Changes of Liver Functions After Albendazole Treatment in Human Gnathostomiasis

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Abstract

Ninety-eight out-patients of the Hospital for Tropical Diseases, Bangkok with clinical diagnosis of cutaneous gnathostomiasis were studied. All patients were treated with albendazole at a dosage of 400 mg (two tablets) twice daily for 14 days. They were seen periodically on day 0, day 14, day 28, day 195 and 1 year after treatment with laboratory investigations for any side effects of the treatment. There was a statistically significant increase of total protein, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values when comparing the different periods. The abnormal results are clearly indicated in AST and ALT values (liver enzyme) especially on day 14 both male and female patients had highest levels. No significant association with time was found in ALP value.

Gnathostomiasis is one of the important parasitic diseases frequently found in Thailand. In humans this disease results from *Gnathostoma spinigerum* infections[1-4]. However, human infections with *G. doloresi, G. hispidum* and *G. nipponica* have also been reported[5]. Man is an accidental host infected by eating improperly cooked fresh water fish (eel, snake-head fish, cat fish), frog, snake, chicken and probably cyclops which harbour the encapsulated third stage larvae[6]. After being ingested by a human host, the parasite cannot fully develop and the larvae move to various organs particularly the subcutaneous tissue and produce symptoms of intermittent migratory swelling. The diseases can be fatal due to cerebral invasion by the parasite[7,8]. The administration of albendazole significantly reduced the number of third stage larvae in mice[9]. This efficacy of albendazole treatment has been investigated in human gnathostomiasis[8,10]. Cure (no further swelling) was seen in 93.9-94.1 per cent of the treatment group[8]. It also increased the rate of outward migration of gnathostomes in the treated group[10]. The adverse effect of albendazole treatment on liver functions

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in albendazole treated patients was investigated in more detail in this study.

SUBJECTS AND METHOD

Subjects

Ninety-eight out-patients who visited the Hospital for Tropical Diseases between 1994 and 1996 with the diagnosis of cutaneous gnathostomiasis were selected for the study. The medians and ranges of age and weight were 32 (18-58) years and 56 (43-90) kilograms. The diagnosis was confirmed clinically by two attending physicians based on the actual observations of migratory cutaneous swellings at different sites or the recurrent swelling at the same site. None had a history of malaria or other liver diseases 60 days prior to admission. All the patients to be treated with albendazole had to have a normal liver fuction test [aspartate aminotransferase (AST) ≤50 IU; alanine aminotransferase (ALT) ≤50 IU; alkaline phosphatase (ALP) ≤45 IU] and a body weight higher than 40 kilograms. Exclusion criteria included known allergy to albendazole or other benzimidazole derivative drugs and women who were pregnant.

Drug administration and liver function assessments

All patients were treated with albendazole at a dosage of 400 mg (two tablets) twice daily for 14 days. They were seen periodically on day 0, day 14, day 28, day 195 or 6.5 months and 1 year after treatment with laboratory investigations for any side effects of the treatment. No other drugs which may influence the aminotransferase enzyme levels were given throughout the experiment.

About ten ml of venous blood was drawn in the morning. The blood samples were tested that morning or stored at 2-5°C until tested on the following day. The serum protein measured as albumin and total protein were determined by dye binding techniques[11]. Serum glutamyl aspartate transaminase (SGPT or ALT), serum glutamyl oxaloacetate transaminase (SGOT or APT) and serum alkaline phosphatase (ALP) were determined by enzymatic methods[12].

Data analysis

The results of liver function tests were summarized as median and range. The data were analysed by the Minitab computer program[13]. The differences in medians among the 5 groups of patients were tested using the Friedman test.

RESULT

Medians and ranges of liver function parameters in gnathostomiasis patients treated with albendazole on day 0, day 14, day 28, 6.5 months and 1 year are shown in Table 1. There are statistically significant differences of total protein, albu-

Table 1. Biochemical parameters in Gnathostomiasis patients treated with albendazole in the duration of Day 0, Day 14, Day 28, 6.5 months and 1 year.

Parameters	Day 0	Day 14	Day 28	6.5 month	1 year	P-value *
Total bilirubin (mg/dl)	0.65 (0.24-1.65)	0.61 (0.15-1.85)	0.64 (0.20-1.56)	0.63 (0.30-2.20)	0.62 (0.27-2.27)	0.0684
Direct bilirubin (mg/dl)	0.13 (0.03-0.37)	0.12 (0.05-0.37)	0.12 (0.05-0.45)	0.12 (0.03-0.55)	0.11 (0.03-0.50)	0.3684
Total protein (g/dl)	7.45 (6.30-9.10)	7.40 (6.50-9.10)	7.20 (6.50-9.60)	7.30 (6.60-8.40)	7.40 (5.50-8.50)	0.0020
Albumin (g/dl)	4.50 (3.70-5.00)	4.40 (3.70-4.90)	4.40 (3.90-4.80)	4.40 (3.90-4.80)	4.45 (2.50-5.00)	0.0021
ALP (IU)	19.55 (11.40-38.90)	19.35 (10.30-62.00)	19.55 (10.80-50.00)	19.65 (11.00-40.50)	21.30 (11.20-38.90)	0.0239
AST (IU)	25.00 (12.00-42.00)	35.00 (16.00-130.00)	26.00 (16.00-261.00)	26.00 (15.00-125.00)	25.00 (12.00-104.00)	0.0000
ALT (IU)	20.00 (10.00-50.00)	36.00 (13.00-273.00)	26.50 (8.00-482.00)	22.00 (10.00-210.00)	21.00 (8.00-239.00)	0.0000

*Friedman related sample test

Table 2. Number of abnormal AST and ALT test (≥ 50 IU) in gnathostomiasis patient treated with albendazole in day 14, 28, 6.5 months and 1 year.

Parameters	Day 14	Day 28	6.5 month	1 year
AST				
Male:	6/30 (20.0%)	2/30 (6.7%)	2/30 (6.7%)	1/30 (3.3%)
Female:	13/68 (19.1%)	5/68 (7.3%)	4/68 (5.9%)	2/68 (2.9%)
ALT				
Male:	12/30 (40.0%)	8/30 (26.7%)	2/30 (6.7%)	1/30 (3.3%)
Female:	22/68 (32.4%)	10/68 (14.7%)	3/68 (4.4%)	4/68 (5.9%)

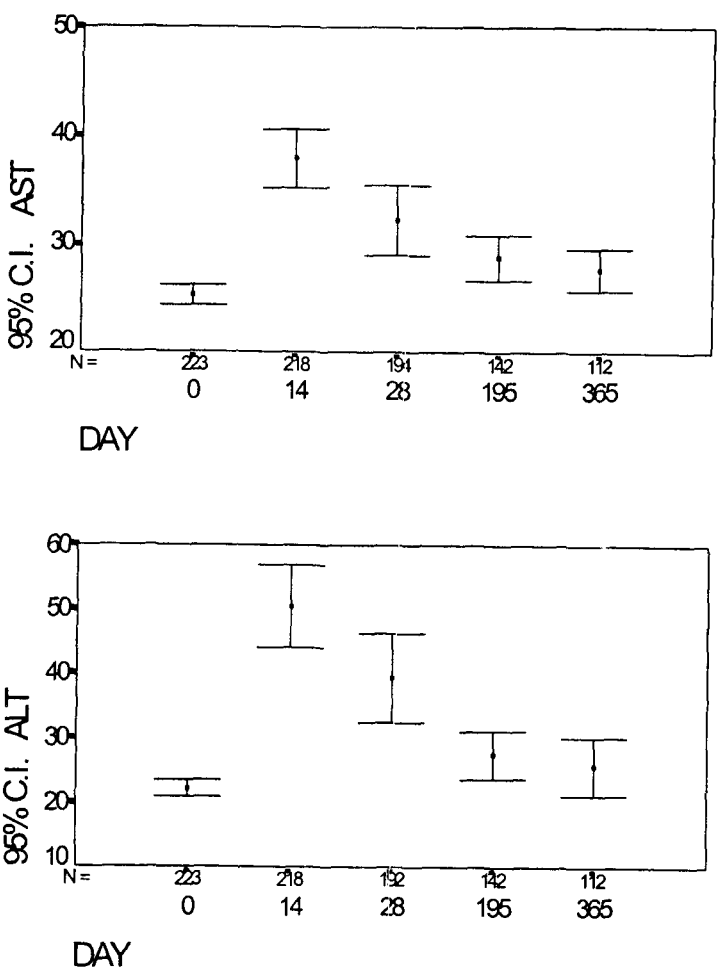

Fig. 1. 95% confidence interval of AST, ALT plot on day 0, 14, 28, 195 and 1 year.

min, ALP, AST and ALT values when comparing the different periods ($P<0.05$). However, the abnormal results are clearly indicated in AST and ALT values especially on the day 14 period. The prevalences of abnormal AST and ALT levels (≥50 IU) are shown in Table 2. The highest percentage was shown in day 14 both in male and female patients (Table 2).

Fig. 1 also shows 95 per cent confidence interval of medians of AST, ALT enzyme values related to the duration. However, no significant change of ALP was found at any time of follow-up.

DISCUSSION

At the present time, no specific drug for the treatment of gnathostomiasis has been found, although a great many, including thiabendazole[14], praziquantel[14], ivermectin[14,15], metronidazole[6], diethyl carbamazine and quinine[8], have been investigated in either experimental animals or man without success.

Studies on albendazole in rats[16] and cats[17] have shown good efficacy with death of the parasite. Maleewong et al[9] showed that a complete larvicidal effect was obtained only with albendazole at the dosage of 90 mg/kg twice daily for 21 consecutive days. A preliminary trial in man using 400 mg albendazole twice a day for 10 days with no clinical and laboratory side effects has been reported[6]. However, this study was done in only a few subjects. Suntharasamai et al[10] reported a double blind trial with placebo controlled trial albendazole in humans at a dosage of 400 mg twice daily for two weeks, and it was observed that *Gnathostoma spinigerum* larvae tended to migrate outward as a result of the treatment. Therefore, albendazole might be the drug of choice for treatment of gnathostomiasis. However, this study showed that there were changes of liver functions in the patient who was treated with albendazole. Serum AST, ALT were high on day 14 of treatment. The high prevalence was shown in day 14 and slightly declined in day 28. The side effects related to treatment were different from those reported by Horton et al who stated that there was no evidence of liver function disturbances associated with high dose albendazole regimens (400-800 mg/day, 21 days) used for hydatid disease[18]. However, Pungpak et al[19] reported transient elevation of liver enzymes (86 and 185 U AST/ml and 122 and 177 U ALT/ml on day 7 post-treatment) in two giardia infected patients. There are reports of slight side effects of albendazole treatment in other parasitosis such as hookworm[20], strongyloidiasis[21], fasciolopsis[22] and opisthorchiasis[23]. Our results were similar to a previous study in the same setting[10] which followed the side effects of albendazole treatment and reported the high enzyme ALT (SGPT) level in some gnathostomiasis patients[10]. The abnormalities reverted to normal within 2-4 weeks in this study as well as that reported by Suntharasamai[10]. It should be noted here that there were some patients with high ALT/AST (more than 200 IU) in our study, those patients probably had some complications from other diseases. However, Pungpak et al reported that there were some elevations in serum aminotransferase from strongyloidiasis patients who were treated with albendazole and these patients had a history of rheumatoid arthritis[21]. Therefore, although we checked all patients before they were treated in the experiment, some patients might have had prior underlying liver diseases.

It can be concluded from this observation that albendazole at this dosage can be useful for treating gnathostomiasis. However, a higher dose might increase the side effects in the liver function test and should be avoided, even though anti-parasitic activity might increase. Therefore, albendazole is still recommended for the treatment of gnathostomiasis in dosages of 400 mg twice daily for 14 days with some adverse effects. Further study might be required for reducing the dose or the duration of drug administration.

SUMMARY

The adverse effects of albendazole treatment on liver functions of gnathostomiasis patients were investigated in ninety-eight out-patients at the Hospital for Tropical Diseases, Bangkok with a clinical diagnosis of cutaneous gnathostomiasis. The patients were seen periodically on day 0, day 14, day 28, day 195 and 1 year after treatment with laboratory investigations. A dosage of 400 mg (two tablets) was used twice daily for 14 days. There were statistically significant increases of total protein, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values when comparing the different periods. The enzyme AST and ALT values (liver enzyme) had highest levels both in male and female patients especially on day 14. No significant association with time was found in ALP value.

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ผลของยาอัลเบ็นดาโซล หลังจากใช้รักษาพยาธิตัวจี๊ด ต่อการทดสอบสมรรถภาพตับ

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คณะผู้วิจัยได้ทำการศึกษาผลข้างเคียงของยา albendazole โดยตรวจหาค่าทางชีวเคมีซึ่งบ่งชี้หน้าที่ของตับของผู้ป่วยตัวจี๊ดที่ได้รับการรักษาด้วยยา albendazole จำนวน 98 คนซึ่งเป็นผู้ป่วยนอกของโรงพยาบาลเวชศาสตร์เขตร้อน กรุงเทพฯ ผู้ป่วยแต่ละรายจะได้รับยาในขนาด 400 มิลลิกรัม (2 เม็ด) เช้า-เย็น เป็นเวลา 14 วัน ทำการติดตามผลโดยตรวจหาค่าทางชีวเคมีของการรักษาในระยะเวลาที่ 0, 14 วัน, 28 วัน, 195 วัน และ 1 ปี ตามลำดับ พบว่าระดับของโปรตีน อัลบูมิน, alkaline phosphatase, enzyme AST และ ALT มีระดับที่เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติเมื่อนำมาเปรียบเทียบกันตามระยะเวลาที่ติดตามผลทั้งในเพศชายและเพศหญิง ความผิดปกติของ enzyme AST และ ALT (liver enzyme) พบได้ชัดเจนในการติดตามผลหลังการให้ยา 14 วัน โดยจะมีระดับที่สูงสุด แต่ไม่พบความแตกต่างอย่างชัดเจนนักของระดับ enzyme ALP

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