

IS ORAL PENICILLIN AN EFFECTIVE CHEMOPROPHYLAXIS AGAINST LEPTOSPIROSIS? A PLACEBO CONTROLLED FIELD STUDY IN THE KANDY DISTRICT, SRI LANKA

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Abstract. Leptospirosis poses a severe threat to the lives of farmers in Sri Lanka, thus, development of an effective chemoprophylaxis is deemed essential. We tested oral penicillin as chemoprophylaxis against leptospirosis in high transmission areas in central Sri Lanka in October 2005. Eight hundred active farmers were randomly assigned to take either oral penicillin (500 mg bid) or a similar looking placebo over a month during active farming season. The primary study point was the incidence of serologically confirmed leptospirosis. Data were available for 602 subjects of whom 319 (152 taking penicillin and 167 taking placebo) had good compliance, shown by tablet count. Of 5 subjects hospitalized with fever, 3 had serological evidence of leptospirosis, all of whom belonged to the placebo group. Therefore, oral penicillin may be effective chemoprophylaxis against leptospirosis.

INTRODUCTION

Leptospirosis is a zoonosis caused by spirochetes belongs to the genus *Leptospira*, commonly transmitted to man from infected urine of rats, other mammals, birds, reptiles and rarely fish (Farrar, 1995). Leptospirosis is an occupational disease of paddy farmers, workers of coconut plantations and sugar cane industries. The illness is characterized by rapid onset of fever, myalgia, icterus and extreme prostration. Five percent of patients succumb to severe complications of infection, such as acute hepatic or renal failure or myocarditis (Farrar, 1995). Sri Lanka, being an agricultural country, has a high incidence of leptospirosis, where the farmer, the breadwinner of the nation, suffers heavily. Prevention of leptospirosis

remains the priority since eradication is not a realistic goal. Currently recommended preventive methods include the use of protective clothing, safe animal husbandry and immunization of animals. However, to implement these preventive methods is financially not practical for resource limited developing countries where the disease exists. Hence, cost-effective methods, such as controlling the rat population and chemoprophylaxis of people at risk, should be considered. Controlling rat populations is a daunting task and practically impossible. Thus, giving chemoprophylaxis to vulnerable people would seem a plausible method. This idea is not novel, since chemoprophylaxis with doxycycline 200 mg weekly was tested and shown to be effective in 1984 (Takafuji *et al*, 1984). However, doxycycline is relatively unsafe for prolonged use. However, penicillin is the most effective antibiotic for treating leptospirosis and is safe for prolonged use. This prompted us to test the efficacy of oral penicillin as potential chemoprophylaxis against leptospirosis in Sri Lankan farmers.

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MATERIALS AND METHODS

The study was conducted in a high transmission area in the Medical Officer of Health (MOH) division of Yatinuwara and Udunuwara in the Central Province, Sri Lanka. The total population in these divisions was 215,607 people. The study was carried out during the northeast monsoon-season since active farming takes place during this period under the guidance of the Agrarian Services Department (ASD). We conducted three workshops to educate officers of the ASD of the respective divisions and they were made responsible for selecting farmers based on inclusion criteria and to monitor the compliance of subjects during the study period. We recruited fulltime male farmers, age 20 to 80 years, who engaged in active farming on most days during the study period in October 2005. Farmers allergic to penicillin and those taking other antibiotics during the study period were excluded. The objectives of the study were explained to the farmers who agreed to take the full course of the antibiotic and informed consent was obtained. Based on inclusion criteria 800 farmers were recruited for the study.

The study was a placebo controlled field trial where subjects and investigators were blind to the chemoprophylaxis given. The ethics committee of the Faculty of Medicine approved the protocol of this trial. Eight hundred white, similar appearing, containers were used to keep the oral penicillin and placebo in equal numbers. Thus, 400 containers with oral penicillin (250 mg), each containing 120 tablets were prepared and numbered by an independent team. These were distributed to the study subjects at 2 centers on 2 days. Each subject randomly selected a container, then was advised to take 2 tablets twice a day for one month beginning the day before they started farming. They were instructed to attend the Teaching Hospital, Peradeniya or to the clos-

est government hospital in the event of a febrile illness lasting more than 2 days duration and to report to the study team during and after the study period. The medical officers of the relevant government hospitals were informed about the study and were requested to fill out a data sheet given to them by the subject and to inform the investigators. The subjects were given an instruction sheet and a clinical data sheet consisting of a checklist of symptoms of leptospirosis in the local vernacular. Furthermore, they were given a trial identity card, which had the telephone numbers of the investigators for any clarification. Two members of the research team and the officers of the ASD visited the subjects regularly to determine compliance. Paired blood samples taken 10 days apart for leptospira serology were obtained from each subject who entered the hospital with a febrile illness. The clinical picture of febrile illnesses was also utilized to identify the affected patients with leptospirosis.

RESULTS

Of the 800 subjects who took either oral penicillin or placebo data were available for 602 subjects. Table 1 shows the age distribution of the subjects in both groups. Tablet counts indicated that 283 subjects (140 in the penicillin group and 143 in the placebo group) did not take the pills according to instructions. Five subjects were admitted to the hospital with clinical features of leptospirosis and their paired sera were tested 10 days apart for leptospira serology by micro agglutination test (MAT). Of those 5 patients, 3 were positive for leptospirosis, and all of them were in the placebo group (Table 2). Statistical analysis was not possible as the number of patients was too few.

DISCUSSION

This study suggests that oral penicillin may be an effective chemoprophylactic in pre-

Table 1
Distribution of subjects by age in penicillin and placebo groups.

Age groups in years	Number on oral penicillin	Number on placebo	Total
20-30	35	42	77
31-40	38	40	78
41-50	85	93	178
51-60	86	87	173
61-70	43	44	87
71-80	5	4	9
Total	292	310	602

Table 2
Leptospiral antibody titers (MAT) in subjects on oral penicillin and placebo.

Index number	Drugs	Acute sample	Convalescent sample
73	Placebo	Negative	1/800
235	Placebo	Negative	1/800
250	Placebo	Negative	1/100
297	Penicillin	Negative	Negative
83	Placebo	Negative	Negative

venting leptospirosis since none of the subjects in the treatment group developed a confirmed infection. The incidence of leptospirosis during the study was comparable to previous year. The year 2003 had the highest incidence of leptospirosis in the Kandy District, particularly from the study area, totaling 43 cases, representing half the 95 cases reported for the district. Normally the illness exhibits seasonal variation mainly related to rain fall and farming activities in Sri Lanka but occasionally there are unpredictable outbreaks.

Penicillin is the drug of choice for the treatment of leptospirosis. It may also be used for prevention. Doxycycline also has proven benefit, even though it has several drawbacks (Takafuji *et al*, 1984; Sehgal *et al*, 2000). There are no studies comparing these two drugs, and a well designed study in the future would be useful. The challenge posed by leptospirosis for the poor farmer is daunting and should draw more attention of health administrators

and researcher. We conclude that oral penicillin may be effective chemoprophylaxis against leptospirosis.

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