278	426	1758
Prevalence (%)	1.0	3.0	10.7	14.2	28.6	24.5	26.3	16.9

Table 2. Distribution of *C. sinensis* Patients by Age by Village

Village	Positive	M	F	-10	10-19	20-29	30-39	40-49	50-59	60+
Kankou	15	14	1	1	1	2	1	2	2	6
Fukuei	20	13	7	0	0	0	2	3	4	11
Peishan	19	10	9	0	1	0	2	7	1	8
Nankang	54	33	21	0	3	2	9	10	15	15
Shihmen	13	8	5	0	0	0	2	3	3	5
Kuohsing	32	18	14	0	0	0	4	8	5	15
Tachi	19	14	5	0	0	0	3	3	7	6
Peikang	38	26	12	0	0	5	1	9	9	14
Changfu	21	9	12	0	0	2	0	4	8	7
Kanlin	9	8	1	0	0	0	1	1	3	4
Changfeng	29	19	10	0	0	1	5	8	7	7
Changliu	28	18	10	1	0	0	3	8	4	12
Total	297	180	107	2	5	12	33	66	68	112
%	100	1.68	1.0	0.67	1.68	4.04	11.11	22.20	22.80	37.50

Table 3. Educational Distribution of Respondents

Education	Illiterate	Primary	Junior High	Senior High	Univ. & College	Post-graduate	Others
No. uninfected	307	551	201	128	53	7	154
No. surveyed	385	688	231	148	64	7	168
%	23	41	14	9	4	0.4	10

Table 4. Distribution by Occupation of Respondents

Occupation	Government Service	Industry	Commerce	Agriculture	Service	Student	Unemployed
No. uninfected	60	36	49	482	23	224	527
No. surveyed	73	46	68	640	26	229	607
%	4	3	4	38	2	26	36

Table 5. Analysis of questionnaire returned from 1758 persons

Items of Questionnaire	No. (%)# Infected	No./not infected No.*
1. Considering no infection caused by eating raw fish	187(10.64%)	(45/142)
2. Feeding fishes with feces	31(1.76%)	
3. Eating raw fishes:	931(53.00%)	(230/701)
one or more times/week	45(2.56%)	(3/ 42)
one or more times/month	239(13.59%)	(60/179)
one or more times/year	647(36.80%)	(167/480)
4. Not eating raw fish	827(47.00%)	(50/777)
5. Knowing raw fish causing infection yet insisting on having it	126(7.17%)	(18/108)

* $P < 0.05$ comparing those infected and not infected, Chi-square test

Relative risk $RR = (771 \times 230) / (701 \times 50) = 5.1$

Using 1,758 as denominator

Table 6. Self-Reported Symptoms of 241 Patients

Symptoms	No.	%
Indigestion	48	21.3
Upper abdominal pain	9	4.0
Stomach pain	45	20.0
Abdominal pressure	59	26.2
Nausea	69	30.7
Headache	41	18.2
Discomfort all over	5	2.2

Table 7. Dose-Effectiveness of Praziquantel

Group	2 months after			6 months after			12 months after		
	Case	Cured	Rate	Case	Cured	Rate	Case	Cured	Rate
A	83	68	81.9	78	71	91.0	78	60	76.9
B	71	60	84.5	73	66	90.4	68	53	77.9
C	71	68	95.8	70	68	97.1	70	63	90.0

A: Praziquantel at 40 mg/kg st; B: at 20 mg/kg bid; and C: at 25 mg/kg tid.

Table 8. Side Effects of Praziquantel (%)

Group	A	B	C
Abdominal angina	0	0	1
Nausea	5	3	3
Stomach pain	2	1	2
Stomach discomfort	2	0	3
Dizziness	8	11	7
General discomfort	0	3	0
Allergy	1	1	0
Total side effects	18	19	16
% and number of persons with side effects	15 (28 2)	16 (33 3)	11 (23 4)
No persons tested	52	48	47

Total % with side effects = (total number with side effects/total number tested) × 100
= (15 + 16 + 11) / (51 + 48 + 47) × 100
= 21%