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Original Article

Green Tobacco Sickness Among Tobacco Harvesters in a Korean Village

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ABSTRACT

Background: Green tobacco sickness (GTS), an occupational disease in tobacco harvesters, is a form of acute nicotine intoxication by nicotine absorption through the skin from the wet green tobacco plant. We carried out a questionnaire survey and measured cotinine concentration, the metabolic product of nicotine, to determine the prevalence, incidence, and risk factors of GTS in Korean tobacco harvesters.
Methods: We measured cotinine concentrations, and administered a questionnaire survey to tobacco harvesters in Cheongsong-gun, Gyeongsangbuk-do, Korea. We repeatedly measured urine cotinine concentration five times with a questionnaire survey.
Results: Cotinine concentration at dawn was significantly higher than that at other times; it was significantly lower during the nonharvesting period than during the harvesting period. However, little change in cotinine concentration was detected in the daytime during the harvesting period. Study participants included 20 men and 20 women. The prevalence of GTS was 37.5% and was significantly higher in women than in men (55.0% vs. 20.0%, $p < 0.01$). GTS incidence according to number of workdays was 3.4 occurrences/100 person days.
Conclusion: In this study, nicotine exposure and metabolism were experimentally determined from the time of cotinine exposure, and biological monitoring was performed in each season. In the future, this information may be valuable for medical decision-making in GTS prevention.

1. Introduction

Green tobacco sickness (GTS), an occupational disease seen among tobacco harvesters, is a form of acute nicotine intoxication via the absorption of nicotine through the skin from the wet green tobacco plant [1]. Health issues in tobacco harvesters were first recorded in 1713; Ramazzini reported headaches and gastrointestinal disorders in Italian tobacco harvesters, and the occupational disease was first reported in 1970 by Weizenecker and Deal [2]. GTS mainly occurs when the clothes or tobacco leaves become wet with rain, dew, or sweat. The major symptoms are dizziness, headache, nausea, vomiting, and even seizure [3,4].

In Korea, there are an estimated 11,000 tobacco harvesters, and the production of tobacco leaves was 8.4 million kg in 2014 [5]. In the aspect of history and scope of tobacco leaf harvesting, there are many suspected GTS cases in Korea, and even more in other Asian countries including China and India, but studies on GTS have not been performed in Korea until now. GTS was mainly reported in American tobacco harvesters [4]. However, recently, cases have been reported in India [3,6], Japan [7], Malaysia [8], Poland [9], Brazil [10], and Thailand [11]. In Korea, since Lim and Lee [12] reported the first GTS case, studies regarding the prevalence rate, incidence rate, risk factors, and preventive methods have been conducted [13,14].

To date, GTS has been known globally as a disease occurring by the absorption of nicotine through the skin [6,7,15–18]. However, Park et al. [19] and Yoo et al. [20] recently introduced the possibility of absorption through respiratory routes.

Regarding GTS in Korea, there are currently no national movements to use specific intervention measures for prevention, as nicotine poisoning among tobacco harvesters has only been vaguely understood. Additionally, because of the lack of awareness about GTS among medical personnel, many cases are misdiagnosed as pesticide poisoning or high temperature damage [1].

The aim of this study was to observe tobacco harvesters prior to and after working, and observe the temporal change in urine cotinine during tobacco harvesting and nonharvesting to propose an accurate diagnostic method for GTS.

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2. Materials and methods

2.1. Participants

Our study was conducted in Cheongsong-gun, a rural city located in Gyeongsangbuk-do, Korea. Forty participants were enrolled; surveys and urine sampling for GTS were conducted in all participants. This study was approved by Dongguk University Hospital's clinical research review board prior to study commencement (Gyeongyak Article No. 08-14). Written informed consent was obtained from each participant prior to administering the survey.

2.2. Sampling

From July 20, 2008 to July 30, 2008, urine samples were obtained four times per day (immediately after waking, after working in the morning, after the afternoon work, after having dinner). After the samples were collected, they were immediately placed in the freezer. In the fields, during collection, the samples were placed in an icebox, and immediately after returning to the house, they were placed in the freezer. The following year (2009), urine was collected again from each participant during the non-harvesting period.

2.3. Analysis

High performance liquid chromatography (HPLC) assay was used to estimate cotinine concentration by modified Takeda methods. For extraction, 3 mL of urine was added to 2 mL of dichloromethane and 0.6 mL of 5M sodium hydroxide, and vortexed for 15 minutes; then, the mixture was centrifuged at 3,000 rev/min (5 minutes). The supernatant was dried under N_2 gas, and 10 μL of it was injected in the HPLC column; cotinine concentration values were read at a wavelength of 254 nm. The assay was performed using a reversed phase C_{18} column in an isocratic mode. The HPLC unit consisted of a pump (model 2695; Waters, Milford, MA, USA) and a variable-wavelength ultraviolet detector (model 2996; Waters, USA) with a deuterium lamp. We used a 250 mm × 4.6 mm XTerra column (Waters, USA) with a 5-μm particle size, and an injector with a 10-μL loop. The mobile phase used was a mixture of 85% dibasic phosphate (20 mmol of each per liter) containing 3 mmol of sodium 1-decanesulfonate and 150 mL of acetonitrile per liter (pH 4.5). The flow rate of the mobile phase was 1.0 mL/min, and the column pressure was 140.6 kgf/cm^2. Creatinine correction was used to measure the creatinine concentration with the Jaffe method, and the cotinine concentration per excreted creatinine 1 mol was calculated.

2.4. Surveys

The survey was administered to all participants; it was developed based on a summary of previous domestic research [13,14]. The presence of GTS was determined with the following criteria: (1) the presence of symptoms related to tobacco and harvesting tobacco, (2) headache or dizziness, and (3) nausea and vomiting. Complaints of symptoms were severe enough to warrant visiting a medical institution. Questionnaire items retrieved information on sex, age, smoking status, acreage (a), purchase amount (kg), harvesting time (hours), presence of symptoms during harvesting (headache, dizziness, nausea, and vomiting), previous hospitalization, and whether motion sickness pills were taken.

2.5. Statistical analysis

We used MS Excel for Windows to record survey items and SPSS for Windows (ver. 18.0; SPSS Inc., Chicago, IL, USA) for statistical analysis. The Friedman test was used to compare cotinine concentration over time (T1–T5), and survey information for risk factors associated with GTS was analyzed using the chi-square test. In analyzing GTS symptoms in farmers, a receiver operating characteristic analysis was performed using MedCalc Statistical Software version 16.1 (MedCalc Software bvba, Ostend, Belgium) to establish the cutoff value of urine cotinine concentrations.

3. Results

3.1. Concentrations of cotinine

Urine samples were collected at the following times: morning (T1), after morning work (T2), after afternoon work (T3), after dinner, prior to bedtime (T4), and the following year when the participant was not working (T5). As indicated, urine cotinine was measured a total of five times. The concentration was highest at T1 by 500.71 (geometric standard deviation, 4.67) ng/mg Cr, but there was no significant difference by time (T1–T4). The concentration in participants during the nonworking period [135.40 (1.73) ng/mg Cr; T5] was significantly lower than that seen when they were working ($p < 0.01$; Table 1).

3.2. Incidence of GTS from survey results

Among the cases that met the definition of GTS, the incidence was 15 out of 40 people (37.5%). By sex, women had a significantly higher incidence (55%) than men (20%; $p < 0.05$). There was no significant difference in age (Table 2). In addition, GTS incidence was significantly higher in nonsmokers than in smokers (57.7% vs. 0%, $p < 0.01$; Table 3).

GTS cutoff urine cotinine concentrations were 290.03 ng/mg Cr, 720.54 ng/mg Cr, 1,211.97 ng/mg Cr, and 1,022.49 ng/mg Cr at T1, T2, T3, and T4, respectively (Table 4).

4. Discussion

At present, cotinine has been shown to be the best available biomarker of nicotine exposure [21]. Cotinine is the major nicotine metabolite, and an average of 72% of nicotine was converted to cotinine [22]. The use of urine cotinine is illustrated in several circumstances where smoking status assessment is of interest. Such situations include evaluation of the impact of smoking cessation programs, monitoring of pregnancy and other groups at risk, assessment of occupational exposure to industrial pollutants, validation of phase I clinical trials, and the assessment of life insurance candidates [23].

Table 1
Time-phased urine cotinine concentration

Time*	No.	GM (GSD), ng/mg Cr
T1	39	500.71 (4.67)
T2	40	482.16 (5.26)
T3	40	465.15 (4.66)
T4	40	460.63 (4.44)
T5	39	135.40 (1.73)†

* T1, early morning; T2, after working A.M.; T3, after working P.M.; T4, prior to bedtime; T5, nonworking.
† By Friedman test.
GM, geometric mean; GSD, geometric standard deviation.

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