Comparative effect of albendazole and diethylcarbamazine in the treatment of toxocariasis in children from Sri Lanka: A preliminary study

S. D. Fernando¹, V. P. Wickramasinghe²*, R. L. Dewasurendra¹ and G. M. G. Kapilananda¹

¹Department of Parasitology, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 8, Sri Lanka.
²Department of Paediatrics, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 8, Sri Lanka.

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Toxocariasis is a helminthozoonotic disease with significant morbidity. Diverse medications and different regimens are used in its treatment. Toxocariasis has a significant prevalence among Sri Lankan children, yet its treatment has not been evaluated. This was a preliminary study to determine the impact of ALB and DEC on the levels of anti-Toxocara antibodies and eosinophil count in 19 children who were tested positive for Toxocariasis, using the Microwell Serum Elisa Kit. Of these children, 10 were treated with ALB and 9 with DEC. Treatment response was defined as a significant reduction in the eosinophil count and anti-Toxocara antibody levels from the baseline level following treatment. There was a significant reduction in the anti-Toxocara antibodies with ALB as compared to DEC. Both drugs also showed a significant reduction in the eosinophil count post treatment as compared to baseline. The ALB regimen that was used of shorter duration course with a slightly higher dose as compared to other published literature. The dose was well tolerated and its compliance was good. Considering efficacy and acceptability, ALB (50 mg/kg/day) in 2 divided doses for 3 days is effective for treatment of toxocariasis in Sri Lankan children.

Key words: Albendazole, children, diethylcarbamazine, eosinophil, toxocariasis.

INTRODUCTION

Diseases caused by infections with helminthes are considered as neglected tropical diseases, and the study of these diseases receive less than 1% of global research funds (Hotez, 2008). Most infections left untreated result in chronic inflammatory disorders that can last several years and cause both concurrent and delayed-onset pathology to the afflicted human host (King, 2007; Benthory et al., 2006; Budke et al., 2005). Toxocariasis is a neglected helminthozoonotic disease caused by the larvae of dog and cat nematodes, Toxocara canis and Toxocara cati, respectively. The understanding of the global impact and cost of human toxocariasis is poor because there is insufficient clinical awareness and no clear repository for the efficacy of clinical, laboratory and treatment interventions (Smith et al., 2009).

The diagnosis of human infection by Toxocara canis relies heavily upon serological tests, the specificity of which can be inadequate in regions of endemic helminthiasis (Taylor and Holland, 2001). Seroprevalence of Toxocariasis in Sri Lanka is shown to be 43% in rural areas (Iddawela et al., 2003) and 20% in urban hospital population (Fernando et al., 2007). Human toxocariasis gives a diversity of clinical conditions ranging from non specific covert toxocariasis to compartmentalized(ocular or neurological) toxocariasis (Pawlowski, 2001). The classic visceral larva migrans (VLM) syndrome

*Corresponding author. E-mail: pujithaw@yahoo.com.
usually occurs in pre-school children who often present with mild fever, lymphadenopathy, hepatomegaly, respiratory symptoms and non specific symptoms, such as joint and abdominal pain (Smith et al., 2009). A high eosinophil count is characteristic of toxocariasis (Taylor and Holland, 2001; Kwon et al., 2006). Multiple ecchymotic lesions could occur due to associated thrombosthenia (Wickramasinghe et al., 2001). Although, all cases of VLM need to be treated, covert toxocariasis could be left alone as it is self limiting (Smith et al., 2009). However, due to the increase risk of larval migration and localization in the brain, it is recommended to treat even occult toxocariasis with mild eosinophilia and elevated serology (Pawlowski, 2001).

Of the four groups of anthelmintics used to treat systemic helminth infections, benzimidazole derivatives (albendazole (ALB), thiabendazole and mebendazole) and Diethylcarbamazine (DEC) are preferred over Ivermectin and Praziquantel in the treatment of toxocariasis (de Silva et al., 1997). Of the benzimidazole derivatives, mebendazole is absorbed poorly and thiabendazole is tolerated poorly, thus leaving ALB as a better choice for treatment (de Silva et al, 1997). The duration of treatment for toxocariasis varies depending on the medication. DEC has a long course duration of 21 days, while ALB has a 3 to 5 day regimen (Magnaval, 1995; Pawlowski, 2001). As there are no studies evaluating the management of toxocariasis in Sri Lankan children, this study was carried out to evaluate the efficacy of ALB and DEC in the management of paediatric patients with toxocariasis.

MATERIALS AND METHODS

The study was carried out at the University Paediatric Unit of Lady Ridgeway Hospital, Colombo, Sri Lanka, as part of a large study to assess the seroprevalence of toxocariasis among asthmatic children (Fernando et al., 2009). The study population comprised 198 children between the ages of 5 and 12 years, presenting to the hospital with or without bronchial asthma. With the exception of bronchial asthma in 98 of these children, all were asymptomatic and did not present with any clinical manifestations of toxocariasis, such as fever, hepatomegaly, splenomegaly or ocular compromise. Moreover, ophthalmoscopic examination was normal. The children had no concomitant disease or altered liver or kidney function. Their visit to the hospital was for convalescent follow up of illness they had a few weeks before.

Children were enrolled for the study after obtaining informed written consent from their parents or guardian. An aliquot of 2 ml of blood was collected under aseptic conditions by trained nurses and separated for haematological and serological assessment.

EDTA blood was immediately used for white blood cell count using the haemocytometer and a differential count was done using a counting chamber. Eosinophilia was considered when the absolute count was over 400/mm². Blood for serology was centrifuged at 800 g for 5 min, after which the sera was collected and stored at -20°C until it was used. Diagnosis of Toxocara seropositivity was based on Toxocara serology Microwell Serum Elisa Kits (Diagnostic Automation INC. California, USA: Cat No. 8206-3). Serum was re-centrifuged at 3,000 r.p.m for 10 min. Subsequently, 100 μL of the test sera was added to each micro-well with positive and negative controls in separate wells. This was incubated at room temperature for 10 min to enable the Toxocara specific antibodies (if present) to bind to the wells which are coated with an excretory / secretory antigen from the Toxocara larvae. The plate was washed 3 times with diluted wash buffer and then 2 drops of enzyme conjugate was added to each well. This was incubated at room temperature for 5 min. The plate was washed 3 times with diluted wash buffer and any trace of wash buffer was removed by flip drying. Two drops of the chromogen was added to the wells and the plate was incubated at room temperature for 5 min. Two drops of the stop solution was added to each well. The plate was read using an ELISA reader at 450 nm wavelength. The ELISA test was regarded as positive when the optical density (OD) units were 0.3 or above. Technical officers performing the investigations were blind to the clinical status, age and sex of the child.

Thirty nine children were positive for Toxocara serology (OD ≥ 0.3) and eligible for enrolment into the study. As the parents of 14 children did not give consent for treatment, 25 children were alternatively assigned to receive treatment with either ALB or DEC (Figure 1).

ALB (Ubenzole -400®; Umedica Laboratories Pvt. Ltd, India) was given at 50 mg/kg/day in two divided doses for 3 days. The maximum dosage given was decided according to the age of the child (Rochette, 1985):

1. Age <5 years maximum dosage is 400 mg/day.
2. Age 5 to 10 years maximum dosage is 600 mg/day.
3. Age >10 years maximum dosage is 800 mg/day.

DEC (State Pharmaceutical Corporation, Sri Lanka) was given as 6 mg/kg/day in three divided doses for 21 days. Prior to assignment of treatment, it was confirmed that none of the children had been treated with benzimidazole the previous year. A sample of faeces was collected from each child and examined for helminth ova and protozoan cysts by saline and iodine smears to exclude infections with other nematodes.

The children were requested to come for follow up at the end of 3 months to assess the anti Toxocara antibodies and eosinophil counts following treatment (Figure 1). Ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, Colombo and the Ethics Review Committee of the Lady Ridgeway Children’s Hospital.

Statistical analysis

Wilcoxon Signed Rank Test for matched pairs was performed to determine whether there was a significant reduction in the antibody levels and mean absolute eosinophil count after treatment with either ALB or DEC. Mann – Whitney test was used to assess whether or not there was a significant difference in the antibody levels of the two treatment groups after treating with the respective anthelmintic medication. Data were analyzed using SPSS version 15.0 for Windows system.

RESULTS

Prior to enrolment in the study, the stool sample
examined for intestinal parasites were found to be negative. Thereby, it is assumed that the study would have overcome the cross reactions that may have been present between the *Toxocara* ELISA assay and other antibodies of helminth parasites.

Only 19 (48.7%) children presented for follow up (Figure 1). Of the 19 children, 12 were females and 7 were males. 10 children were treated with ALB and 9 with DEC. All children treated with DEC and the 6 children treated with ALB were asthmatic. Table 1 gives the characteristics and laboratory findings of the study population.

Wilcoxon Signed Rank Test showed (Table 2) that at the end of 3 months, there was a significant reduction in anti-*Toxocara* antibody levels in the group treated with ALB (p = 0.028, 95%CI). Although a reduction of the antibody levels in the group treated with DEC was observed, the reduction was not statistically significant (p = 0.260, 95%CI). A significant reduction of the eosinophil counts was observed in both groups (p = 0.037 for ALB, and p = 0.011 for DEC).

Mann-Whitney test showed that there was no significant difference in the *Toxocara* antibody levels after being treated by either ALB or DEC (p = 0.079). A similar test was carried out to determine whether or not there was a difference in the eosinophil counts after treatment with the two drugs. Again, no significant difference was seen (p = 0.842) (Table 2). No side effects were recorded with the drugs during follow up.

**DISCUSSION**

Human toxocariasis is primarily a soil transmitted helminthozoonosis. Geophagia, a specific type of pica, pet ownership, school location, host age and sex have
Table 1. Characteristics of 19 patients positive with *Toxocara* serology.

<table>
<thead>
<tr>
<th></th>
<th>Treated with Albendazole (n = 10)</th>
<th>Treated with DEC (n = 9)</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female 6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Male 4</td>
<td>3</td>
</tr>
<tr>
<td>Median (range) age in years</td>
<td>9 (4 – 11)</td>
<td>6 (4 – 13)</td>
</tr>
<tr>
<td>Children with Asthma</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Mean (range) <em>Toxocara</em> antibody test (OD units)</td>
<td>Before treatment</td>
<td>0.73 (0.34 – 1.22)</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>0.02 (0.01 – 1.4)</td>
</tr>
</tbody>
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OD: Optical density.

Table 2. Comparison of median optic density (OD) and eosinophil count of the two groups before and after treatment (Wilcoxon signed rank test).

<table>
<thead>
<tr>
<th></th>
<th>Median OD (before treatment)</th>
<th>Median OD (after treatment)</th>
<th>p</th>
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<tbody>
<tr>
<td>ALB group</td>
<td>0.715</td>
<td>0.244</td>
<td>0.028</td>
</tr>
<tr>
<td>DEC group</td>
<td>0.928</td>
<td>0.612</td>
<td>0.260</td>
</tr>
<tr>
<td>p *</td>
<td>0.079</td>
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Mean Eosinophil count (x10^3/µL) before treatment
<table>
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<tr>
<th></th>
<th>Mean Eosinophil count (x10^3/µL) (after treatment)</th>
<th>p</th>
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<tbody>
<tr>
<td>ALB group</td>
<td>484.2</td>
<td>342.5</td>
</tr>
<tr>
<td>DEC group</td>
<td>740.0</td>
<td>314.8</td>
</tr>
<tr>
<td>p *</td>
<td>0.842</td>
<td></td>
</tr>
</tbody>
</table>

p * (Comparison of median ODs after treatment in two groups – Mann Whitney test).

It has been identified as risk factors for developing the disease (Holland et al., 1995). Proper disposal of pet litter, deworming infected pets, complete cooking of meats, thorough rinsing of fruits and vegetables, and good handwashing practices are important measures for preventing human infections (Harvey et al., 1991). Covering sandpits in common playgrounds and outdoor vegetable gardens is also helpful, since it prevents contamination (Uga and Kataoka, 1995).

It has been demonstrated that the E-S antigens widely used in the immunodiagnosis of toxocariasis in humans are cross-reactive against serum samples from patients with a variety of helmitch infections (Magnaval et al., 1991; Jacquier et al., 1991; Gillespie et al., 1993; Lynch et al., 1988, 1993; Yamasaki et al., 2000). Therefore, to overcome such problems, a recombinant *T. canis* antigen has been developed (Yamasaki et al., 2000) and its high specificity and usefulness has been demonstrated.

Treatment of human toxocariasis is unsatisfactory, and the decision to treat can be difficult. In general, treatment is unlikely to be provided unless the patient exhibits very severe symptoms as most often the disease is subclinical or self limiting (Caumes, 2003).

This was a preliminary study to determine the impact of ALB and DEC on the levels of anti-*Toxocara* antibodies and eosinophil count in 19 children who were tested positive for *Toxocara* using the Microwell Serum Elisa Kit. Treatment response was defined as a significant reduction in the eosinophil count and anti-*Toxocara* antibody levels from the baseline level following treatment. In this study, there was a significant reduction in the anti-*Toxocara* antibodies with ALB as compared to DEC. Both drugs also showed a significant reduction of the eosinophil count post treatment acompanied to baseline. The ALB regimen that was used was a shorter duration course with a slightly higher dose as compared to other published literature (Pawlowski, 2001; Sturchler et al., 1989). The dose was well tolerated and its compliance was good. Considering efficacy and acceptability, ALB (50 mg/kg/day) in 2 divided doses for 3 days is effective for treatment of toxocariasis in Sri Lankan children.
Most drug efficacy trials on toxocariasis have been done involving small sample sizes. Large control trials are needed to evaluate the best medication, as well as the most appropriate dose and regimen. A number of preparations, including fenbendazole, mebendazole and DEC, have been used for treatment of toxocariasis in humans, but good evidence for their efficacy based upon well-designed, double blind clinical trials are few (Taylor and Holland, 2001). Pawlowski (2001) suggested the use of several criteria to determine commencement of treatment. Patient characteristics, history, clinical symptoms and signs, positive serology, eosinophilia and increased levels of IgE were assessed to initiate treatment with ALB (15 mg/kg body weight) daily for 5 days. Following this, he observed an improvement in haematological and serological parameters over 4 weeks. Apart from treating the symptomatic, it was recommended to give a single ALB dose to eradicate migrating larva in the asymptomatic patients (Pawlowski, 2001).

Magnaval et al. (1992) reported the results of a double-blind, placebo-controlled, randomized study on the efficacy of mebendazole for the treatment of human toxocariasis. Patients were selected on the basis of seropositivity and clinical and biological symptoms, including total and specific Toxocara IgE. On the basis of the results, the authors concluded that mebendazole was only moderately effective against human toxocariasis. Magnaval (1995) went on to assess the relative efficacy of DEC and mebendazole, using an open random study design. Both treatments showed a good clinical response with significant reduction in eosinophil count, but mebendazole showed more pronounced effects on Toxocara specific IgE kinetics. As patients receiving DEC reported significantly more adverse effects, the author advocated the use of a five day mebendazole course over DEC for the treatment of human toxocariasis (Magnaval, 1995).

Sturchler et al. (1989) assessed a 5-day treatment course of thiabendazole (25 mg/kg twice a day) or ALB (5 mg/kg twice a day) for toxocariasis. Tolerability, at the end of the course, was 40 and 58% for thiabendazole and ALB, respectively. After a mean period of 30 weeks, 27 and 32% of patients receiving thiabendazole and ALB, respectively, were clinically cured. Due to the high tolerability and fewer adverse effects, the authors recommended a minimum dose of ALB (10 mg/kg) daily for 5 days to treat ocular and visceral toxocariasis.

Conclusions

This preliminary study revealed that ALB had a significant effect in reducing the Toxocara antibody levels as compared to DEC with a significant reduction in the mean eosinophil count as compared to the baseline. In addition, ALB has a shorter treatment course duration when compared to DEC and was well tolerated. This is especially useful in children in order to maintain the compliance and achieve optimum clearance of the parasite from the body. However, the results of this study have to be confirmed with a larger prospective study.

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REFERENCES


