CHAPTER 9

The effect of albendazole on
Oesophagostomum bifurcum infection and pathology
in children from rural northern Ghana

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Chapter 9

ABSTRACT

Ultrasonography has already revealed that up to 50% of individuals in some villages in northern Ghana have colonic pathology induced by *Oesophagostomum bifurcum*. Approximately 2% of those affected progress to clinical oesophagostomiasis if left untreated. In the present study, ultrasound-positive children living in a heavily infected community were each given 5 days of treatment with albendazole (10 mg/kg/day), early in the dry season.

Treatment reduced the prevalence, number, size and half-life of the ultrasound-visible nodules, stopped the excretion of *O. bifurcum* eggs, and reduced the development of clinical oesophagostomiasis during the subsequent 8 months. However, treatment had no impact on the new infections that occurred during the following rainy season, and no impact on nodule prevalence by the end of that rainy season. Surgical management may not be essential in non-acute cases of clinical oesophagostomiasis, as albendazole may kill the nodule-dwelling worms.
INTRODUCTION

Each year, approximately 50 cases of oesophagostomiasis present at Nalerigu Hospital, in the centre of the area of northern Ghana where *Oesophagostomum bifurcum* is endemic. There are two distinct clinical presentations of the granulomatous lesions produced by the helminth, both containing thick yellow–green pus and live, white, 12-mm-long, juvenile parasites. Those suffering from the multinodular disease present with vague symptoms of general abdominal pain, persistent diarrhoea and severe wasting, but hundreds of nodules, each 2–10 mm in diameter, can be found throughout the wall of the colon. Cases with the other presentation, the Dapaong tumour, each have a palpable abdominal mass, approximately 40 mm in diameter, which is commonly painful, adhered to the abdominal wall and associated with fever.

There have been varied case reports of oesophagostomiasis, which can now be diagnosed by ultrasound, from Africa, South America and the Far East. Although removal of the lesions, by sectional colectomy, is often recommended, conservative drug treatment, with high doses of albendazole, appears promising (Chapter 4 and 15:152). Prevalence of the disease appears particularly high in northern Ghana and Togo, where the results of parasitological surveys indicate that 250,000 people may be infected with *O. bifurcum*. In this endemic area of West Africa, human-to-human transmission occurs during the rainy season; the route is assumed to be oral, but the mode of infection is not known. The life-cycle of *O. bifurcum* is presumed to be similar to that described for the *Oesophagostomum* spp. infecting animals other than man: the parasites are ingested, as third-stage larvae (*L*₃), develop into fourth-stage larvae (*L*₄) within nodules in the intestinal wall, and <3 weeks post-infection, re-enter the intestinal lumen, where the *L*₄ develop into egg-laying adults. The eggs pass out with the host's faeces onto the ground, and then, under suitable environmental conditions, take 7 days to develop into *L*₃. Arrested larval development, in which larvae remain within nodules while the climate is harsh but continue their development into lumen-dwelling, egg-laying adults once conditions improve, has been described for some *Oesophagostomum* spp.

Given the high prevalence of *O. bifurcum* infection in parts of West Africa, surprisingly few cases of clinical oesophagostomiasis are observed in this region. Many of the 250,000 individuals infected with the lumen-dwelling adults appear to have tolerated the preceding histotrophic phase of the life-cycle without developing severe symptoms. However, ultrasonography has revealed that colonic nodules are common in asymptomatic individuals, and can be detected in up to 50% of individuals in some
villages within the endemic area (Chapter 5). The asymptomatic nodules visualized with ultrasound have a mean diameter of 18 mm, although nodules as small as 7 mm in diameter can be visualized. *Oesophagostomum bifurcum* larvae of the same developmental stage as those found in the nodules of symptomatic cases (L₃) have been isolated from these asymptomatic nodules during surgery (Chapter 6). It is not known whether the asymptomatic nodules are part of the normal life-cycle of the parasite or if they result from an aberrant migration and are dead-end stages of the parasite. Approximately 2% of the people with these nodules do develop clinical disease if left untreated (Chapter 8).

Albendazole is the drug recommended by the Ghanaian Ministry of Health for the treatment of intestinal worms, and is the most effective anti-helminthic for removal of lumen-dwelling, adult *O. bifurcum*⁹⁴. Compared with adults from the same communities, children are more frequently found infected with *O. bifurcum*, both by ultrasound (Chapter 8) and by parasitological methods¹⁴⁶, and are more likely to suffer from clinical oesophagostomiasis¹⁵². The aim of the present study was to evaluate the impact of high-dose treatment with albendazole, early in the dry season, of school-age children found to have the colonic pathology induced by *O. bifurcum*.

**SUBJECTS AND METHODS**

Overall, 134 children were included in the study, on the basis of having ultrasound-visible pathology indicative of oesophagostomiasis, in November 1997, at the start of the dry season. The children were all from schools and villages in the Bunkpurugu area, which is inhabited by the Bimoba tribe and has the highest prevalences of *O. bifurcum* infection in northern Ghana. Approximately 500 children aged 5 years or more were screened to identify the 134 ultrasound-positives. Stool samples were taken from the 134 subjects, and abdominal palpation was performed on each. All the subjects gave their informed consent and ethical approval was given by the Ghanaian Ministry of Health.

All the nodules visible by ultrasound and any palpable masses possibly attributable to oesophagostomiasis were counted and measured. Each stool sample was cultured⁴³ to produce L₃ from any eggs and so allow *O. bifurcum* and hookworm to be differentiated (the eggs of these helminths being morphologically identical). The number of larvae produced from two, 2-g subsamples of each stool sample was counted and the counts used to categorize each infection as low (one to nine larvae), moderate (10–32 larvae) or high (>32 larvae) intensity.
The subjects were divided into a control group, consisting of 69 children from Mangol, and a treatment group of 65 children from three nearby schools. Each of the children in the treatment group was given approximately 10 mg albendazole/kg daily for 5 days (i.e. one 200-mg tablet daily to each child weighing <30 kg, and two 200-mg tablets to each of the heavier children). Treatment was supervised by the parents of each child after the regimen had been explained to them.

On three occasions during the subsequent 12 months, in the February (late dry season), June (mid rainy season) and October (late rainy season) of 1998, the children were examined by ultrasound, abdominal palpation and stool culture. The whole study cohort was treated with albendazole at the end of the study.

**Statistical Methods**

The gender and age distribution of the children in the control and treatment groups were compared using the chi-square and the independent-samples t-tests, respectively. Between-group differences in the prevalence and number of ultrasound-detectable nodules, at each of the four test times (i.e. on enrollment and at each follow-up), were investigated using the chi-square and Mann–Whitney tests. The same tests were used to compare the prevalences of *O. bifurcum* in the stool samples and the intensities of the infections. For each group, the McNemar and Wilcoxon tests were used to investigate the statistical significance of the temporal differences observed in the prevalence and intensity of the ultrasound-detectable colonic pathology and of stool infection, between the tests in November 1997 and October 1998. The sizes of the nodules seen in the control and treatment groups were compared using independent-samples t-tests, after log transformation of the sizes to normalize the data. The between-group differences in the numbers of new ultrasound-, abdominal-mass- or stool-positive subjects detected during the rainy season were investigated using the chi-square test.

**RESULTS**

Data analysis was limited to the 109 subjects (81% of those enrolled) who attended all three of the scheduled follow-ups. The 25 non-completers (14 from the control group and 11 from the treatment group) had similar baseline data to these 109 children.

There was no significant difference in the gender distributions of the two groups (*P*=0.49) but the members of the treatment group were, on average, slightly but significantly older than the children in the control group (*P*=0.005).
Effect of Treatment on the Ultrasound-visible Nodules

On enrollment in November 1997, all the subjects had colonic nodules detectable with ultrasound, and the children assigned to each group had similar numbers of detectable nodules ($P=0.13$). The prevalence and intensity of the ultrasound-visible pathology decreased in both groups during the course of the dry season, and increased again during the late rainy season (Figure 1). In February 1998 and again in June 1998, the prevalence and intensity of the pathology were significantly lower in the treated group than in the control group ($P<0.05$ for each). In October 1998, however, the prevalence and number of nodules in the two groups were similar ($P>0.3$ for each). Eight children remained ultrasound-positive throughout the course of the study but only one of these was from the treatment group.

In November 1997, the nodules detected in the control group were of a similar size to those seen in the treatment group ($P=0.43$; Table 1). Although the mean size of the nodules in the treatment group remained constant throughout the study, that of the nodules in the control increased between November 1997 and February 1998 and again between February 1998 and June 1998, before decreasing between the June and October of 1998. In the February follow-up, the nodules seen in the control group were, on average, significantly larger than those found in the treatment group ($P=0.025$). In October 1998, however, the between-group difference in nodule size was not significant.

During the study, one (2%) of the children in the control group presented at Nalerigu Hospital, in the middle of the rainy season, with acute abdominal pain and a periumbilical mass consistent with oesophagostomiasis. She was treated with 400 mg albendazole daily for 5 days, and made a speedy recovery. None of the children in the treatment group developed abdominal symptoms.
Effect of Treatment on the Palpable Abdominal Masses
In November 1997, the prevalence of palpable nodules and the mean number of such masses/subject were similar in the two groups ($P>0.7$ for each). The prevalence of palpable masses diminished throughout the year of the study in both groups, but more rapidly in the treatment group (Figure 2). In June 1998 (mid rainy season), the prevalence of palpable masses and the mean number/subject were both significantly higher in the control group than in the treatment group ($P=0.005$ for each).

Effect of Treatment on Egg Excretion in Stools
In November 1997 there were no significant between-group differences in either the prevalence of stool positivity or the numbers of $L_3$ found in the stool cultures ($P>0.5$ for each). In the control group, stool positivity and the intensity of stool infection remained high throughout the year, reaching a peak during the mid rainy season (Figure 3) before returning to pre-rain levels (similar to those found in November 1997) by October 1998 ($P>0.3$ for each). Although every subject in the treatment group was stool-negative during the first two follow-ups after albendazole treatment, some of the members of this group were found stool-positive at the last follow-up, although the prevalence and intensity of stool infection then remained significantly less
than at enrollment ($P<0.04$; Figure 3). At the final follow-up, in October 1998, not only were twice as many people in the control group excreting eggs as in the treatment group, but the mean number of eggs being excreted by each stool-positive was also much higher in the control group than in the treatment group ($P<0.001$ for each).

Table 1: Temporal variation in the sizes of colonic nodules detected by ultrasound, in 55 control children and 54 treated children

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<tbody>
<tr>
<td>Control group</td>
<td>17.1</td>
<td>22.1</td>
<td>27.4</td>
<td>17.3</td>
</tr>
<tr>
<td>Treatment group</td>
<td>17.8</td>
<td>16.3</td>
<td>17.7</td>
<td>16.6</td>
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Patterns of Natural Progression and Re-infection at an Individual Level

Approximately 40% of the study children became newly ultrasound-positive between June and October 1998 (during the late rainy season), with no significant between-group difference in this proportion ($P>0.4$). Eighteen (46%) of the 39 June-negatives in the control group and 20 (39%) of the 52 June-negatives in the treatment group were found to be ultrasound positive in October (Figure 4).

In the control group, during the early rainy season (between February and June 1998), seven (25%) of the 28 children found stool-negative in February began excreting eggs, and 17 (63%) of the 27 children already positive in February showed an increase in egg excretion. No child in the treatment group resumed excreting eggs until October 1998, in the late rainy season (Figure 3).

Ultrasound and stool positivity at an individual level did not show any association at any follow-up assessment, and there were many subjects who were concurrently positive for one parameter and negative for the other (data not shown). However, 10 children in the treatment group were found stool-positive, for the first time post-treatment, in October 1998, and seven of these were only found ultrasound-positive post-treatment at the same time. Thirteen of the 20 treated children who became newly ultrasound-positive in October did not become stool-positive.
The half-life of the colonic nodules in the children appeared to be reduced by treatment, from 3-4 months (in the untreated children) to 1-2 months (Table 2).

<table>
<thead>
<tr>
<th>Assessment date</th>
<th>Control group (n = 55)</th>
<th>Treatment group (n = 54)</th>
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</thead>
<tbody>
<tr>
<td>November 97</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>February 98</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>June 98</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>October 98</td>
<td>16</td>
<td>4</td>
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</table>

Figure 4: Seasonal emergence and regression patterns of ultrasound visible nodules in both groups.

Table 2: Longevity of the colonic nodules detected with ultrasound, in 55 control children (150 nodules) and 54 treated children (87 nodules).
DISCUSSION

High-dose albendazole treatment, administered early in the dry season to a group of ultrasound-positive children living in a heavily infected community, reduced the prevalence, number, size and half-life of the nodules visible by ultrasound, stopped the excretion of *O. bifurcum* eggs, and reduced the development of clinical oesophagostomiasis. Toxic shock (secondary to antigen release) can occur when the tissue-dwelling helminths responsible for cystercercosis, toxocariasis and onchocerciasis are killed. In the present study, however, there was no evidence to show that treatment resulted in an exacerbation of the inflammatory reaction surrounding the parasites in the colonic wall.

As clinical oesophagostomiasis can present at any time of the year, the 5-day treatment early in the dry season appeared to be of benefit not only for that dry season but also the subsequent early rainy season. However, 12 months post-treatment, at the end of the rainy season, there were no significant differences in the prevalences and intensities of the ultrasound-visible nodules in the treated and control groups. The numbers of subjects becoming newly ultrasound-positive during the rainy season were also similar in the two groups. Emergence of an ultrasound-detectable nodule presumably indicates a new infection with *O. bifurcum*. Therefore, the treatment of a highly infected, selected portion of the study population at the end of the 1997 transmission season had no impact on the new infections occurring during the following rainy season, and no impact on nodule prevalence by the end of that rainy season. The similar incidences of re-infection seen in the two groups indicate that the new infections were obtained from larvae present in the environment at large, and were not the result of self-infection at habitually visited defecation sites, for example.

In the control group, the prevalence and intensity of stool positivity were increasing during the early rainy season, each apparently peaking around June (Figure 3). However, no subject in the treatment group was found to be excreting eggs until the late rainy season in October, and then the prevalence and intensity of egg excretion were still far lower than in the control group. The temporal pattern seen in the prevalence and intensity of egg excretion by the untreated children (Figure 3) is probably the result, at least in part, of lumen-dwelling adults, from the rainy season preceding the present study, surviving the dry season and continuing to excrete eggs into the subsequent rainy season. However, the pattern also hints at the possibility of arrested larval stages exiting from their dry-season, arrested state in nodules. There would be no evidence of such arrested
development in the treatment group because the histotropic stages of *O. bifurcum* were (presumably) killed by the albendazole.

At the final (October) follow-up, some individuals in the treatment group were found ultrasound- and stool-positive for the first time post-treatment, but others in the same group became newly ultrasound-positive in October without becoming stool-positive, and *vice versa*. The ultrasound equipment used in the present study can only reveal nodules larger than 7 mm (Chapter 7), although some *Oesophagostomum* spp., such as *O. dentatum* in pigs\(^{155}\), produce nodules that are <5 mm in diameter. The number of L\(_3\) detected by the standard method of stool culture is approximately equal to the number of egg-laying adult worms present in the intestine\(^{52}\). Biopsies from cases of clinical oesophagostomiasis reveal that there is only one worm/nodule\(^{52}\). Taken together, these observations indicate that some egg-laying adults develop from larvae in nodules that are too small to be visible by ultrasound, and that some nodules visible by ultrasound still contain their worms. The stool-culture technique used in the present study has been shown to have a sensitivity and specificity of >90%\(^{156}\). However, the sensitivity and specificity of the ultrasound test used are impossible to determine, although the technique has only a small degree of intra- and inter-observer variation (Chapter 7).

The larvae within the nodules may be unable to develop into lumen-dwelling adults, the nodules resolving spontaneously or developing into Dapaong tumours during the course of the dry season. It is also possible that some of the juvenile stages of *O. bifurcum* within the ultrasound-visible nodules are viable. They may soon pass into the intestinal lumen and release eggs, or do so after an arrested period. It is not known which type or types of nodule were detected in the present study, and it may be that several types occur from one infection with *O. bifurcum* L\(_3\).

The possibility that the larvae of *O. bifurcum* can temporarily arrest their development in humans has important implications for the planning and implementation of control strategies. If latent worms in the colonic nodules form a reservoir of infection from the previous year, then treatment of a population must be potent enough to kill these worms, and treatment efficacy cannot be assessed until the following rainy season. If 'ALD nodules' exist, stool cultures are not a comprehensive method of estimating the prevalence of infection.

The cure rates achieved in the present study—of 96.3% for the colonic pathology 8 months post-treatment and of 100% for the infections with lumen-dwelling adults 4
months post-treatment—are impressive. However, the drug regimen employed is rather impractical for use in a community-based control programme. Such programmes should include treatment of a larger proportion of the population at risk, to prevent re-infection. The significant reduction of colonic pathology seen gives further hope for use of the present, 5-day, albendazole regime (Chapter 4 and 152) for the non-surgical treatment of non-acute cases of clinical oesophagostomiasis.