The Use of Prednisone in the Treatment of Trichinellosis

Zvi Shimoni MD[1,2], Zeev Klein MD[3], Paltiel Weiner MD[4], Marc Victor Assous MD PhD[5] and Paul Froom MD MOccH[6]

[1]Infections Disease Unit and Departments of Internal Medicine [2]B and [3]D, Laniado Hospital, Netanya, Israel
[4]Department of Internal Medicine A, Hillel Yaffe Medical Center, Hadera, Israel
[5]Government Central Laboratories, Ministry of Health, Jerusalem, Israel
[6]Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: symptoms, worsening, trichinellosis, pork, prednisone

Abstract

Background: It is not entirely clear when and how steroids should be used to treat trichinellosis.

Objectives: To describe the course of consecutive patients with trichinellosis treated with antihelminthic drugs with and without the addition of prednisone.

Methods: We extracted data from the hospital records of 30 patients hospitalized for trichinellosis contracted after eating poorly cooked pork that came from two wild pigs killed in the Golan Heights, and contacted them for follow-up 5–6 weeks and 6 months after hospital discharge.

Results: All the patients who attended a party and ingested the infected pork (100% attack rate) were hospitalized after 2–16 days (median 9 days); 29 were symptomatic and 1 patient without symptoms had creatine phosphokinase levels 17.9 times above the upper limit of normal. Twelve of 23 patients (52%) treated with antihelminthic drugs without prednisone were rehospitalized with worsening fever, increased peripheral blood eosinophil counts, but decreasing CPK values. These patients and another seven at the time of admission were treated with prednisone 40 mg/day for 5 days in addition to antihelminthic drugs for at least 14 days. All became asymptomatic within 24 hours and were asymptomatic 6 weeks and 6 months later.

Conclusions: Worsening symptoms in patients treated with antihelminthic drugs alone is common. A short course of prednisone is safe and alleviates symptoms due to tissue larvae in patients with trichinellosis.

IMAJ 2007;9:537–539

Trichinellosis is common in Thailand and other developing countries where domestic swine is often the main source of infection [1,2]. In Israel, trichinellosis is rare and is mostly seen in individuals who eat uncooked meat from wild animals [3]. The disease develops when undercooked flesh (classically pork) contaminated with infected larvae is eaten. The organisms are freed from the cyst walls by acid-pepsin digestion in the stomach and pass into the small intestine. Larvae invade the epithelium of the small intestine and then develop into adult worms. Mating ensues and 5 days later newborn larvae are shed via the bloodstream to skeletal muscles where they may remain viable for several years.

The severity of the disease is related to the number of larvae ingested; most infections are asymptomatic. During the first week after ingestion the symptoms are usually diarrhea, vomiting and abdominal discomfort. During the second week after infection, the symptoms are attributable to systemic invasion by larvae and include fever, periorbital edema, myositis, and rash. Rarely, death may occur from myocarditis, encephalitis or pneumonitis [4].

It is not entirely clear when and how steroids should be used to treat trichinellosis [4-10]. There is general agreement that steroids can rapidly alleviate acute symptoms [3,7], and might be used for critically ill patients even though the evidence for efficacy is equivocal [4]. Part of the reluctance to use steroids is that they have been shown in some animal studies to prolong the life of the adult parasites as well as rapidly increase the number of intestinal parasites [7,8]. Others advocate the use of corticosteroids simultaneously with antihelminthic therapy [5,9], while most experts recommend as standard therapy albendazole 400 mg orally twice a day for 8–14 days and concomitant prednisone 40–60 mg for an unspecified number of days [10]. The antihelminthic therapy is only effective for treating the intestinal larvae whereas prednisone acts systemically to alleviate the effects of tissue larvae.

Treatment with prednisone might prevent worsening symptoms [11] and shorten the symptomatic period in patients presenting with trichinellosis. We describe our experience with the treatment and follow-up of 30 patients presenting with trichinellosis, 19 of whom received prednisone in addition to antihelminthic therapy.

Patients and Methods

We extracted data from the hospital records of 30 patients hospitalized for trichinellosis contracted after eating poorly cooked pork from two wild pigs killed in the Golan Heights, and contacted them for follow-up 5–6 weeks and 6 months after hospital discharge. For continuous variables, median values were calculated. The Kruskal-Wallis test was used to compare the results of laboratory tests. Two-tailed Fisher's exact test was used to compare the proportion of patients with an elevated temperature (≥ 38ºC) at first admission and after recurrent symptoms.

Results

All 30 patients, male foreign workers aged 22–42, who ate partially cooked pork at a party became ill 2–4 days after the party and were hospitalized 2–16 days (median 9 days) after

CPK = creatine phosphokinase

Table 1. Laboratory findings in 30 patients infected with trichinellosis

	Mean ± SD	Minimum	Maximum
Age (yrs)	32 ± 6	22	42
Latency (days)	8 ± 4	2	16
SBP (mmHg)	120 ± 13	98	150
Heart rate (bpm)	76 ± 17	60	120
Temperature (°C)	37.0 ± 0.8	36	39
WBC (/µL)	9610 ± 3280	4800	18,500
Eosinophils (%)	13 ± 10	1.5%	38%
Hemoglobin (g/dl)	14.2 ± 1.7	11.2	20.0
Hospitalization (days)	5 ± 3	3	12
CPK*	15.0 ± 20.4	0.4	82.3
Creatinine*	0.7 ± 0.2	0.4	1.3
LDH*	1.4 ± 0.8	0.5	3.7
AST*	1.7 ± 1.9	0.3	6.7
BUN*	0.8 ± 1.0	0.3	5.9

* Value/upper limit of normal

SD = standard deviation, latency = days from party until hospitalization, SBP = systolic blood pressure, bmp = beats per minute, WBC = white blood cells, LDH = lactate dehydrogenase, AST = aspartate aminotransferase, BUN = blood urea nitrogen

Table 2. Comparison of findings at presentation and at the time of worsening symptoms in 12 patients

	Presentation	Rehospitalization	*P*
Temperature (C degrees ≥ 38)	2 (17%)	10 (83%)	0.003
CPK*	22.6 (3.5–82.4)**	2.9 (0.4–9.9)	0.025
WBC (x 1000/µl)	9.1 (4.8–15.8)	14.6 (8.2–18.2)	< 0.001
Eosinophils (%)	8.0 (1.5–38.0)	19 (2.0–48.0)	0.047
Total eosinophils (cells x 1000/µl)	0.68 (0.14–6.0)	3.08 (0.17–9.46)	0.007

* Units divided by the upper limit of the reference range

** Median (range)

eating the infected meat (attack rate of 100%). Twenty-nine were hospitalized with symptoms compatible with acute trichinellosis, while one worker was asymptomatic but brought to the emergency room with his fellow workers. He was hospitalized with a creatine phosphokinase value 17.9 times above the upper limit of normal reference range, and a 14% eosinophil count. Of the 30 patients, 26 (86.7%) complained of myalgia. The other four did not have muscle pain but three had other symptoms and all had elevated CPK values. The following other symptoms were present on admission: headache in 7 (23%), vomiting in 4 (13%), diarrhea in 5 (17%), fever ≥ 38ºC in 5 (17%), and orbital edema in 5 (17%). There was an increase in the average proportion of eosinophils, and values of CPK, lactate dehydrogenase and aspartate aminotransferase [Table 1]. Serology was obtained in 20 patients on the first follow-up visit and was positive in 15 (tested with the LMD Trichinella serology microwell enzyme-linked immunosorbent assay kit, Remel, Ramsey, MN55303, USA). Specificity in our laboratory was found to be 96% (positive in 7 of 197 hospitalized patients without trichinellosis), similar to the specificity reported in the package insert (93%). The 15 positive results included 4 patients with negative serology on admission to the hospital.

Various physicians from two different hospitals treated the patients differently. All patients received either mebendazole, 400 mg three times a day (12 patients), or albendazole, 400 mg twice a day (18 patients) for at least 14 days. Prednisone (40 mg/day for 5 days) was given initially in 7 patients or after worsening symptoms in 12 of the 23 patients treated with antihelminthic drugs alone (9 of 18 who had received albendazole, and 3 of 5 who had received mebendazole). In the patients treated at presentation with antihelminthic drugs alone, there was no significant differences in clinical and laboratory variables between those with worsening symptoms (n=12) and those who were asymptomatic on follow-up (n=11), except for borderline significance of CPK values on presentation (median 22.7 versus 7.3 times the upper limit of normal respectively, $P = 0.056$). The time from the start of antihelminthic treatment until worsening symptoms was 4–17 days with a median of 9 days, and two patients had already finished a 14 day course of antihelminthic treatment. They were readmitted with fever (10 of the 12 patients), worsening headache (n= 4), myalgia (n=7), and/or abdominal pain (n=3) after having been discharged previously with minimal symptoms and without fever. One of the two patients without fever had a new onset of severe headaches and the other had severe myalgia. The symptoms resolved rapidly (within 24 hours) after the initiation of prednisone treatment.

Compared to values from the first hospital admission in those with worsening symptoms, CPK decreased dramatically [Table 2], whereas body temperature rose, as did the total white count and total eosinophil count.

There were some differences between patients treated initially with prednisone (n=7) and those who received only antihelminthic therapy initially (n=23), such as a longer period until presentation to the hospital (median 9 days vs. 5 days, $P = 0.01$) and a lower CPK (1.2 vs. tenfold the upper limit of normal, $P < 0.001$) suggesting a more mild disease. There were no significant differences between the two groups when comparing values for white blood counts, total eosinophil counts, and clinical symptoms. A rapid decrease in CPK values (on average around a 50% decrease) was observed in 18 of 30 patients who had repeat CPK levels 1–2 days after the beginning of treatment, independent of treatment with prednisone (results not shown).

At 5–6 weeks after infection, all 30 patients were working, and only 1 complained of continuing headache (non-prednisone group). None had abdominal pain, nausea, diarrhea or muscular pain. No side effects of prednisone therapy were observed. All patients had completed at least 14 days of antihelminthic therapy. At 6 months, all 30 patients were working and had no complaints of abdominal pain, nausea, diarrhea or muscular pain.

Discussion

Most outbreaks of trichinellosis reported globally are caused by *Trichinella spiralis* [13]. The disease is rare in Israel since the vast majority of Jews and Muslims do not eat pork. Until 1997 only

six small outbreaks were reported in humans, whereas from 1998 to 2004 there were 10 trichinellosis outbreaks [14] involving 200 Thai migrant employees. In most areas in Israel 3–4% of wild pigs are infected, whereas in the Golan Heights the rate of infection has been found to be around 10% [Personal communication, A Markovics, Kimron Veterinary Institute, Beit Dagan, Israel]. Our attack rate of 100% is similar to the 85% rate reported previously in Israel [14]; however, 29 of the 30 patients were symptomatic in this outbreak, whereas 45% of Thai employees in a previously reported outbreak were symptomatic. This suggests that patients in this outbreak ingested a larger number of larvae.

A major finding of our study is that 52.2% of our patients had worsening symptoms after their initial response to treatment with antihelminthic drugs. To our knowledge this is the first time that the frequency and characteristics of such reactions are reported in patients treated for trichinellosis, occurring as early as 4 and as late as 17 days after the beginning of antihelminthic drugs with fever, a decrease in CPK values, and an increase in the peripheral blood eosinophil count. An exacerbation of the disease appears unlikely since CPK levels were greatly decreased. The mechanism for these reactions and the systemic inflammatory reaction observed on presentation is unclear but is largely mediated by eosinophils and thought to be provoked by larval forms [5].

The 19 patients who received prednisone were asymptomatic 5–6 weeks and 6 months later, suggesting that this treatment does not cause an increase in chronic disease or in late relapses, contrary to suggestive findings in animal studies [7,8]. Our study presents only limited support for the hypothesis that treatment with prednisone at presentation will prevent recurrent reactions because it was not randomized and that those treated with prednisone at presentation probably had a milder disease, but supports the observations of others that a short course of prednisone in addition to antihelminthic drugs is associated with a rapid decrease in symptoms [5]. Our results support current recommendations [10] that symptomatic patients should receive prednisone, and demonstrate that 5 days of treatment with prednisone without tapering is long enough to shorten the symptomatic period and prevent recurrent symptoms.

The early response to treatment in our study is consistent with findings in 44 patients who received antihelminthic therapy along with prednisone for a longer period (average 8 days) [5]. However, they reported symptoms at 6 months in about half of their patients, and a few of these patients never had a symptom-free period. Others have also reported continued symptoms for 6 months up to 10 years [6] after treatment for acute disease. Reinfection and lack of compliance are two possible explanations for the chronic symptoms found in those studies. Our patients received almost all their antihelminthic therapy in the hospital and subsequently were monitored by their employers. They did not eat raw pork during the follow-up period.

In conclusion, our study suggests that worsening of symptoms during treatment with antihelminthic medication for trichinellosis is common. Randomized controlled studies in various settings are warranted, but until such studies are done we recommend that prednisone be given with antihelminthic drugs to prevent worsening symptoms and to shorten the symptomatic period in patients presenting with trichinellosis.

References

1. Roy SL, Lopez AS, Schantz PM. Trichinellosis surveillance – United States 1997-2001. MMWR 2003;52:1–8.
2. Khamboonruang C. The present status of trichinellosis in Thailand. *Southeast Asian J Trop Med Public Health* 1991; 22(Suppl):312–15.
3. Hefer E, Rishpon S, Volovik I. Trichinosis outbreak among Thai immigrant workers in the Hadera sub-district. *Harefuah* 2004;143:656–60 (Hebrew).
4. Grove DI. Tissue nematodes (Trichinosis, Dracunculiasis, Filariasis). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. Philadelphia: Churchill Livingstone, 2005:3267–9.
5. Cabie A, Bouchaud O, Houze S, et al. Albendazole versus thiabendazole as therapy for trichinosis: A retrospective study. *Clin Infect Dis* 1996;22:1033–5.
6. Harms G, Binz P, Feldmeier H, et al. Trichinosis: a prospective controlled study of patients ten years after acute infection. *Clin Infect Dis* 1993;17:637–43.
7. Capo V, Despommier DD. Clinical aspects of infection with trichinella spp. *Clin Microbiol Rev* 1996;9:47–54.
8. Stewart GL, Kramar GW, Kramar M, Charniga L. The effects of cortisone on fecundity, number and distribution of adult trichinella spiralis and on trichinous enteritis in the host. *J Parasitol* 1982;68:909–15.
9. Clausen MR, Meyer CN, Krantz T, et al. Trichinella infection and clinical disease. *Q J Med* 1996;89:631–6.
10. Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA, eds. The Sanford Guide to Antimicrobial Therapy. 36th edn. Hyde Park, VT, USA: Antimicrobial Therapy Inc, 2006:101.
11. Leven ML. Treatment of trichinosis with mebendazole. *Am J Trop Med Hyg* 1983;32:980–3.
12. Watt G, Saisorn S, Jongsakul K, Sakolvaree Y, Chaicumpa W. Blinded, placebo-controlled trial of antiparasitic drugs for Trichinosis myositis. *J Infect Dis* 2000;182:371–4.
13. Schellenberg RS, Tan BJK, Irvine JD, et al. An outbreak of trichinellosis due to consumption of bear meat infected with Trichinella nativa in 2 Northern Saskatchewan communities. *J Infect Dis* 2003:188:835–43.
14. Marva E, Markovics A, Gdalevich M, et al. Trichinellosis outbreak. *Emerg Infect Dis* 2005;11:1979–80.

Correspondence: Dr. P. Froom, Dept. of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.

Phone: (972-50) 626-1353; Fax: (972-4) 624-3302

email: paulfr@clalit.org.il

Good books don't give up all their secrets at once

Stephen King (1947-), American novelist whose genres are horror, fantaty and science fiction