

Treatment of angiostrongyliasis using a combination of albendazole and dexamethasone: the results of a retrospective and comparative study

Z. DIAO*, J. WANG*, H. QI, X. LI, X. ZHENG and C. YIN

Beijing Tropical Medicine Research Institute, Beijing Friendship Hospital, Capital Medical University, 95 Yong-An Road, Beijing 100050, China

Received 13 August 2010, Revised 1 October 2010,

Accepted 6 October 2010

As the information available on the treatment of angiostrongyliasis with a combination of albendazole and dexamethasone is limited, the efficacy of such therapy was assessed using data collected during the 2006 outbreak of angiostrongyliasis in Beijing. In a retrospective and controlled study, 35 patients treated with albendazole–dexamethasone (given 20 mg albendazole/kg and 3 mg dexamethasone daily for 7 days) were compared with 34 controls who were treated only symptomatically (with acetaminophen or other drugs). Compared with the controls, the patients given the combination were less likely to have headaches after 7 days ($P=0.038$), tended to have headaches that cleared quicker ($P=0.010$), and received fewer doses of acetaminophen ($P=0.036$). Since no serious adverse effects were observed, a 1-week treatment with a combination of albendazole and dexamethasone appears both safe and beneficial in the treatment of angiostrongyliasis.

Angiostrongylus cantonensis, the rat lungworm, is the principal cause of human angiostrongyliasis world-wide. Land and aquatic snails are the parasite's primary intermediate hosts, and humans become infected by ingesting the parasite's larvae in raw or undercooked snails, contaminated water or contaminated vegetables. Over the last decade, the incidence of angiostrongyliasis appears to have markedly increased, and several outbreaks have been reported, including one in Beijing in 2006 (Lv *et al.*, 2008).

The most common presenting symptom of angiostrongyliasis is severe headache, with non-focal neurological findings often observed (Slom *et al.*, 2002). Treatment relies mainly on symptomatic relief, using drugs such as acetaminophen and anti-inflammatory corticosteroids. The efficacy of anthelmintic drugs for the treatment of

this infection has not been well established, and the results of attempts to find a specific and effective treatment have so far been generally inconclusive. A combination of mebendazole and corticosteroids has been used clinically, with promising results (Chotmongkol *et al.*, 2006), and a combination of albendazole and a corticosteroid also appeared to be effective, albeit in an observational study that did not include controls (Chotmongkol *et al.*, 2004). In the present study, the efficacy of albendazole–dexamethasone in the treatment of angiostrongyliasis patients from the 2006 outbreak in Beijing was evaluated.

PATIENTS AND METHODS

Study Design and Ethics

In this retrospective and comparative investigation, confirmed angiostrongyliasis cases treated for 1 week with a combination

Reprint requests to: C. Yin.

E-mail: modscn@yahoo.com.cn.

*Z. Diao and J. Wang contributed equally to this article.

of albendazole (at 20 mg/kg.day) and dexamethasone (at 3 mg/day) at the Beijing Friendship Hospital (BFH) were compared with cases (the 'controls') who were initially treated, at other Beijing hospitals, only symptomatically (with acetaminophen and some other drugs). The patients given the combination therapy had been diagnosed as angiostrongyliasis cases after presenting at the BFH whereas the controls had presented at other hospitals in Beijing (and were not identified as angiostrongyliasis cases until they were referred to the BFH). For each case considered in the present study, at least 16 days passed between the initial presentation and a confirmed diagnosis of angiostrongyliasis. All the data analysed in the present study came from the medical records of the BFH.

The controls were all given the combination treatment after they had been referred to the BFH. The study protocol was approved by the BFH's Ethics Committee.

Study Population

The Beijing 2006 outbreak of angiostrongyliasis ran from June to September and involved 160 cases (about the same number of cases as recorded in China over the previous decade; Wang *et al.*, 2008). Most (141) of the cases were diagnosed and treated at the BFH (81 as inpatients).

The patients included in the present study had to be adult (≥ 18 years of age) when they first presented and to have been diagnosed as cases of angiostrongyliasis. Diagnosis was based on:

- (1) epidemiology (a history of eating the snail intermediate hosts, transport hosts, such as frogs and fish, and/or raw vegetables that might have been contaminated with the human-infective larvae of *A. cantonensis*);
- (2) clinical symptoms (particularly headache but also fever, neck stiffness, nausea, vomiting and/or skin paresthesia);
- (3) haematology (elevation in the percentage of leucocytes that were eosinophils);
- (4) cerebrospinal fluid (raised pressure and eosinophilia);
- (5) immunology (serum positive for anti-*A. cantonensis* antibodies and/or *A. cantonensis* circulating antigen);
- (6) imaging [evidence of eosinophilic meningitis in a lung X-ray and/or cranial scans by computed tomography or magnetic resonance imaging (MRI)]; and
- (7) parasitology (*A. cantonensis* detected in cerebrospinal fluid and/or eyes).

Any patient found harbouring *A. cantonensis* larvae was considered a confirmed case. Those displaying criteria (1)–(4) from the above list were considered clinically positive, whereas those showing criteria (5) and/or (6) were considered to be displaying auxiliary signs consistent with angiostrongyliasis.

Patients were excluded if they had undergone repeated lumbar punctures (although all of the patients were offered repeated lumbar punctures, most refused such procedures) or had received albendazole alone and/or antibiotics after the onset of their illness.

Evaluation

The primary measurement in this study was the number of patients who still had headaches after 1 week of treatment. The second measurement was the duration of each patient's headache (i.e. the length of time between the start of treatment and the first acetaminophen-free day that the patient thought his or her headache had disappeared). Adverse events and the frequency of acetaminophen use were also analysed.

Statistical Analysis

Data were analysed using descriptive statistics, Student's *t*-tests, and χ^2 tests, as appropriate. A *P*-value of < 0.05 was considered indicative of a statistically significant difference.

RESULTS

Pre-treatment Evaluation

Sixty-nine patients (35 given the combination therapy and 34 controls) were enrolled in the study. At presentation, the two groups had similar clinical manifestations and gave similar results in laboratory tests (Table 1). All but five of the 69 cases initially presented with headache and all 69 had eaten snails (*Pomacea canaliculata*) ≤ 31 days before the onset of their symptoms.

Thirty-seven of the patients included in the study (19 given the combination treatment and 18 controls) had been given brain and spinal MRI scans; 20 (nine given the combination and 11 controls) exhibited linear enhancement in localized areas of the meninges but the remaining 17 appeared MRI-normal.

Post-treatment Outcome (Table 2)

Compared with the controls, the patients given the combination treatment were less likely to be still suffering from a headache at the end of 7 days of treatment ($\chi^2=4.284$; $P=0.038$) and tended to lose their headaches quicker ($t=0.661$; $P=0.010$) and be

given acetaminophen less frequently ($t=2.152$; $P=0.036$). The only adverse effects observed were abnormalities in liver-function tests (seen in 19 of the patients given the combination and five of the controls) and these were always mild, self-limiting and short-lived.

DISCUSSION

Almost all adult patients infected with *A. cantonensis* suffer from headache and this is the commonest symptom of angiostrongyliasis (Chotmongkol *et al.*, 2004). Although the headache is not fatal, it is a distressing symptom that interferes with the personal and professional lives of patients. Supportive treatments, such as analgesic drugs and repeated lumbar punctures, are recommended (Sawanyawisuth and Sawanyawisuth, 2008). All the patients investigated in the present study, however, rejected repeated lumbar punctures and took acetaminophen for pain relief.

In previous investigations on angiostrongyliasis, treatments with a combination of a

TABLE 1. *Initial presenting condition of patients*

Feature	Controls	Combination therapy	Test statistic		
			<i>t</i>	χ^2	<i>P</i>
NO. OF PATIENTS					
Enrolled	34	35			
Male	19	17		0.369	0.543
Presenting with:					
Headache	32	32		0.000	1.000
Vomiting	12	10		0.359	0.549
Stiff neck	29	28		0.336	0.562
Fever ($\geq 37.5^\circ\text{C}$)	4	3		0.002	0.968
Skin paresthesia	23	24		0.007	0.934
Blurred vision or photophobia	6	4		0.153	0.695
AGE (years)					
Mean and (S.D.)	37.50 (8.51)	35.66 (9.71)	0.838		0.405
Range	23–57	18–55			
Mean (S.D.) incubation period (days)*	12.06 (7.22)	14.94 (8.55)	1.512		0.135
Mean (S.D.) duration of headache before presentation	24.88 (13.32)	20.71 (10.40)	1.451		0.151

*The time between the day when infection is presumed to have occurred and the onset of systems.

TABLE 2. *Clinical outcomes*

Variable	Controls	Combination therapy	Test statistic		
			<i>t</i>	χ^2	<i>P</i>
NO. OF PATIENTS WITH HEADACHE:					
After 1 week of treatment	23	15		4.284	0.038
Two weeks after start of treatment	16	4		6.332	0.012
Mean (s.d.) duration of headache after starting treatment (days)	15.6 (13.4)	8.6 (7.3)	2.661		0.01
Mean (s.d.) no. of acetaminophen tablets taken within 7 days of the start treatment	9.9 (8.6)	6.3 (4.9)	2.152		0.036

corticosteroid and an anthelmintic, a corticosteroid alone or an anthelmintic alone have all appeared effective. A 1- or 2-week course of treatment with prednisolone (60 mg/day), for example, helped relieve headache, shortened the mean time until resolution of headache, and reduced the need for acetaminophen (Chotmongkol *et al.*, 2000; Sawanyawisuth *et al.*, 2004). Chotmongkol *et al.* (2006) subsequently found that a 2-week course of prednisolone (60 mg/day) and mebendazole (10 mg/kg.day) was also beneficial in relieving the headache associated with the disease. The efficacy of albendazole monotherapy in the treatment of angiostrongyliasis has been investigated in only one randomized and placebo-controlled trial (Jitpimolmard *et al.*, 2007). In that investigation, which involved 71 subjects, the cases given albendazole (at 15 mg/kg.day) for 2 weeks cleared their headaches quicker (and took fewer acetaminophen tablets for pain relief) than the cases who had received the placebo.

In the present study, the prednisolone used in some previous studies was replaced with low-dose dexamethasone (3 mg/day). Since the combination of this corticosteroid and albendazole appeared to relieve headache, shorten the mean time until the resolution of headache, and reduce the need for acetaminophen, dexamethasone appears to be potentially useful for the treatment of angiostrongyliasis.

The present, encouraging results must be treated with some caution, since they are

based on a study that suffers from several limitations. Firstly, the study was retrospective and some potentially important data (such as information on long-term prognosis) were not available. Secondly, there is no evidence to show that both components of the tested combination are beneficial; Chotmongkol *et al.* (2009) recently found that the addition of an anthelmintic (albendazole) to corticosteroid (prednisolone) treatment offered no added benefit. The efficacy of a combination of albendazole and dexamethasone now needs to be compared against the efficacy of dexamethasone monotherapy.

In conclusion, daily treatment, for a week, with both albendazole and dexamethasone can relieve headache, shorten recovery time and reduce the need for acetaminophen in angiostrongyliasis, without serious side effects. Such therapy should be considered an option for cases of angiostrongyliasis.

ACKNOWLEDGEMENT. This study was supported by grants (B2006003) from the Beijing New Century Millions of Talents Project.

REFERENCES

- Chotmongkol, V., Sawanyawisuth, K. & Thavornpitak, Y. (2000). Corticosteroid treatment of eosinophilic meningitis. *Clinical Infectious Diseases*, **31**, 660–662.
- Chotmongkol, V., Wongjitrat, C., Sawadpanit, K. & Sawanyawisuth, K. (2004). Treatment of eosinophilic meningitis with a combination of albendazole and

- corticosteroid. *Southeast Asian Journal of Tropical Medicine and Public Health*, **35**, 172–174.
- Chotmongkol, V., Sawadpanitch, K., Sawanyawisuth, K., Louhawilai, S. & Limpawattana, P. (2006). Treatment of eosinophilic meningitis with a combination of prednisolone and mebendazole. *American Journal of Tropical Medicine and Hygiene*, **74**, 1122–1124.
- Chotmongkol, V., Kittimongkolma, S., Niwattayakul, K., Intapan, P. M. & Thavornpitak, Y. (2009). Comparison of prednisolone plus albendazole with prednisolone alone for treatment of patients with eosinophilic meningitis. *American Journal of Tropical Medicine and Hygiene*, **81**, 443–445.
- Jitpimolmard, S., Sawanyawisuth, K., Morakote, N., Vejjajiva, A., Puntumetakul, M., Sanchaisuriya, K., Tassaneeyakul, W., Tassaneeyakul, W. & Korwanich, N. (2007). Albendazole therapy for eosinophilic meningitis caused by *Angiostrongylus cantonensis*. *Parasitology Research*, **100**, 1293–1296.
- Lv, S., Zhang, Y., Steinmann, P. & Zhou, X. N. (2008). Emerging angiostrongyliasis in mainland China. *Emerging Infectious Diseases*, **14**, 161–164.
- Sawanyawisuth, K. & Sawanyawisuth, K. (2008). Treatment of angiostrongyliasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **102**, 990–996.
- Sawanyawisuth, K., Limpawattana, P., Busaracome, P., Ninpaitoon, B., Chotmongkol, V., Intapan, P. M. & Tanawirattananit, S. (2004). A 1-week course of corticosteroids in the treatment of eosinophilic meningitis. *American Journal of Medicine*, **117**, 802–803.
- Slom, T. J., Cortese, M. M., Gerber, S. I., Jones, R. C., Holtz, T. H., Lopez, A. S., Zambrano, C. H., Sufit, R. L., Sakolvaree, Y., Chaicumpa, W., Herwaldt, B. L. & Johnson, S. (2002). An outbreak of eosinophilic meningitis caused by *Angiostrongylus cantonensis* in travelers returning from the Caribbean. *New England Journal of Medicine*, **346**, 668–675.
- Wang, Q. P., Lai, D. H., Zhu, X. Q., Chen, X. G. & Lun, Z. R. (2008). Human angiostrongyliasis. *Lancet Infect Diseases*, **8**, 621–630.