

# COMPARATIVE CLINICAL TRIALS OF NICLOSAMIDE AND TETRACHLORETHYLENE IN THE TREATMENT OF *FASCIOLOPSIS BUSKI* INFECTION

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## INTRODUCTION

*Fasciolopsis buski* infection in human is known to occur in Southeast Asia, East Pakistan, India, Central and South China, Formosa, Borneo and Sumatra (Belding, 1965a). The infection is predominant in children and young adults with a peak age incidence between 5 and 14 years old (Saovakontha *et al.*, 1965; Manning *et al.*, 1969; Plaut *et al.*, 1969). The clinical spectrum of the infection ranged from non-symptomatic to a moderate degree of illness characterized by abdominal pain, diarrhoea, oedema, some degree to malnutrition and growth retardation; death has been recorded in an individual associated with 501 flukes (Sadun, 1953).

Carbon tetrachloride and beta-naphthol were the two chemotherapeutic agents for this infection in the early days (Stoll *et al.*, 1926; Barlow, 1927). Hexylresorcinol has been shown to be superior in its efficacy and safety (McCoy and Chu, 1937), and has been recommended as a textbook treatment for the infection (Belding, 1965 b; Hunter *et al.*, 1966; Wilcocks and Manson-Bahr, 1972; Faust *et al.*, 1970). However, the investigations by Saovakontha *et al.*, (1965) and Manning *et al.*, (1969) suggested that tetrachlorethylene (TCE) is more effective than hexylresorcinol. Nevertheless the administration of this drug in children is troublesome regarding the adjustment of dosage and the high probability of chewing the encapsulated drug. Besides,

even though the drug is relatively nontoxic, various side-effects are not rare.

Niclosamide ('Yomesan') has been shown to be an effective, nontoxic agent for therapy of several species of tapeworm infections (Nagaty *et al.*, 1962; Mastrandrea and Cigala, 1963; Kahra and Veharanta, 1963; Gherman, 1968; Perera *et al.*, 1970) as well as in intestinal trematode infection-heterophysiasis (Khalil *et al.*, 1964). The drug inhibits oxidative phosphorylation in cestode mitochondria. The worms are killed on contact and evacuated in the faeces (Meyer *et al.*, 1972). The chewable preparation of this drug makes the administration in children to be quite simple. As niclosamide has been shown to be safe and without harmful effect on the hepatic, renal and haematologic systems (Knorr, 1960), a pilot study of the efficacy of this compound in human fasciolopsiasis with mild symptoms was undertaken.

## MATERIALS AND METHODS

The investigation was carried out in 40 children and young adults naturally infected with *F. buski* admitted to the Bangkok Hospital for Tropical Diseases. All cases were from the same district of Ayudhaya, 80 kilometers north of Bangkok. For comparative purposes 13 cases were treated, with suggested standard treatment of tetrachlorethylene and 27 cases with niclosamide. The age and sex distribution of the two groups are shown in Table 1.

Table 1

Age and sex distribution of *Fasciolopsis buski* infected patients treated with niclosamide and tetrachlorethylene.

	Niclosamide	Tetrachlorethylene
Age (yrs)	0-5	1
	6-10	5
	11-15	6
	16-20	1
range	6-16	3-20
Sex	Male	9
	Female	4
Total No. of cases	27	13

The egg output per gram faeces were determined thrice before and thrice two weeks after treatment by Stoll's egg count and formalin ether concentration techniques (Belding, 1965c). From all the faecal specimens collected individually for 72 hours after the administration of the drug, flukes were seived, identified and counted.

The percentage egg reduction was individually computed from the mean of the 3 pretreatment egg count and the mean of the 3 egg counts determined two weeks after treatment. Those whose 3 faecal specimens collected two weeks after treatment did not reveal any fasciolopsis ova when examined by concentration method were labelled as 'cure'.

Niclosamide was given at the dosage of 43-160 mg per kg body weight and the TCE at the dosage of 0.08-0.14 ml per kg body weight. The drugs were given after 8 hours fasting and 2 hours before light breakfast. No purgative was given. There were two schedules for the administration of niclosamide: a one morning treatment and a two consecutive morning treatment. The means and

standard errors of pre-treatment egg output per gram faeces in the group treated with TCE were  $3593 \pm 997$ , in the group treated with one day niclosamide were  $5702 \pm 1803$  and in the group treated with two day niclosamide were  $15410 \pm 3737$ .

Concerning the side effects, all cases were asked and observed in the morning of treatment for any untoward symptoms.

## RESULTS

Table 2 shows the efficacy of TCE and the two regimes of niclosamide in terms of percentage egg reduction and cure rates. There was no significant difference between the percentage egg reduction of the two regimes of niclosamide treatment. The mean and standard error of the pooled data were  $40.7 \pm 15.8$  per cent. This was significantly lower than the egg reduction of  $96.9 \pm 2.6$  per cent produced by TCE ( $t = 3.51$ ;  $P < 0.01$ ). In this series of studies the maximum number of flukes expelled in an individual was 320.

Table 2

Percentage egg reduction, cure rates and number of flukes expelled in *Fasciolopsis buski* infected patients treated with niclosamide and tetrachlorethylene.

	Niclosamide		Tetrachlorethylene
	1 day dose	2 day dose	
Percentage egg reduction			
Mean	30.8	46.2	96.9
SE	34.5	16.2	2.56
Cure rate	10%	12%	77%
No. of flukes expelled			
Mean	67	45	41
SE	33	18	15

All worms expelled in the study were *F. buski*. The cure rate was highest in the TCE treated group.

The side-effects of the treatments are shown in Table 3. It appeared that TCE

Table 3

Side-effects in the treatment of *Fasciolopsis buski* infection with niclosamide and tetrachlorethylene.

	Niclosamide	Tetrachlorethylene
Nausea	1 (4%)	11 (85%)
Vomiting		9 (70%)
Abdominal pain	5 (19%)	1 (8%)
Headache		2 (15%)
Dizziness	1 (4%)	3 (23%)
Vertigo		4 (31%)
Weakness		1 (8%)
Hypotension		1 (8%)
Urticaria		1 (8%)

produced more severe and frequent side-effects than did the niclosamide. The three most frequent complaints produced by TCE were nausea, vomiting and vertigo. There was one case that suffered from hypotension, nausea, vomiting and urticaria half-an hour after taking TCE. After symptomatic and supportive treatment he recovered completely within 6 hours. In the niclosamide treated group, abdominal pain was the only major complaint and occurred in only 5 cases. All were mild, transient and self-limited. Laboratory investigation including renal, liver and hematological functions were not effected after either medications.

### DISCUSSIONS

The result of the treatment in the above data shows that anthelmintic activity does not confine only in the cestode infection but also

extends to some trematode infections. The first trematode that has been shown to be affected by niclosamide was *Heterophyes heterophyes* (Khalil *et al.*, 1964).

In *F. buski* infection, there was a fairly large variation in the efficacy of niclosamide between the individuals treated. On an average niclosamide was inferior to the TCE in its anthelmintic action against the infection. Also, if there was no host or parasitic difference interaction with the treatment in the present study and in the study by Hsieh *et al.*, (1963) it was also inferior to stilbazium iodide (Monopar). However, Hsieh *et al.*, found that vomiting and abdominal discomfort were not uncommon.

Therefore on the grounds that the side-effects due to niclosamide treatment were mild, infrequent and transient, the use of niclosamide in the *F. buski* infection is at least indicative in cases with poor general condition, in places where instant medical care for possible serious side-effects of TCE are not available or in small children with a tendency to chew the medicine.

### SUMMARY

Forty patients infected with *Fasciolopsis buski* infection were treated with niclosamide or tetrachlorethylene (TCE). Niclosamide given to 27 patients at a dosage of 43-160 mg per kg body weight, induced an egg reduction of  $40.7 \pm 15.8$  per cent. TCE given at a dosage of 0.08-0.14 ml per kg body weight induced an egg reduction of  $95.9 \pm 2.6$  per cent.

Side-effects were mild, transient and uncommon in the niclosamide treated group but were severe and frequent in the TCE treated group. Therefore niclosamide is not the first drug of choice in treating fasciolopsiasis but indicative for treating the severely ill patients and for small children with a tendency to chew the medicine.

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REFERENCES

- BARLOW, C.H., (1927). The treatment of fasciolopsiasis. *Chinese Med. J.*, 41 : 253.
- BELDING, D.L., (1965a). *Textbook of Parasitology*. Appleton-Century-Croft, New York, p. 671.
- BELDING, D.L., (1965b). *Ibid.* p. 1288.
- BELDING, D.L., (1965c). *Ibid.* pp. 1171 & 1175.
- FAUST, E.C., RUSSELL, P.F. and JUNG, R.C., (1970). *Clinical Parasitology*. 8th. ed. Lea & Febiger. Philadelphia. p. 544.
- GHERMAN, I., (1968). Observation on the treatment of taeniasis with niclosamide *Bull. Soc. Path. Exot.*, 61 : 432.
- HSIEH, H.C., BROWN, H.W., CHEN, E.R., CHEN, C.Y. and SHIH, C.C., (1963). Treatment of *Fasciolopsis buski*, *Ancylostoma duodenale*, *Ascaris lumbricoides*, *Trichiuris trichirua* and *Enterobius vermicularis* infections with stibazium iodide *J. Parasit.*, 49 : 425.
- HUNTER, G.W., FRYE, W.W. and SWARTZWELDER, J.C., (1966). *A Manual of Tropical Medicine*. 4th ed. W.B. Saunders Co. Philadelphia. p. 544.
- KAHRA, A. and VEHRANTA, T., (1963). Expulsion of tapeworm with Yomesan. *Suom Laak.*, 18 : 325.
- KHALIL, H.M., RIFAAT, M.A. and KOURA, M., (1964). A further trial of 'Yomesan' in *Heterophyes heterophyes* infection. *J. Trop. Med. Hyg.*, 62 : 286.
- KNORR, R., (1960). Treatment of tapeworm infestation with Yomesan: a report of 36 cases. *Med. Klin.*, 55 : 1937.
- MANNING, G.S., SUKHAWAT, K., VIYANANT, V., MANIT, S. and LERTPRASERT, P., (1969). *Fasciolopsis buski* in Thailand, with comment on other intestinal parasites. *J. Med. Ass. Thailand*, 52 : 905.
- MASTRANDREA, G.G. and CIGALA, O., (1963). Therapeutic results in cestodiasis treated with a salicylamide derivative. *Arch. Ital. Sci. Med. Trop.*, 44 : 61.
- MCCOY, O.R. and CHU, T., (1937). *Fasciolopsis buski* infection among school children in Shaoshing and treatment with hexylresorcinol. *Chinese Med. J.*, 51 : 937.
- MEYER, F.H., JAWETZ, E. and GOLDFEIN, A., (1972). *Review of Medical Pharmacology*. Lange Medical Publications. Los Altos. p. 607.
- NAGATY, H.F., RIFAAT, M.A. and SALEM, S., (1962). Clinical trials with 'Yomesan' in *Hymenolepis nana* infection. *J. Trop. Med. Hyg.*, 65 : 128.
- PERERA, D.R., WASTERN, K.A. and SCHULTZ, M.G., (1970). Niclosamide treatment of cestodiasis : clinical trials in the United States. *Amer. J. Trop. Med. Hyg.*, 19 : 610.
- PLAUT, A.G., KAMPANART-SANYAKORN, C. and MANNING, G.S., (1969). A clinical study of *Fasciolopsis buski* infection in Thailand. *Trans. Roy. Soc. Trop. Med. Hyg.*, 62 : 470.
- SADUN, F.H., (1953). *Fasciolopsis buski* (Lankester) in Central Thailand. *J. Parasit.*, 39 (Suppl.) 443.
- SAOVAKONTHA, S., CHAROENLARP, P., RADOMYOS, P. and HARINASUTA, C., (1965). A new endemic area of fasciolopsiasis in Thailand. *J. Med. Ass. Thailand*, 48 : 263.
- STOLL, R.N., CORT, W.W. and KWEI, W.S., (1926). Egg-worm correlations in cases of *Fasciolopsis buski* with additional data on the distribution of this parasite in China. *J. Parasit.*, 13 : 166.
- WILCOCKS, C. and MANSON-BAHR, P.E.C., (1972). *Manson's Tropical Diseases*, 8th. ed. Williams and Wilkins Co. Baltimore. p. 323.