

ASSESSMENT OF THE EFFICACY, SAFETY, AND TOLERABILITY OF PRAZIQUANTEL AND TRICLABENDAZOLE IN THE TREATMENT OF PARAGONIMIASIS

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Abstract. This was a community-based, double-blind, randomized, controlled therapeutic trial undertaken at the municipality of Roxas to determine the efficacy, safety and tolerability of triclabendazole (10 mg/kg, single dose) versus praziquantel (25 mg/kg, three times daily) for three days at 30, 60, and 90 days posttreatment. This study concludes that triclabendazole administered at 10 mg/kg single dose has comparable efficacy, safety, and tolerability with praziquantel 25 mg/kg given three times a day for three days.

INTRODUCTION

Pulmonary paragonimiasis is a parasitic infection caused by lung flukes of the genus *Paragonimus*, of which *P. westermani* is the most common species infecting humans. It is acquired through ingestion of metacercariae, which are found in freshwater crabs and crayfish. Once ingested, the metacercariae are released, develop in the gut, and then migrate to other organs, most commonly to the lungs. Paragonimiasis manifests as fever, chest pain, cough, hemoptysis, dyspnea, and night sweats. The most sensitive, reliable method of diagnosis is the identification of *Paragonimus* eggs in the sputum, stool, or pleural fluid (Beaver *et al*, 1984).

Paragonimiasis is endemic in identified rural communities in the Philippines. These endemic areas are in the provinces of Mindoro, Camarines, Sorsogon, Samar, Leyte, Davao, Cotabato, and Basilan. There has been a re-emergence of cases of pulmonary paragonimiasis; such that, more recently, the provinces of Davao Oriental, and Zamboanga del Norte have been added to the list of endemic areas (Cabrera, 1979; Belizario and Malte, 2004).

The drug of choice for pulmonary paragonimiasis is praziquantel at 25 mg/kg, three times daily, for three days (Johnson *et al*, 1985). It causes flaccid paralysis of the fluke by blocking calcium homeostasis. It also damages the fluke's tegument, which makes it susceptible to host defense mechanisms (Pearson and Guerrant, 1983). Cure rates for praziquantel have been reported to approximate 100% (Calvopina *et al*, 1998); however, in rural communities, patient compliance has been demonstrated to be negatively influenced by adverse drug reactions and the need to take the drug for three consecutive days (Calvopina *et al*, 2003).

Compliance of patients to the prescribed medication contributes significantly to the control of paragonimiasis. Compliance, in turn, is dictated by the availability, ease of administration, safety, and tolerability of medications.

Triclabendazole is a benzimidazole compound with the following selective actions against trematodes; it produces metabolites that block ATP production by inhibiting protein synthesis, and inhibits microtubule formation. Triclabendazole targets both mature and immature flukes (Laburte, 1999). Based on limited published literature, it is a highly effective drug, with an efficacy rate comparable with praziquantel. Moreover, patients who were treated with triclabendazole reported clinical tolerance to its adverse effects that is superior to that of praziquantel. Gastrointestinal symptoms were much less common, and no serious adverse events were noted in patients

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treated with triclabendazole (Calvopina *et al*, 1998, 2003).

Because of the above findings, it is valid to explore the use of triclabendazole, with its documented efficacy and tolerability, in endemic areas to improve the control of paragonimiasis. This study was undertaken to determine the efficacy, safety, and tolerability of triclabendazole, using the following criteria: (1) improvement in clinical symptoms and physical findings; (2) cure rates or absence of lung fluke ova in the sputum at 30, 60, and 90 days posttreatment; and (3) occurrence of adverse drug events.

MATERIALS AND METHODS

Study site and patient selection

This double-blind, randomized, controlled, therapeutic trial was conducted at the Municipality of Roxas in Zamboanga del Norte Province, from December 2005 to March 2006. The site was

chosen because it was known to be endemic for paragonimiasis, with a prevalence rate of 27.2% in 2002 (de Leon and Piad, 2005). Moreover, the Roxas Municipal Health Office reported that paragonimiasis ranked as the fourth-leading cause of morbidity in 2003 (Roxas RHU, 2003).

Roxas Municipality has a total land area of 27,082.28 hectares, mostly with hilly to mountainous topography. One-third of the municipality is situated along a 10-kilometer coastline. Four wide rivers (Dohinob Daku, Dohinob Diut, Tangian, and Piao) and three prominent creeks (Irasan, Langatian, and Minang) traverse this municipality (Roxas RHU, 2003). The location of the barangays surveyed in the study relative to these rivers and creeks is described in Fig 1. *Kampays*, or freshwater crabs, which abound in these natural bodies of water, serve as the intermediate hosts of *Paragonimus*.

Roxas Municipality comprises 31 barangays, 26 of which are dependent on agriculture, while the remaining five depend on marine-related livelihood. Health needs are provided by a main health center located within the Poblacion area, and nine barangay health stations are dispersed throughout the municipality. Roxas has 53 traditional birth attendants (38 trained and 15 untrained) and 33 active barangay health workers (BHWs) (Roxas RHU, 2003).

Currently, Roxas is a third-class municipality; that is, having an average annual income, during the last three calendar years, of 21,000,000-27,000,000 pesos. Farmers comprise 62% of the working population (Roxas RHU, 2003). The *kampays*, which are readily available from rivers, are frequently eaten raw, a delicacy with low costs. Informal interviews with the participants in the study provided information that this cultural practice was popular in the municipality.

The sample size required for the study was 72 (36 patients for each treatment group) and was estimated based on the assumption that the cure rates for the two treatment groups will be the same, with an allowable difference of 5%. Power Analysis and Sample Size (PASS, version 1.0) software was used to verify the calculated sample size.

The following inclusion criteria were applied

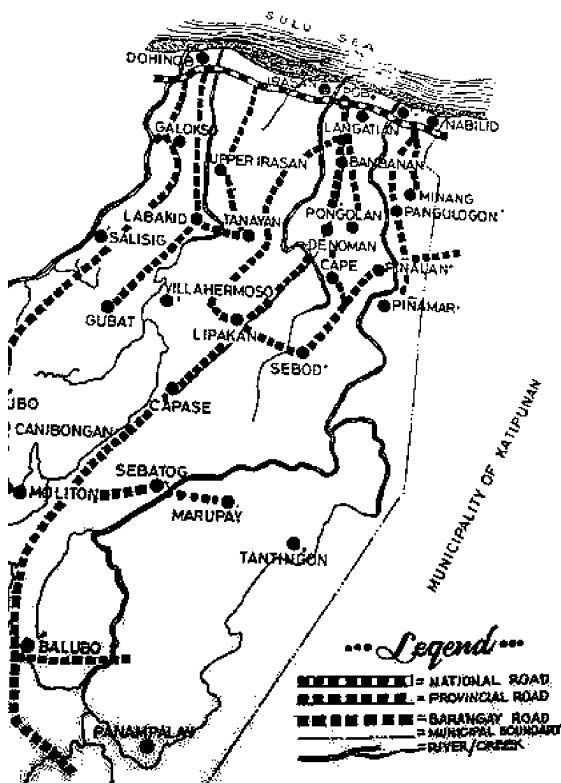


Fig 1- Map of municipality of Roxas, Zamboanga del Norte (Roxas RHU, 2003).

in the study: presence of chronic productive cough lasting for at least four weeks, or history of anti-TB treatment without observable clinical improvement; positive *Paragonimus* eggs on sputum examination; patients with the following characteristics were excluded from the study; age less than 15 years; pregnancy; history of acute or chronic disease of the liver or kidney; and history of drug hypersensitivity.

Treatment designation

Patients who were enrolled in the study were randomly assigned to either praziquantel or triclabendazole treatment groups. The patients who belonged to the praziquantel group were given praziquantel 25 mg/kg, three times daily, for three days; while those included in the triclabendazole group received triclabendazole 10 mg/kg, in a single dose.

Triclabendazole (Egaten®) was provided by Novartis International AG, (Switzerland), while praziquantel (Distocide®) was provided by Shin Poong Pharmaceutical (Korea). All drugs were procured by the World Health Organization (WHO) and forwarded to the University of the Philippines Manila (UP Manila).

Patient and parasitologic assessment

Baseline clinical assessment, which focused on history-taking and chest auscultation, was done on the patients. The patients were monitored for the occurrence of adverse drug events at 30 minutes, 24 hours, 48 hours, and 72 hours post-treatment. Patients who experience severe adverse events (SAE) were to be reported promptly to the Clinical Safety and Epidemiology, Novartis Healthcare Philippines. Compliance to the drugs was subjectively assessed through direct inquiry of the patients.

Sputum specimens were assessed for color and consistency; and were processed using 3% sodium hydroxide (NaOH) and centrifuged at high-speed setting for five minutes, after which, the resulting sediment was examined. A reference microscopist validated all positive specimens and re-read all negative specimens.

Statistical analysis

Results of the clinical and parasitologic

assessments were encoded using EpiInfo (v 6) software. Re-encoding was done to ensure accuracy of data entry. Accordingly, actual values were used to describe efficacy, safety, and tolerability data. Fisher's exact probability test was utilized to compare and determine significant differences between the parasitologic and clinical cure rates of praziquantel and triclabendazole.

An intention-to-treat approach was applied in this study to account for the dropouts in both treatment groups. Dropouts were assigned the worst possible outcome, described as follows: no improvement in reported symptoms, no resolution of previous abnormal chest examination findings, and positive *Paragonimus* egg in sputum specimen.

Ethical considerations

The study was undertaken in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and was approved by the Technical and Ethical Review Board, Research Implementation and Development Office (RIDO), College of Medicine, UP Manila. For ethical reasons, all patients screened with documented pulmonary paragonimiasis were given treatment.

RESULTS

Baseline findings

A total of 378 patients qualified for sputum examination. Of the 378 patients screened, 56 had positive *Paragonimus* eggs in their sputum, or paragonimiasis prevalence rate of 14.8%. Nine patients, found to be infected, were excluded from the study. Reasons for their exclusion included failure to indicate informed consent, anticipated difficulty in follow-up due to distance of place of residence, and physical disability.

Of the 47 patients enrolled in the study, 23 were randomly assigned to the praziquantel group, and 24 were assigned to the triclabendazole group. Thirty participants were < 45 years of age, while the remaining 17 participants belong to the ≥ 45 years age group. The gender distribution was nearly equal, with 24 males and 23 females. Almost half (42.6%) of the participants resided in Barangay Sibatog (Table 1).

Table 1
Paragonimus infection rates and distribution of study participants, by barangay.

Barangay	Number surveyed	No. positive for <i>Paragonimus</i> (%)	No. participants included in study (%)
Sibatog	86	24 (27.9)	20 (42.6)
Marupay	58	9 (15.5)	9 (19.1)
Piñalan	55	8 (14.5)	9 (19.1)
Piñamar	49	4 (8.2)	3 (6.4)
Pangologon	25	3 (12.0)	3 (6.4)
Tantingon	30	5 (16.7)	1 (2.1)
Sebod	12	3 (25.0)	2 (4.3)
Others: Balubo, Canubongan, Capasi, Coribongon, Denoman, Gubot, Moliton, Panapaloy	63	0 (0)	0 (0)
Total	378	56 (14.8)	47 (12.4)

Chronic productive cough was the most common clinical manifestation elicited during history-taking, with all participants in both treatment groups complaining of it. Baseline abnormal breath-sound findings were minimal for both treatment groups. On auscultation, only five patients in the praziquantel group and six patients in the triclabendazole group were documented to have crackles/rales. Wheezing was noted in one patient in each of the treatment groups.

Sputum submission and clinical re-examination during follow-up were completed for 30 and 60 days post-treatment. However, on day 90, four patients in the praziquantel group and five patients in the triclabendazole group were unavailable for physical examination. Moreover, four patients in the praziquantel group and three patients in the triclabendazole group failed to submit sputum specimens on day 90.

Treatment efficacy

For the clinical response to treatment based on change in symptoms from initial assessment to day 90 follow-up, all except one patient in the praziquantel group and all patients in the triclabendazole group reported an improvement relative to their previous complaint of chronic productive cough. All patients in the praziquantel group and all but two patients in the

triclabendazole group reported an improvement relative to the initial complaint of weight loss. All patients in both treatment groups reported improvements relative to initial complaints of hemoptysis, dyspnea, fever, and night sweats during day 90 follow-up. The difference in improvement in symptoms on day 90 between the two treatment groups was not statistically significant (Table 2).

Crackles/rales resolved in three-out-of-five patients in the praziquantel group. Of the six patients with crackles/rales at day 0 in the triclabendazole group, crackle/rales resolved in three patients. The remaining three patients in the same group dropped out of the study. Wheezing in one patient in the praziquantel group resolved at day 90, while another patient with wheezing in the triclabendazole group was lost to follow-up. Nonetheless, the difference in the resolution of abnormal chest findings on day 90 between the treatment groups was not statistically significant (Table 3).

For parasitologic cure, the number of infected patients rapidly dropped from an initial 23 to only five patients for the praziquantel group, while 11 out of 24 patients remained infected in the triclabendazole group on first follow-up (day 30). On day 60, the patients with *Paragonimus* infection further reduced to two in the praziquantel

group, while 11 patients were still infected in the triclabendazole group. On day 90, one patient in the praziquantel group remained infected, while six patients still had positive sputum findings in the triclabendazole group (Fig 2). The cure rate of praziquantel was 96.0%, while that of triclabendazole was 75.0%, on day 90 post-treatment. Intention to treat analysis showed no significant difference in the cure rates between praziquantel and triclabendazole (Fisher's exact probability = 0.29).

Compliance

All patients in the praziquantel group reported completing their intake of all tablets provided for

the prescribed three-day period. All patients in the triclabendazole group took the drug provided on the first day of treatment.

Safety and tolerability

A total of sixteen patients reported adverse events that were assessed to be mild (Table 4). Of the 16 patients, nine belong to the praziquantel group, while seven belong to the triclabendazole group. There was no serious adverse event reported or observed.

Headache was the most common complaint of patients 30 minutes post-treatment in both groups. Dizziness was more frequently reported in the praziquantel than in the triclabendazole group.

Table 2
Status of reported symptoms, by treatment group, days 0 and 90.

Reported symptoms	Praziquantel				Triclabendazole				Fisher's exact probability ^a
	Day 0	Day 90			Day 0	Day 90			
		No. improve-ment	With improve-ment	Lost to follow-up		No. improve-ment	With improve-ment	Lost to follow-up	
Chronic productive cough	23	1	18	4	24	0	19	5	1.00 ^b
Hemoptysis	16	0	13	3	22	0	17	5	1.00 ^b
Dyspnea	11	0	9	2	12	0	9	3	1.00 ^b
Fever	8	0	5	3	8	0	7	1	0.57 ^b
Weight loss	11	0	9	2	13	2	6	3	0.10 ^b
Night sweats	15	0	14	1	16	0	12	4	0.33 ^b

^aFisher's exact probability computed using data applied with intention to treat analysis

^bnot statistically significant

Table 3
Status of abnormal chest findings, by treatment group, days 0 and 90.

Abnormal chest findings	Praziquantel			Triclabendazole			Fisher's exact probability ^a
	Day 0	Day 90	Lost to follow-up	Day 0	Day 90	Lost to follow-up	
Crackles/Rales	5	2	0	6	0	3	1.00 ^b
Wheezes	1	0	0	1	0	1	1.00 ^b

^aFisher's exact probability computed using data applied with intention to treat analysis; ^bnot statistically significant

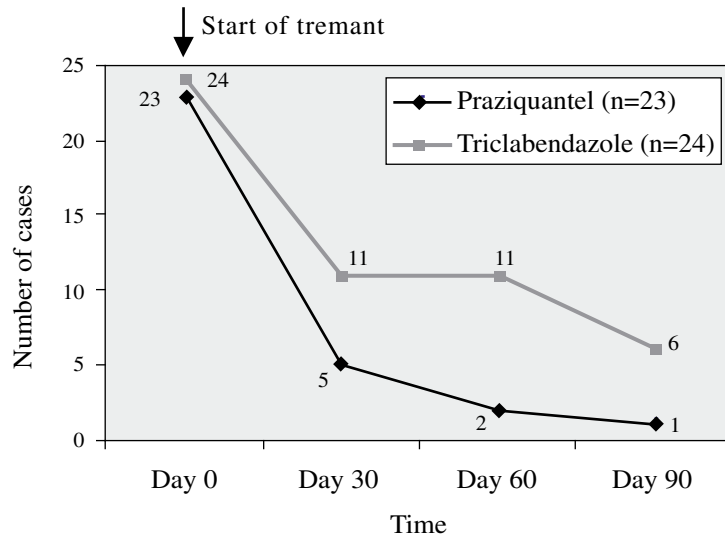


Fig 2- *Paragonimus* infection according to treatment group from day 0 to day 90.

Table 4
Adverse drug events and status, 30 minutes up to 24 hours posttreatment, according to treatment groups.

Adverse Event	No. of reported adverse events	Praziquantel				No. of reported adverse events	Triclabendazole			
		Re-solved	Im-proving	Con-tinuing	Wor-sening		Re-solved	Im-proving	Con-tinuing	Wor-sening
Headache	4	2	2	0	0	5	2	2	0	0
Dizziness/vertigo	4	4	0	0	0	1	1	0	0	0
Nausea/vomiting	1	1	0	0	0	0	0	0	1	0
Chest pain	0	0	0	0	0	1	0	0	0	0
Fever	0	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0
Allergic reaction/urticarial	0	0	0	0	0	0	0	0	0	0
Others	0	0	0	0	0	0	0	0	0	0
Total	9	7	2	0	0	7	3	2	1	0

One patient complained of nausea/vomiting in the praziquantel group, while another reported chest pain in the triclabendazole group.

Headache resolved in the two patients from

each of the treatment groups within 24 hours post-treatment. The other two patients from each group, who complained of headache, noted continuing improvement within 24 hours post-

treatment. The status of headache in one patient in the triclabendazole group was not determined. Nausea/vomiting resolved in all patients from both treatment groups who complained initially of it. Chest pain persisted but resolved within 24 hours in a patient in the triclabendazole group.

DISCUSSION

The prevalence rate of paragonimiasis in the municipality, as determined in the study, was 14.8%. This was much lower when compared with the previous prevalence rate of 27.2% in the area, in 2002 (de Leon and Piad, 2005). It should be noted that, in that particular study, surveillance was conducted only in Barangay Sibatog, which has the highest infection rate among the barangays. As such, the prevalence rate in that study would likely be higher than the one found in this study. Another important implication of this current prevalence rate is the probable ineffectiveness of the existing control program to curb paragonimiasis in the municipality. Possibly, residents in the municipality remain infected or they become continually re-infected after being previously cured. The former possibility may reflect inaccessibility to medical care due to topographical limitations imposed by the area, while the latter may reflect the difficulty of changing eating practices through health promotion and education.

The prevalence rate in Roxas is comparable to that of other areas in the country. As early as 1974, the prevalence rate of paragonimiasis was found to be high, at 12.5% in the province of Leyte (Cabrera and Fedival, 1974). In 1992, *Paragonimus* eggs were found in the sputum smears of patients from Basilan who were notable due to their lack of response to anti-TB medications (Infante *et al*, 1992). In Sorsogon Province, the municipality of Irosin had a prevalence rate of 16.3%, while that of the municipality of Casiguran was 25% (Belizario *et al*, 1997a,b;1998). In Davao del Norte Province, a project team from the DOH found an infection rate of 18.8% among 320 subjects (Zuazula *et al*, 2000).

The study confirmed the efficacy of praziquantel against paragonimiasis. The rapid

decrease in the number of infected patients from day 0 to day 90 and the marked improvements on symptoms reported by patients validate the efficacy of praziquantel, which agrees with previous studies (Johnson *et al*, 1985; Calvopina *et al*, 1998). However, for community-based control of paragonimiasis, the use of praziquantel poses problems because compliance by patients with the drug would be discouraged by the three-day dosage requirement as well as the frequency of the adverse events due to it (Calvopina *et al*, 2003). In this study, compliance, which was assessed subjectively, was satisfactory; however, it was not validated through an objective means.

Triclabendazole was shown to have a comparable efficacy with praziquantel in this study. Clinical improvement in triclabendazole was comparable with praziquantel. It must be noted, however, that the time of resolution of the symptoms was not determined in this study. Therefore, there are no findings to compare the immediacy with which either drug accorded symptomatic relief.

For parasitologic cure, although the praziquantel group showed a more rapid drop in infection rate and a smaller number of infected patients relative to the triclabendazole group, the statistical difference between the two cure rates was not significant. This finding is in agreement with a previous similar trial (Calvopina *et al*, 1998). The 10 mg/kg dose used in this study, which was proven effective in significantly reducing fluke burden in patients, was similar to the dose tested in the previous trials on triclabendazole in the treatment of paragonimiasis (Ripert *et al*, 1992; Calvopina *et al*, 2003).

In a study by Calvopina *et al* (1998), the clearance from *Paragonimus* eggs in the sputum of patients was 100% (15/15 subjects) for praziquantel and 87.5% (14/16 subjects) for triclabendazole by 90 days post-treatment. In this trial, six patients in the triclabendazole group and another patient in the praziquantel group remained infected on day 90 post-treatment. A high parasitic load might explain these findings. It was observed that most of the patients who failed to clear of *Paragonimus* eggs had high fluke burdens (Calvopina *et al*, 2003).

Unfortunately, the fluke burden of the patients was not determined in this study. Failure to clear *Paragonimus* eggs may possibly be explained by a continuing re-exposure to the parasite, which may have resulted in reinfection after the initial treatment. Persistence of infection suggests two recommendations. For such patients, a 2-dose regimen of triclabendazole (*ie*, 10 mg/kg given on two consecutive days) may be advocated, or the administration of another course of praziquantel, using 25 mg/kg three-times daily, for three days, may be considered (Calvopina *et al.*, 2003). Moreover, health education regarding transmission and changes in cooking/eating practices must be strengthened.

In this study, one patient treated with praziquantel was found to be positive for *Paragonimus* eggs on day 90, following previous negative readings. Moreover, for the triclabendazole group, one patient remained persistently infected from day 60 onwards, after being cleared on day 30, while another patient had a negative sputum finding on day 30, but was positive on day 60, then negative again on day 90 post-treatment. These findings may be explained by possible false negative readings of the sputum specimens. It is worth mentioning that patients with low fluke burden may be completely asymptomatic, and sputum examination may be negative. *Paragonimus* ova may only be found in the stool for such patients (Yokogawa, 1965). As a recommendation, the sensitivity of sputum examination for *Paragonimus* eggs can be improved with a 24-hour collection (Johnson *et al.*, 1985).

As for safety and tolerability, triclabendazole had slightly lower reporting of adverse drug events compared to praziquantel. It is also worth mentioning that both treatment groups did not yield any serious adverse drug events. Previous studies also found that triclabendazole was well tolerated by patients (Ripert *et al.*, 1992; Calvopina *et al.*, 1998, 2003).

This study therefore concludes that triclabendazole, administered at 10 mg/kg, in a single dose, has comparable efficacy, safety, and tolerability when compared to praziquantel 25 mg/kg, given three-times daily, for three days. It can thus be recommended as an alternative drug for paragonimiasis.

Because of the low sample size, the power of this study is limited. It is recommended that a larger sample size be used in a similar study. For efficacy, the earliest time of the resolution of clinical symptoms may be monitored and compared with parasitologic cure times. More objective measurements of clinical cure, such as chest radiograph and blood work-up, may be utilized to complement the physical examination findings. A more objective means of measuring compliance with medications may also be utilized.

Pursuant to the decentralization of health delivery and management as advocated by the Health Sector Reform Agenda, the task of safeguarding the people health of the people has been relegated to the local government units (LGUs). This community-based trial was undertaken in collaboration with the provincial and municipal governments of Roxas, Zamboanga del Norte. Highly organized field work by the RHU staff resulted in satisfactory follow-up among the patients included in the study. LGUs, through the rural health units (RHUs), have a great but mostly untapped potential to initiate and spearhead surveillance and control projects. The surveillance process in this study may be used by the Roxas municipal government to jumpstart a larger surveillance and control project for paragonimiasis. Alternatively, the project may be integrated into the more established surveillance and control scheme of pulmonary tuberculosis (TB), which exists in this area and is misdiagnosed as paragonimiasis.

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