BRIEF REPORT

Initial Assessment of the Ability of Ivermectin to Kill *Ixodes scapularis* and *Dermacentor variabilis* Ticks Feeding on Humans

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Objective.—The purpose of this study was to determine *Ixodes scapularis* and *Dermacentor variabilis* tick mortality when fed on humans who have consumed 400 µg/kg oral ivermectin.

Methods.—Six study subjects, 3 in each group, were randomly assigned to receive either 400 µg/kg ivermectin or placebo in a blinded manner. After consuming either ivermectin or placebo, each study subject had 2 colostomy bags attached to his or her abdomen. One of the colostomy bags contained 7 *I scapularis* nymphs and 7 adults. The other colostomy bag contained 7 *D variabilis* nymphs and 7 adults. Tick mortality was recorded over the next 24 hours.

Results.—Fifty-five percent (6 of 11) of the attached *I scapularis* nymphs exposed to ivermectin had morbidity (3 of 11) or died (3 of 11), compared with 0% morbidity and mortality in the 2 *I scapularis* nymphs that attached in the placebo group. No *I scapularis* adults or *D variabilis* nymphs attached to feed. Among *D variabilis* adults that attached to feed, there was a 0% mortality rate for both the placebo group (0 of 6) and the ivermectin group (0 of 8).

Conclusions.—We demonstrate a novel method to confine ticks to human subjects to study tick-borne diseases. While there was a trend toward *I scapularis* morbidity and mortality in the ivermectin arm, the low number of ticks that attached in the placebo group limited our analysis. Most ticks began feeding in the last 12 hours of the experiment, significantly limiting their exposure to ivermectin. Ivermectin does not cause early death in *D variabilis* adults.

Key words: ivermectin, tick, *Ixodes scapularis*, *Dermacentor variabilis*, tick-borne disease, Lyme disease

Introduction

Ticks are obligate blood-sucking insects with a worldwide distribution. Hard ticks such as *Dermacentor variabilis* (American dog tick) and *Ixodes scapularis* (black-

legged tick, or deer tick) transmit the majority of tick-borne diseases to humans in the United States.

Lyme disease, caused by *Borrelia burgdorferi*, is responsible for more than 90% of all human vector-borne disease in the United States.¹ It causes an estimated 35,000 cases a year in the United States, mostly in the Northeast and Midwest, and approximately 60,000 cases in Europe.^{1,2} Lyme disease is transmitted by *I scapularis* in the Northeastern and Midwestern United States and *I pacificus* in the Western United States.³ The *I scapularis* nymphs are the most important vectors for transmitting Lyme disease in the United States, although adults are also capable of transmitting the disease.^{1–4} *Ixodes* ticks must feed for about 36 to 48 hours before Lyme disease can be transmitted to humans.^{1–4} Untreated Lyme disease can produce a multitude of symptoms including

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cardiac, neurologic, and rheumatologic sequelae.^{1–5} Only 50% to 70% of people diagnosed with Lyme disease report a history of being bitten by a tick, and the hallmark erythema migrans rash develops only in 70% to 80% of infected people.^{1–5}

The risk of tick borne-diseases in humans can be minimized by reducing populations of deer and mice, avoiding wooded and grassy areas, applying topical insect repellents, wearing insecticide-treated clothing, promptly removing ticks from skin and clothing, wearing light-colored clothing to aid in the identification of ticks, and tucking pant legs into socks.³ These control strategies have limited effectiveness and are often not practical. Ticks are small, hard to identify, and easily missed on skin inspection. In addition, ticks can wander on a human host for hours to days before they find a suitable attachment site and start to feed.

Ivermectin is one of the most ubiquitous antiparasitic drugs sold worldwide. More than 5 billion doses of ivermectin-containing products have been sold in the past 3 decades.⁹ Ivermectin has been extensively used in veterinary medicine to control fleas and ticks but has never been tested for this purpose in humans.^{6,7} A dose of 150 $\mu\text{g/kg}$ to 200 $\mu\text{g/kg}$ ivermectin has shown effectiveness against numerous human parasites, including strongyloidiasis, ascariasis, trichuriasis, filariasis, scabies, enterobiasis, lymphatic filariasis, and onchocerciasis.^{6,7} Hundreds of millions of people have been treated during the past 20 years with ivermectin in a global effort to control onchocerciasis.⁶ Although a 400 $\mu\text{g/kg}$ ivermectin dose is not approved by the Food and Drug Administration, high doses have been safely used in humans.¹⁰

Ivermectin acts on the glutamate-gated chloride channel, and to a lesser extent, the γ -aminobutyric acid (GABA)-gated chloride channel, causing hyperpolarization of invertebrate nerve and muscle cells.^{6,7,9} Ivermectin causes paralysis of tick somatic and pharyngeal muscles, causes damage to tick dermal glands, dorsoventral muscles, and inhibition of epidermal cell activity.^{6–8} In humans, ivermectin is widely distributed in the body, with a peak-plasma level occurring about 4 hours after drug consumption.^{6–9} Ivermectin has a half-life of approximately 18 to 22 hours, although antiparasitic effects appear to persist much longer.⁶ The peak concentration of ivermectin in sebum, sweat, and squames is about 8 hours after drug consumption, and drops after 24 hours. Ivermectin is extensively metabolized by P4503A4 and excreted primarily in the feces. Humans lack glutamate-gated chloride channels, and ivermectin only minimally crosses an intact blood-brain barrier.⁶ Overall, ivermectin is a very safe drug with only rare and mild side effects, which can include gastrointestinal upset, fatigue,

abdominal pain, dizziness, rash, somnolence, transaminitis, and leukopenia.

The objective of the study was to determine whether ivermectin is able to cause morbidity and mortality in ticks feeding on humans. Ticks with morbidity and mortality are not likely to transmit diseases to humans.

Methods

The Institutional Review Boards of Eastern Virginia Medical School and Old Dominion University approved this study. All study subjects were adults between the ages of 18 and 30 years, were not pregnant or trying to get pregnant, were not breastfeeding, were not taking daily medications, and were able to visualize the ticks. All women had a negative urine pregnancy test on the day of the experiment. Study subjects were excluded if they had ever had a seizure, orthostasis, an abnormal heart rate, Stevens-Johnson syndrome, toxic epidermal necrolysis, human immunodeficiency virus/acquired immunodeficiency syndrome, acquired or congenital immune deficiency, known malignancy, were on a regimen of immunosuppressive drugs, or had asthma, vision loss, conjunctival hemorrhage, hepatitis, edema, or a history of headaches. Moreover, taking the following medications precluded study participation: warfarin, benzodiazepines, barbiturates, sodium oxybate, valproic acid, clotrimazole, amprenavir, rifampin, ritonavir, St. John's Wort, phenothiazines, amiodarone, erythromycin, verapamil, tamoxifen, quinidine, ketoconazole, cyclosporine, or carvedilol owing to theoretical potential interactions with the metabolism of ivermectin. All study subjects were compensated \$300 at the completion of the study.

We performed a randomized double-blinded, placebo-controlled clinical trial to determine whether orally administered 400 $\mu\text{g/kg}$ ivermectin is able to kill *I. scapularis* and *D. variabilis* ticks that are feeding on humans. The optimal dose of ivermectin to kill ticks is not known. We received Food and Drug Administration Investigational Drug approval to use the 400 $\mu\text{g/kg}$ ivermectin because that dose has previously been shown to be safe in humans, and we wanted to only give a one-time large dose of the drug. It has been shown that the antiparasitic effects of ivermectin persist longer than the parent drug is present, suggesting that the metabolites may have antiparasitic effects, although the exact mechanism is not known.

Study investigators could not find other published reports on specific methods to attach ticks to humans. We used pathogen-free *I. scapularis* and *D. variabilis* ticks (obtained from Dr Michael Levin at the Medical Entomology Laboratory, Rickettsial Zoonoses Branch, US Centers for Disease Control and Prevention, Atlanta, Georgia). Three study subjects received placebo (empty

Figure. Study subjects showing off their tick-filled colostomy bags at the start of the experiment.

gel capsules) and 3 received ivermectin (3-mg Stromectol tablets [Merck Sharp & Dohme, Whitehouse Station, NJ]) by direct observation of a study coordinator 2 hours before each study subject had 2 colostomy bags attached to their abdomen. One of the colostomy bags contained approximately 7 *I. scapularis* nymphs and approximately 7 adults. The other colostomy bag contained approximately 7 *D. variabilis* nymphs and approximately 7 adults. In most cases, 7 of each tick species and developmental stage were in each colostomy bag, but sometimes that number was 6 or 8 due to technical difficulties sorting the ticks into groups before the start of the experiment. The quantity of each species and developmental stage in the colostomy bag was known at the start of the experiment (Figure).

Each colostomy bag had small pinholes placed to facilitate gas exchange. The bags remained attached to study subjects for a total of 24 hours, after which all ticks were removed, examined, and killed. Study subjects recorded the number of ticks that were attached and dead, attached and alive, unattached and dead, and unattached and alive at 1 hour and at 2, 3, 4, 5, 6, 12, and 24 hours. Definitive tick morbidity and mortality was determined at 24 hours by Dr Sonenshine, a tick scientist with more than 30 years' experience, who was blinded to whether the ticks were attached to study subjects receiving placebo or ivermectin. Morbidity was defined as a severely lethargic and premorbid.

Aside from minor skin irritation where the ticks fed, no study participant reported any side effects from study participation, except for 1 woman receiving the placebo who reported intermittent and self-resolving dizziness, lightheadedness, anxiety, restlessness, itching, tingling, and constipation during the 24 hours of study participation. Follow-up communication demonstrated that all her symptoms resolved.

Results

Twenty-four hours after colostomy bags containing ticks were placed on human study subjects, we observed in the *I. scapularis* nymph ivermectin group that 55% (11 of 20)

were attached to human study subjects. Of those that were attached, 27% of ticks (3 of 11) had died, 27% (3 of 11) were premorbid, and 45% (5 of 11) appeared well. Overall, 40% (8 of 20) did not attach and were alive. One tick escaped from the colostomy bag. In the *I. scapularis* nymph placebo group, 11% (2 of 19) attached. On examination, all the *I. scapularis* nymphs that attached in the placebo group were well. Eighty-four percent (16 of 19) *I. scapularis* nymphs in the placebo group did not attach; of those, 25% (4 of 16) were dead, and 75% (12 of 16) alive. One tick escaped from the colostomy bag.

In the *I. scapularis* adult ivermectin group, 0% (0 of 21) ticks attached. One unattached tick died and 20 were unattached and alive. In the *I. scapularis* adult placebo group, 0% (0 of 19) ticks attached. Three unattached ticks died, and 16 were unattached and alive.

The *D. variabilis* nymphs do not typically feed on humans, and it is not entirely clear if any of the ticks actually fed on our human study subjects. At 24 hours, none of the *D. variabilis* nymphs—18 in the ivermectin group and 19 in the placebo group—were feeding on humans. One tick in the ivermectin group escaped the colostomy bag.

Ticks in the *D. variabilis* adult ivermectin group had 40% of ticks (8 of 20) attach, and all appeared well. Of the remaining ticks, 60% (12 of 20) were alive and unattached. Ticks in the *D. variabilis* adult placebo group had 32% (6 of 19) attach, and all appeared well. Of the remaining ticks, 68% (13 of 19) were alive and unattached.

A majority of the ticks that did attach to feed did so at the end of the experiment. Table 1 summarizes our data at 24 hours, and Table 2 shows how many ticks were attached in each group at various times after the colostomy bags were attached.

Discussion

We demonstrate a novel method for containing ticks on human study subjects. During our experiment, 2% of ticks (3 of 156) escaped from the colostomy bags, and 5% of the unattached ticks (8 of 156) died (7 of which were in placebo groups). Our study was limited by the

Table 1. Tick morbidity and mortality at 24 hours

Tick	Attached and dead	Attached and premorbid	Attached and not sick	Unattached and dead	Unattached and alive	Escaped from bag
<i>Ixodes scapularis</i> nymph, placebo (<i>n</i> = 19)	0	0	2	4	12	1
<i>I scapularis</i> nymph, ivermectin (<i>n</i> = 20)	3	3	5	0	8	1
<i>I scapularis</i> adult, placebo (<i>n</i> = 19)	0	0	0	3	16	0
<i>I scapularis</i> adult, ivermectin (<i>n</i> = 21)	0	0	0	1	20	0
<i>Dermacentor variabilis</i> nymph, placebo (<i>n</i> = 19)	0	0	0	0	19	0
<i>D variabilis</i> nymph, ivermectin (<i>n</i> = 19)	0	0	0	0	18	1
<i>D variabilis</i> adult, placebo (<i>n</i> = 19)	0	0	6	0	13	0
<i>D variabilis</i> adult, ivermectin (<i>n</i> = 20)	0	0	8	0	12	0

low number of ticks that attached in the allotted time frame. Ticks feed slowly, and most ticks attached late in the experiment, thus limiting their exposure to ivermectin. There may be increased morbidity and mortality among the *I scapularis* nymphs exposed to ivermectin but because few *I scapularis* nymphs in the placebo group attached, no firm conclusions can be drawn.

It would be unethical to allow *I scapularis* infected with *B burgdorferi* to feed on humans to determine whether ivermectin can prevent disease transmission regardless of overt tick morbidity and mortality. Therefore, we used uninfected ticks, and used tick death as the primary outcome as dead ticks cannot transmit disease. For many tick-borne diseases, including Lyme disease, the transmission of the pathogen is an active process. Because ivermectin paralyzes somatic and pharyngeal muscles in the ticks before they die, a well-appearing live tick exposed to ivermectin may still be prevented from transmitting tick-borne diseases. In animals, ticks exposed to ivermectin took smaller blood meals, had fewer engorged females, and had a high mortality rate. We are

not aware of any studies showing that ivermectin can prevent tick-borne disease transmission.

It is unclear why *D variabilis* adults exposed to ivermectin did not show signs of morbidity and mortality. The *D variabilis* adults are much larger than the *I scapularis* nymphs, and therefore may require higher doses or longer exposure to ivermectin. As *D variabilis* is the vector for Rocky Mountain Spotted Fever, a disease that is transmitted only after a few hours of feeding, ivermectin may not be helpful to prevent Rocky Mountain Spotted Fever. Future research could involve a larger number of ticks being observed for a longer period in a pediatric colostomy bag. The use of ostomy glue may reduce the number of ticks that escape from the bag. In addition, ivermectin can be studied in an animal model to see if tick-borne disease transmission can be prevented.

LIMITATIONS

Our study is limited by the low number of ticks that attached during the 24-hour period of observation, lim-

Table 2. Number of ticks that attached at different times during the experiment

Tick	Number attached at hour 4	Number attached at hour 6	Number attached at hour 12	Number attached at hour 24
<i>Ixodes scapularis</i> nymph, placebo (<i>n</i> = 19)	1	0	2	2
<i>I scapularis</i> nymph-ivermectin (<i>n</i> = 20)	2	2	7	11
<i>I scapularis</i> adult-placebo (<i>n</i> = 19)	0	0	0	0
<i>I scapularis</i> adult-ivermectin (<i>n</i> = 21)	0	0	0	0
<i>Dermacentor variabilis</i> nymph, placebo (<i>n</i> = 19)	0	0	0	0
<i>D variabilis</i> nymph, ivermectin (<i>n</i> = 19)	1 ^a	0	1 ^a	0
<i>D variabilis</i> adult, placebo (<i>n</i> = 19)	1	2	4	6
<i>D variabilis</i> adult, ivermectin (<i>n</i> = 20)	0	0	3	8

^a The nymphal stage of this species is not known to feed on humans, and it is unclear whether these ticks were truly attached or just on the skin.

iting broad conclusions about the ability of ivermectin to cause tick mortality within 24 hours. Even though we had more *I scapularis* nymphs attach in the ivermectin group than in the placebo group, we are highly skeptical that this is an effect of ivermectin and believe it more likely reflects our small sample size. In a few instances, there were 6 or 8 ticks of a particular species and developmental stage in the colostomy bag instead of the planned 7, although this discrepancy was accounted for in our analysis.

Conclusions

It may be possible that a single dose of ivermectin, taken within 24 hours of being at risk for tick exposure, can prevent tick-borne diseases, including Lyme disease. If that is shown to be the case, it could be of interest to hikers, backpackers, soldiers, loggers, and outdoor enthusiasts who may find that taking a pill to prevent tick-borne diseases is easier and more effective than using repellents or promptly finding and removing ticks. Ivermectin has many attractive features—it is inexpensive and safe, and has a long half life. More research needs to be done to determine whether ivermectin can be used to prevent tick-borne diseases in humans.

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