# A CLINICAL TRIAL OF ORAL DEHYDROEMETINE IN OPISTHORCHIASIS

LAVAN MUANGMANEE, NALINEE ASWAPOKEE, NIBHA JAROONVESAMA and VIKIT VIRANUVATTI

Tropical Medicine Unit, Department of Medicine, Siriraj Hospital Faculty of Medicine, Mahidol University, Bangkok, Thailand.

## INTRODUCTION

In Thailand, *Opisthorchis viverrini* was first reported by Leiper in 1911 from a human autopsy in Chiengmai. Wykoff *et al.*, (1965) did an extensive survey and estimated that 3.5 million people in the northeastern part of Thailand harboured *O. viverrini.* This represents a major clinical and public health problem in the country. Many drugs have been tried in opisthorchiasis and clonorchiasis but so far there has been no ideal drug.

Dehydrometine (as a late release tablet), which has been used in the treatment of intestinal amoebiasis, was reported by Rim in 1972 to have satisfactory effect in treating clonorchiasis using high dosage. This study was therefore carried out to evaluate the efficacy of dehydroemetine in opisthorchiasis, for up to date none of the many agents proposed for the treatment of the disease have proved effective.

## MATERIALS AND METHODS

The clinical trial was carried out from March 1972 to December 1973 at Siriraj Hospital Faculty of Medicine, Mahidol University, Bangkok.

Seventeen patients, residents from the northeastern part of Thailand were treated as outpatients. There were 13 males and 4 females. Twelve of them came to the hospital complaining of flatulence, feeling of 'hot sensation' and fullness in the epigastrium or in the right hypochondrium. The duration of these symptoms were from one month to 2-3 years. None gave a history of jaundice. The other five were asymptomatic; only *Opisthorchis* ova were found in their faeces in the routine medical examination.

Physical examination, observation and laboratory investigations including liver function tests, alkaline phosphatase, serum glutamic oxaloacetic and serum glutamic pyruvic transaminase levels were carried out before treatment, every two weeks during treatment, and monthly at the follow-up visits.

All of them were followed up monthly for six months by one of the authors while seven were followed up monthly upto 8 to 18 months (mean 14.3 months).

The egg counts were determined by Stoll's method (1923) at each visit, the mean pretreatment egg count was obtained from 2-3 specimens. The Stoll egg count ranged from 1,000-6,000 per gramme of faeces; except in one patient who had 22,000 per gramme. During the period of treatment, 3-8 examinations were performed and the mean values were recorded as shown in Table 1.

**Dosage**: Sugar coated Dehydroemetine as a late release tablet of 100 mg was administered at 2.5 mg per kg body weight in three doses after meals on alternate days for 30 days (two months period).

## RESULT

Seventeen patients were treated, two were withdrawn from the trial due to intolerable side effects.

Table 1

The Stoll's egg count of 15 opisthorchiasis patients treated with oral dehydroemetine.

| Nos. | Age | Sex | Mean pretreatment | Number of eggs (1,000 per gramme of faeces) During treatment mean | During treatment %red[n] | 6 months follow-up mean | 6 months follow-up %red[n] | 8to18 months follow-up mean | 8to18 months follow-up %red[n] | Follow up period months |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 20 | M | 1.8 | 0.6 | 66.6 | 0.37 | 79.4 | 1.55 | 13.8 | 16 |
| 2 | 18 | M | 0.8 | 0.25 | 68.7 | 0.2 | 75.0 | - | - | - |
| 3 | 18 | M | 1.07 | 0.51 | 52.3 | 0.3 | 72.9 | 0.22 | 79.4 | 12 |
| 4 | 13 | M | 2.23 | 2.27 | −17.9 | 2.16 | 31.5 | 1.35 | 39.4 | 8 |
| 5 | 49 | M | 1.07 | 0.8 | 25.2 | 0.4 | 62.6 | - | - | - |
| 6 | 36 | M | 1.5 | 0.9 | 40.0 | 0.03 | 98.0 | - | - | - |
| 7 | 18 | M | 2.55 | 1.03 | 55.6 | 0.13 | 94.9 | 0.54 | 78.8 | 18 |
| 8 | 26 | M | 3.9 | 0.73 | 81.2 | 0.2 | 94.9 | - | - | - |
| 9 | 49 | M | 17.15 | 2.28 | 86.7 | 0.6 | 96.5 | 0.54 | 96.8 | 18 |
| 10 | 63 | M | 1.63 | 0.32 | 79.1 | 0.2 | 87.7 | - | - | - |
| 11 | 53 | F | 0.37 | 0.18 | 50.0 | 0.06 | 83.9 | 0.28 | 24.3 | 14 |
| 12 | 21 | F | 0.33 | 0.017 | 94.8 | 0.01 | 96.9 | 0.35 | −6.0 | 14 |
| 13 | 18 | M | 0.03 | 0.08 | −166.6 | 0 | 100 | - | - | - |
| 14 | 24 | M | 2.3 | 0.43 | 81.3 | 0 | 100 | - | - | - |
| 15 | 18 | M | 0.93 | 0.93 | 70.9 | 0 | 100 | - | - | - |
| | Mean | | | | 56.01 | | 84.9 | | 46.6 | 14.3 |

During the course of treatment, egg reduction was obtained in all cases, except two (Nos. 4 and 13). After six months follow-up, further reduction in egg count was observed. In three patients (Nos. 13, 14, 15), the egg counts were negative from the third to the sixth month. Seven patients were followed up to 8-18 months, the egg count further declined in three patients (Nos. 3, 4 and 9) whose reduction of egg count maintained respectively at 8, 12 and 18 months later. There was a slight increase in the count in the other four patients.

The follow-up at six months showed mean egg reduction of 84% while at 8 to 18 months, the mean egg reduction was 47%, as shown in Table 1.

**Side Effects**: Table 2. A common side effect was generalised muscular weakness, especially in the lower limbs. Twelve out of fifteen patients (80%) complained of walking with difficulty due to lack of strength. Blood electrolytes was determined in four patients, the results were within normal limits. The

Table 2

Side effects of oral dehydroemetine in opisthorchiasis.

| Toxic reaction | No. of cases | Per cent |
|---|---|---|
| Weight loss | 15 | 100 |
| Muscular weakness | 12 | 80 |
| Diarrhoea | 10 | 67 |
| Joint pain | 3 | 20 |
| Anorexia | 2 | 13 |

two patients, who were withdrawn from the trial, could not get up from their beds at the early third week of treatment and had a coarse tremor of the hands. The neurological examination was otherwise normal in these two cases. The electrocardiogram showed no significant abnormality in the patients. They also had diarrhoea, anorexia, joint pain and weight loss. Both patients fully recovered in two weeks time following discontinuation of the drug.

In most cases, the symptom of muscular weakness began in the second week after commencement of the drug, and usually subsided in one week after discontinuation of treatment, except in one patient who took one month to recover.

Diarrhoea was noticed in ten patients (67%). Loose stools were common on the drug taking days, usually amounting to 4-5 times. One patient experienced diarrhoea on the following days.

Joint pains were also observed in three patients (20%). It usually began and subsided at about the same time as muscular weakness.

Anorexia was found in two patients (13%). All patients lost at least 2 to 3 kg in weight during treatment but all returned to the pretreatment level or even higher during the following two months.

Concerning laboratory investigations, there were no toxic effects on liver profile and renal function tests were normal. Although reduction in egg count was observed in all the patients, there was no change in symptoms.

## DISCUSSION

Many drugs have been tried in the treatment of clonorchiasis and opisthorchiasis including Furapromidium, Bitoscanate, Quinacrine hydrochloride and prolonged Chloroquine therapy (Sadun *et al.*, 1955; Wang *et al.*, 1965; Rider *et al.*, 1967; Koo *et al.*, 1971). However, clinical improvement and reduction in egg count were unsatisfactory or only temporarily noted, except the two cases with prolonged Chloroquine therapy reported by Rider (1967). In 1964, Lämmler found that chlorinated derivatives of xylol were very effective against liver flukes. These derivatives included chloxyle (hexachloroparaxylol) and hexachlorophene. During 1963-1968, both drugs had been tried on *O. felineus* in Russia (Drozdov, 1965, 1967; Plotnikov *et al.*, 1967; Pantyukov, 1966), and on *C. sinensis* in China (Chung *et al.*, 1965a; Liu *et al.*, 1963, 1965; Wang *et al.*, 1965) showing good results. Yokogawa *et al.*, (1965, 1967) obtained excellent therapeutic effect on *C. sinensis* in animal and human cases. This was confirmed by Harinasuta *et al.*, (1966) and Bunnag *et al.*, (1970) on *O. viverrini* in Thailand and by Seo (1966) and Cho (1966) on *C. sinensis* in Korea. In 1966, the manufacturer reported toxic effects on the kidney and neurotoxic effects in dogs. Anaemia was also reported in dogs and in one human case. The drug was withdrawn from the market.

In 1972, Rim reported that dehydroemetine late release tablets were very effective in the treatment of clonorchiasis sinensis in 40 patients in Korea with the same dosage. In his series, the symptoms and signs and liver function tests were much improved and the drug was well-tolerated and safe even in severe cases of clonorchiasis.

Mean percentage egg reduction in our series was 85 after six months follow-up. At 8-18 months later there was further decline in egg count in three patients (Nos. 3, 4 and 9), while in four patients (Nos. 1, 7, 11, 12) there was an increase in egg count. The mean percentage egg reduction at 8-18 months was 47. Statistically, there was no significant difference between the egg count at six month and 8-18 month follow-up.

Two patients were withdrawn from the series because of side effects. In fifteen patients, the side effects were well-tolerated. The clinical symptoms did not improve much and liver function tests were not altered, which differed from those reported by Rim. This might due to differences in severity of clinical symptoms and in species of the parasites. The above results revealed that this drug has a definite effect on egg production of *Opisthorchis*, even though the therapeutic clinical effect was minimal.

## SUMMARY

A clinical trial of dehydroemetine late release tablets in Opisthorchiasis was carried out in 1972 in 17 patients with egg count of 1,000-22,000 per gramme of faeces. They presented mild or no clinical manifestations except for complaints of flatulence and fullness in epigastrium. The dosage used was 2.5 mg per kg per day on alternate days for 30 days. At 6 month follow-up, the mean percentage egg reduction was 85 per cent. Three patients had negative egg counts from the third to the sixth month. Seven patients were followed up for 8-18 months (mean 14.3 months) and the mean percentage egg reduction was 47 per cent. Major side effects were generalised muscular weakness, diarrhoea, joint pain, anorexia and transient weight loss, all of which subsided after completion or discontinuation of the drug. Clinical symptoms and liver function tests were not altered.

## ACKNOWLEDGEMENTS

The authors wish to thank Dr. Danai Bunnag for his encouragement and advice in presenting this paper and to Messrs. F. Hoffmann La Roche for the supply of dehydroemetine for the clinical trial.

## REFERENCES

BUNNAG, D., HARINASUTA, T., HARINASUTA, C., SUNTHARASAMAI, P., VIRAVAN, C. and PETCHKLAH, S., (1970). Clinical trial of Hetol (1,4 bis-trichloromethylbenzol) in the treatment of opisthorchiasis. *Ann. Trop. Med. Parasit.*, *64*:109.

CHO, M.J., CHO, K.M. and SOH, C.T., (1966). The use of Hetol on the infection of *Clonorchis sinensis*. *Korean J. Parasit.*, *4*:21.

CHUNG, H.L., HSÜ, C.P., TS'AO, W.C., K'O, H.Y., KUO, C.H., HSÜ, H.C., LI, P.S., CHENG, S., CHANG, H.Y., YUAN, C.T. and CHANG, Y.C., (1965a). Hexachloroparaxylol in the treatment of clonorchiasis sinensis in animals and man. *Chin. Med. J.* (Peking), *84*:232.

DROZDOV, V.N., (1965). First experience using Hexachloroparaxylol (Chloxyle) for the treatment of opisthorchiasis in children. *Med. Parazit.* (Moskva), *34* : 414.

DROZDOV, V.N., (1967). An experience of treatment of opisthorchiasis in children with Chloxyle (Hexachloroparaxylol). *Med. Parazit.* (Moskva), *36*:166. (In Russian, English abstract).

HARINASUTA, C., BUNNAG, D., WIRIYAWIT, P. and PETCHKLAH, S., (1966). The treatment of opisthorchiasis viverrini with1,4bis-trichloromethylbenzol(Hetol). *Trans. Roy. Soc. Trop. Med. Hyg.*, *60*: 690. (Correspondence).

KOO, B.Y., LEE, S.H. and SEO, B.S., (1971). Failure of Jonit (phenylene-diisothiocyanate-1,4) in the treatment of clonorchiasis. *Seoul. J. Med.*, *12*:11.

LÄMMLER, G., (1964). Die experimentelle chemotherapie der trematoden infektionen und ihre problematik. 2. Teil. *Z. Tropenmed. Parasit.*, *15*:164.

LEIPER, R.T., (1911). Notes on the occurrence

of parasites presumably rare in man. *J. London Sch. Trop. Med.*, *1*:16.

LIU, J., WANG, C.N., YU, H.H., WANG, M.N., CHANG, C.F. and CHENG, S., (1963). Hexachlorophene in the treatment of clonorchiasis sinensis. *Chin. Med. J.* (Peking), *82*:702.

LUI, J., WANG, C.N., TSENG, F.J., FAN, K.G., TU, C.C., CHANG, T.F., SUN, K.J., CHIN, C.M., CHENG, S. and TU, S.F., (1965). Hexachloroparaxylol in the treatment of chlonorchiasis sinensis. *Chin. Med. J.* (Peking), *84*:8.

PANTYUKOV, A.M., (1966). Treatment of opisthorchiasis with Chloxyle. *Med. Parazit.* (Moskva), *35*:482. (In Russian, English abstract).

PLOTNIKOV, N.N., OZERETSKOVSKAYA, N.N., KARNAUKHOV, V.K., ALEKSEEVA, M.I., TUMOLSKAYA, N.I., LINEVICH, O.M. and TIMINA, V.P., (1967). On the clinical pattern and treatment of opisthorchiasis in the early phase. *Med. Parazit.* (Moskva), *36*:379. (In Russian, English abstract).

RIDER, J.A., DEVEREAUX, R.G. and MOELLER, H.C., (1967). Clonorchiasis. Treatment with chloroquine phosphate. *Gastroenterology*, *52*:267.

RIM, H.J., (1972). Chemotherapy on trematode infections excluding schistosomiasis. *Proceedings of the Tenth SEAMEO-TROPMED Seminar: Symposium on Chemotherapy in Tropical Medicine of Southeast Asia and Far East.* Bangkok. pp. 67-76.

SADUN, E.H., CHAMNARNKIT, C. and CHETANASEN, S., (1955). Studies on the treatment of *Opisthorchis viverrini* in human infections with Quinacrine hydrochloride and Chloroquine phosphate. *Amer. J. Trop. Med. Hyg.*, *4*:1080.

SEO, B.S., RIM, H.J. and LIM, Y.C., (1966). Therapeutic effect of 1,4 bis-trichloromethylbenzol (Hetol) on the clonorchiasis. *Korean J. Parasit.*, *3*:63.

STOLL, N.R., (1923). An effective method of counting hookworm eggs in faeces. *Amer. J. Hyg.*, *3*:81.

WANG, C.N., LIU, J., TU, C.C., TSENG, F.J., CHANG, T.F., FAN, K.C., CHIN, C.M., HSIEH, L.L. and SUN, K.J., (1965). F 30066 (Furapromidium) in the treatment of clonorchiasis sinensis. *Chin. Med. J.* (Peking), *84*:672.

WANG, S.M., CHANG, K.N., SHEN, S.L., HUEI, P.L., CHOU, H.M., HSU, K.S., CHAO, C., WU, S.M., LAN, H.C., TS'AO, S.C., CHENG, S., LI, P.H., CHENG, C. and HSI, H.Y., (1965). Treatment of clonorchiasis sinensis with hexachloroparaxylol in oil. Experimental and clinical observations. *Chin. Med. J.* (Peking), *84*:748.

WYKOFF, D.E., HARINASUTA, C., JUTTIJUDATA, P. and WINN, M.M., (1965). *Opisthorchis viverrini* in Thailand: the life cycle and comparison with *Opisthorchis felineus*. *J. Parasit.*, *51*:207.

YOKOGAWA, M., KOYAMA, H., YOSHIMURA, H. and TSAI, C.S., (1965). Chemotherapy of *Clonorchis sinensis* infection. I. Chemotherapy with 1,4 bis-trichloromethylbenzol (Hetol) for animal infected experimentally with *Clonorchis sinensis*. *Jap. J. Parasit.*, *14*:233.

YOKOGAWA, M., TSUJI, M., ARAKI, K., NOMOT, T., MATSUMOTO, M., YOSHIBA, R., FUKUCHI, S., HIRASUKA, A. and KITAMURA, M., (1965). Chemotherapy of *Clonorchis sinensis*. II. Clinical observations on the treatment of clonorchiasis patients with 1,4 bis-trichloromethylbenzol. *Jap. J. Parasit.*, *14*:526.

YOKOGAWA, M., TSUJI, M., KOYAMA, H., WAKOJIMA, T., OZU, S. and OGINO, Y., (1967). Chemotherapy of *Clonorchis sinensis* III. Treatment of clonorchiasis sinensis with 1,4 bis-trichloromethylbenzol. *Z. Tropenmed. Parasit.*, *18*:82.