Journal of Medicine and Medical Sciences Vol. 6(5) pp. 82-89, June 2015
Available online http://www.interesjournals.org/JMMS
DOI: http:/dx.doi.org/10.14303/jmms.2015.017

Full Length Research Paper

The correlation between pesticide exposure and green tobacco sickness among Thai traditional tobacco farmers in Nan province

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Abstract

Thai traditional tobacco cultivation may lead to adverse health effects due to Green Tobacco Sickness (GTS) and pesticide exposure. Acetylcholinesterase activity (AChE) and plasmacholinesterase (PChE) have been used to monitor the extent of organophosphate and carbamates exposure in Thai traditional tobacco farmers in Nan Province. A cross-sectional study was conducted with 84 Thai traditional tobacco farmers who had exposure to GTS in two Sub-Districts. A face-to-face questionnaire and a blood test with the Test-Mate OP Kit were used in data collection. It was found that the prevalence of risk level of AChE was 61.90% and the safe level was 38.10%, while the risk level of PChE was 42.86% and the safe level was 57.14%. A multivariate analysis revealed that symptoms of GTS were associated with safe level of AChE such as nausea and vomiting, the safe level of PChE were related to dizziness, but headache and increased saliva were correlated with the risk level. In addition, the safe level of AChE was associated with vomiting after being adjusted and the safe level of PChE with dizziness after being adjusted. Furthermore, pesticide was not applied in all periods but symptoms of GTS were still found in some tobacco farmers who had never used pesticides before; thus, it is possible to conclude that safe levels of AChE and PChE contribute to nicotine poisoning or GTS.

Keywords: Pesticide exposure, green tobacco sickness, Thai traditional tobacco farmers

INTRODUCTION

Green tobacco sickness (GTS) is an occupational illness reported by tobacco workers worldwide (Control and Prevention, 1993; Gehlbachet al., 1975; Ghoshet al., 1980; Yokoyama, 2007). The disease is caused by nicotine which penetrates through the skin of the hands of workers who cultivate and harvest tobacco(McKnightet al. 1996; McBrideet al., 1998; Curwin et al., 2005). The GTS morbidity accounts for nearly one-fourth of the tobacco workers. Typical symptoms of GTS include nausea, vomiting, headache, abdominal cramps, breathing difficulty, abnormal body temperature, pallor, diarrhea, chills, fluctuations in blood pressure and heart rate, drenching sweats, and increased salivation (McKnightet al. 1996; McBrideet al., 1998; Curwin et al., 2005). According to definitions presented in many previous studies, GTS refers to acute nicotine poisoning caused by dermal absorption of nicotine from mature tobacco plants. Its symptoms include vomiting, nausea, headaches, and dizziness (Arcury et al., 2003; Arcury et al., 2003). In the northern region of Thailand, Nan Province is a famous area for the Thai traditional tobacco cultivation. Thai traditional tobacco (*Nicotiana Tabacum* L.) is known as a non-Virginia type. Matured leaves from this plant are thicker and shorter and contain three to four times more nicotine compared to the Virginia type (Ghosh et al., 1980).The adverse effects of GTS on farm worker's health, required health care, and loss of farm products make GTS an important occupational health issue

(HIPKE,1993; Quandt et al., 2001; Boylanet al., 1993). The reported prevalence of GTS ranges from 8% to 41% among the tobacco farm workers in previous research (Gehlbach et al., 1975; Ballardet al., 1995; Weizenecker and Deal, 1970; Arcury et al., 2001; Quandt et al., 2000; Gehlbach et al., 1974; Arcury et al., 2001).

Depending upon the toxic potential of the compound, routes of exposure, and exposure time, the symptoms of pesticide exposure vary from headache, vomiting, skin rash, respiratory problems, and convulsions (Dasgupta et al., 2007). Thai farmers have been identified as a high risk group for occupational poisoning because they are used to prolonged exposure to pesticide and accumulate toxic in tobacco (Siriwong et al., 2009). Organo-phosphates and carbamates inhibit acetylcholinesterase which causes accumulation of acetylcholine at nerve endings, resulting in a cholinergic or hypersecretory syndrome (Fuortes et al., 1993). Acetyl cholinesterase (AChE) activity in the red blood cells and butarylcholinesterase activity in plasma have been used to monitor the extent of organophosphate and carbamates exposure (Rama and Jaga, 1992; Rama 1995; Marrs,1993). However, during tobacco plantation seasons, farmers meticulously take care of tobacco plants with fertilizers until the plants are mature. During the process, insecticides are used to protect the roots of the plants. They generally spray insecticides on to young plants when the plants are infested by insects. Organophosphate and carbamates in fertilizers may cause both acute and chronic adverse health effects to the farmers.

With regard to specific symptoms of the tobacco farmers that are similar to GTS, such symptoms may result from accumulation of nicotine and pesticide poisoning. Such an issue needs to be further discussed in detailto further clarify various factors that lead to adverse health effects. Generally, the symptoms of GTS may be identified with an instrument such as a questionnaire that focuses on four main subjective health symptoms including headache, nausea, dizziness, and vomiting. As for the Thai traditional tobacco production process, taking care of tobacco plants particularly by watering means that farmers will come in contact with wet tobacco leaves. Watering activities are usually conducted either in the morning or in the evening, and such activities cause farmers to be exposed to nicotine and pesticides that are left on tobacco leaves. The purpose of this study was to assess whether there were any risks of GTS related to AChE and plasma cholinesterase (PChE) inhibition due to exposure to nicotine and pesticides among Thai traditional tobacco farmers at Praputthabath sub-district of Chiangklang district and Phatow sub-district of Thawangpha district in Nan province, Thailand. It was anticipated that the findings of the present study could be used to explain GTS etiology for farmers. Also, the study findings would shed light on the relationship between GTS and pesticide exposure in Thai traditional tobacco farmers.

MATERIALS AND METHODS

Subjects and sampling

The sample of the present study was Thai traditional tobacco farmers in Phatow sub-district, Thawangpha district, and Praputthabath sub-district, Chiangklang district in Nan province, Thailand. The farmers in the selected sub-districts who met the classification criteria of GTS in our previous study were identified, totaling 107 persons. The sample size for this study was then calculated with 95% of confidence interval. In the end, a total of 84 tobacco farmers were recruited, 40 of whom were from Phatow Yamane's sub-district and 44 from Praputthabath sub-district. The formula used in sample size calculation was as follows:

$n=N/1+N(e)^2$
n = sample size
N = population of GTS farmers (N=107)
e = 0.05

All the study participants were randomly recruited with a drawing technique from the population of farmers living in the selected sub-districts. It is worth noting that all of the participants gave their informed consent before participating in the study. As regards their demographic characteristics, all of them were involved in pesticide application during the process of Thai traditional tobacco cultivation. They were between 25 and 60 years of age. Before data collection commenced, the study participants underwent a physical examination by nurse practitioners working at a health promoting hospital in the areas. The participants' medical records were obtained as well.

Instrumentation

The present study was cross-sectional research which was conducted with 84 randomly selected Thai traditional tobacco farmers involved in pesticide application during the process of tobacco cultivation. During data collection, the farmers were interviewed using a face-to-face questionnaire that had been adapted from a previous study undertaken by Arcury et al. (2002).

It is noteworthy that although there are no firmly established diagnostic criteria for GTS, Arcury et al. had developed a clinically useful case definition of GTS based on symptoms and susceptible working conditions. The identified symptoms of GTS include headache, nausea, dizziness, and vomiting reported after a day of working with tobacco (Arcury et al., 2001). Data regarding demographic characteristics of the study participants elicited in this study included gender, age, family status, level of education, current smoking status, and alcohol

consumption, while data regarding work-related conditions gathered from the participants included process of tobacco seedling and planting involving seedling, planting, watering, fertilizing, and applying pesticides for protection of the roots of the tobacco plants Other data collected involved process of maintaining tobacco plants including watering, cutting the top and axillary buds, dropping a herbicide on the top and buds, fertilizing, getting rid of grass and weeds, and spraying insecticide; picking and curing tobacco leaves including picking tobacco leaves, transferring the leaves from the farm to home, and curing tobacco leaves; dry tobacco producing including removing the stem of tobacco leaves, rolling a bundle of tobacco leaves, cutting tobacco leaves with a cutting machine, putting a slice of tobacco on a bamboo rack, drying the rack of tobacco leaves in the sunlight, reversing the bamboo rack, spraying a tobacco extract to adjust the tobacco color, packing dry tobacco in a plastic bag, and putting away the bamboo rack. The face-to-face questionnaire, the environmental survey, and the measurements of the blood AChE and PChE levels with the Test-Mate OP Kit (EQM Inc, June field, Ohio) were administered in December 2012. This field assay used a modified Ellman method (Ellman et al., 1961) and received extensive field and lab testings (Magnotti et al., 1987; Magnotti Jr. et al., 1988; McConnell et al., 1990; Cole, et al., 1988). AChE activity, measured as absorbance, was corrected for ambient temperature and hemoglobin. Based on the assumption that GTS symptoms may occur only with significant lowering of AChE level in the blood (Namba, 1971), the measurement of the frequency adverse health effects in a population may depend more strongly on the proportion on very low AChE levels than on those whose levels represent the population mean. To account for this possibility, cholinesterase levels were dichotomized to normal and risk categories as well as treated on a continuous scale (Ciesielski et al., 1994). The finger-prick blood of the participants was collected with a capillary tube and the procedure described in the manual of the Test-Mate OP kit was strictly followed. The AChE levels were further grouped into two groups. The values less than 2.7 U/ml were interpreted as ‘risky,’ while those ≥ 2.7 U/ml as ‘safe.’ In addition, the PChE values less than 1.3 U/ml were interpreted as ‘risky,’ while those ≥ 1.3 U/ml as ‘safe.’ The cut-off points for these categories were stated in the manual. It is also worth noting that the ethical approval for the study was obtained from the College of Public Health Sciences, Chulalongkorn University, with COA No.170/2012.

Data Analysis

All data were coded and entered into the Statistical Package for Social Sciences (SPSS) software version 17. conducted using frequency and percentage to describe qualitative data, whereas mean and standard deviation were used to describe quantitative data. Thai traditional tobacco farmers who met the classification criteria of GTS were considered having indicators of the potential for pesticide exposure, and AChE and PChE levels were examined among these farmers. In the second phase of the analysis, the symptoms associated with pesticide exposure were identified. Pesticide exposure was defined by both low AChE levels and a report of exposure during the Thai traditional tobacco cultivation and production process, including use of pesticides. For each of the symptoms, odd ratios were used to estimate the ratio of observed to expected cases. Chi-square and Fisher’s exact test were also employed to find out if there was any association between the symptoms of GTS and AChE levels. In this study, it was assumed that GTS symptoms were associated with AChE levels because GTS and nicotine poisoning inhibit neurotransmitters similar to a reduction in AChE levels.

Also, both GTS and low AChE levels result in similar symptoms including headache, nausea, and vomiting. Finally, adjusted odd ratios were estimated by means of logistic regression analysis. All results were determined to be significant at $P < 0.05$ using 95% confidence interval.

RESULTS

There were 84 Thai traditional tobacco farmers with GTS who participated in the present study. Their blood AChE and PChE levels were measured, and data were gathered by means of the questionnaire interview. Of the 84 study participants, 45.2% were male and 54.8% were female. The mean age of the participants was 46.6 ± 6.5years old (with the range of 25 to 60 years old).

Furthermore, more than half of the participants (52.4%) were housewives, and more than three quarters (78.6%) completed only primary education. As regards their work experience, almost all of them (97.6%) had been working with Thai traditional tobacco plantation for over 20 years, and nearly half of them (46.4%) worked with tobacco around six to ten hours per day. As regards history of cigarette smoking, almost all of them (96.4%) were non-smokers, but 7.1% were living with someone who smoked.

Finally, nearly half of the participants (46.4%) were alcohol consumers. The results regarding demographic characteristics of the study sample are summarized in Table1 below. found that the prevalence of common pesticide symptoms such as nausea or vomiting among the Thai traditional tobacco farmers whose AChE levels were at a safe level were significantly higher than those of the farmers whose AChE level were at a risky level ($p<0.05$). With regard to the PChE levels among the in the first phase of the analysis, statistical analyses were

Table 1: Demographic characteristics of Thai traditional tobacco farmers with GTS (n=84)

Demographic characteristics	Number (n)	Percentage(%)
Gender		
Male	38	45.2
Female	46	54.8
Age (years)		
25 - 46	36	42.9
47 - 60	48	57.1
Status in family		
Head of family	40	47.6
housewife	44	52.4
Education levels		
Primary education	66	78.6
Secondary education	18	41.4
History of cigarette smoking		
No	80	95.2
Yes	4	4.8
Alcohol consumption		
No	45	53.6
Yes	39	46.4
Experiencewith tobacco plantation (years)		
<20	2	2.4
≥20	82	97.6
Approximated daily tobacco exposure (hours)		
0-5	45	53.6
6-10	39	46.4

Table 2: Acetylcholinesterase and plasmacholinesterase values among Thai traditional tobacco farmers with GTS (n =84)

Values	Acetycholinesterase (U/ml)	Plasmacholinesterase (U/ml)
Mean (SD)	2.7(0.6)	1.9 (0.4)
Minimum	1.8	1.1
Maximum	4.4	2.9

study participants, the study results revealed that 42.9% of the participants had their PChE at a risky level, whereas 57.1% had their PChE at a safe level. In addition, the results showed that the common pesticide symptoms that were related to symptoms of GTS were headache (78.6%), dizziness (38.1%), and increased saliva (6.0%). The prevalence of common pesticide symptoms such as headache and increased saliva among the Thai traditional tobacco farmers with PChE at a risky level were significantly higher than those of the farmers with PChE at a safe level ($p<0.05$). On the other hand, the symptom of dizziness experienced by the farmers with PChE at a safe level was significantly higher than that of the farmers whose PChE was at a risky level ($p<0.05$).

Based on the study results, there was no statistically significant difference between AChE levels and PChE levels ($p>0.05$) (See Table 5). Moreover, in the multivariate analysis (See Table 3), two variables with $p<0.05$ in the bivariate analyses were simultaneously analyzed with logistic regression analysis. The results showed that only one variable was significantly associated with AChE levels after being adjusted for the vomiting symptom (ORadj=11.76, 95% CI= 1.34-102.98) (See Table 6 According to the multivariate analysis (Table 4), three variables with $p<0.05$ in the bivariate analyses were simultaneously analyzed using logistic regression analysis. The results revealed that only one variable was statistically significantly associated with PChE levels after being adjusted for the dizziness

Table 3: Association between AChE levels and symptoms of GTS among Thai traditional tobacco farmers (n=84)

Symptoms of GTS	Acetylcholinesteraselevels n(%) Safe[b] (n=32)	Risky[b] (n=52)	Total (%) (n=84)	OR	95% CI	*p*-value[a]
Headache	24(75.0)	42(80.8)	66(78.6)	1.40	0.48-4.02	0.111
Nausea	6(18.8)	0(0)	6(7.1)	0.33	0.24-0.45	*0.002**
Dizziness	16(50.0)	16(30.8)	32(38.1)	0.44	0.17-1.10	0.078
Vomiting	6(18.8)	1(1.9)	7(8.3)	0.09	0.01-0.74	*0.011**
Weakness	31(96.9)	47(90.4)	78(92.9)	0.30	0.03-2.72	0.262
Running eyes	6(18.8)	10(19.2)	16(19.0)	1.03	0.33-3.17	0.957
Blurred vision	0(0)	3(5.8)	3(3.6)	0.60	0.50-0.72	0.166
Increased sweating	8(25.0)	13(25.0)	21(25.0)	1.00	0.36-2.76	1.00
Increased saliva	0(0)	5(9.6)	5(6.0)	0.59	0.49-0.71	0.084

[a]: The p-values were based on the Chi-square test or Fisher's Exact test <0.05.
[b]: A acetylcholinesterase value< 2.77 U/ml. was interpreted as 'risky' and ≥ 2.77 U/ml. as 'safe.'

Table 4: Association between PChE levels and symptoms of GTS among Thai traditional tobacco farmers (n=84)

Symptoms of GTS	Plasmacholinesterase levels n (%) Safe[b] n =48	Risky[b] n =36	Total (%) n=84	OR	95% CI	*p*-value[a]
Headache	34(70.8)	32(88.9)	66(78.6)	3.29	0.98-11.06	*0.046**
Nausea	4(8.3)	2(5.6)	6(7.1)	0.64	0.11-3.74	0.696
Dizziness	23(47.9)	9(25.0)	32(38.1)	0.36	0.14-0.93	*0.032**
Vomiting	4(8.3)	3(8.3)	7(8.3)	1.0	0.20-4.77	1.00
Weakness	43(89.6)	35(97.2)	78(92.9)	4.07	0.45-36.47	0.179
Running eyes	10(20.8)	6(16.7)	16(19.0)	0.76	0.24-2.32	0.630
Blurred vision	1(2.1)	2(5.6)	3(3.6)	2.76	0.24-31.74	0.574
Increased sweating	12(25.0)	9(25.0)	21(25.0)	1.00	0.36-2.71	1.00
Increased saliva	0(0)	5(13.9)	5(6.0)	0.39	0.29-0.51	*0.012**

[a]:The p-values were based on the Chi-square test or Fisher's Exact test <0.05.
[b]:A plasmacholinesterase values< 1.35 U/ml. were interpreted as 'risky' and ≥ 1.35 U/ml. as 'safe.'

Table 5: Association between AChE levels and PChE levels among Thai traditional tobacco farmers with GTS (n=84)

Markers	Plasmacholinesterase levels n (%) Safe	Risky	Total (%)	OR	95% CI	*p*-value*
Acetylcholinesterase levels						
safe	20(41.7)	12(33.3)	32(38.1)	1.42	0.58-3.51	0.436*
Risky	28 (58.3)	24(66.7)	52(61.9)			
Total	48(100)	36(100)	84(100)			

*p>0.05

symptom (ORadj=2.76, 95% CI= 1.07-7.08) (See Table 7).

DISSCUSSION

Based on the study results, it could be concluded that the health effects of tobacco cultivation were known to Thai traditional tobacco farmers; nevertheless, the actual causes of such effects may not have been clearly understood. Such a result was consistent with the result reported by a previous study (McBride et al., 1998). In addition, the results of this study showed that the prevalence ofthe risky level of AChE was 61.9% and the prevalence ofthe safe level was 38.1%. Also, the prevalence of the risky and safe levels of PChE was

Table 6: Logistic regression analysis of acetylcholinesterase (AChE) levels by symptoms of Green Tobacco Sickness (GTS) among Thai traditional tobacco farmers (n=84)

Symptoms	Acetylcholinesterase level n (%)		OR(95% CI)	OR $_{adj}$ (95% CI)	*p*-value*
	Safe n =32	Risky n =52			
Vomiting					
No	26(81.2)	51(98.1)	0.09 (0.01,0.74)	11.76(1.34,102.98)	0.026*
Yes	6(18.8)	1(1.9)			

* The p-value for trend.

Table 7: Logistic regression analysis of plasmacholinesterase (PChE) levels by symptoms of Green Tobacco Sickness (GTS) among Thai traditional tobacco farmers (n=84)

Symptoms	Plasmacholinesterase level n (%)		OR (95% CI)	OR $_{adj}$ (95% CI)	*p*-value*
	Safe n =48	Risky n =36			
Dizziness					
No	25(52.1)	27(75.0)	0.36(0.14,0.93)	2.76(1.07,7.08)	0.035*
Yes	23(47.9)	9(25.0)			

* The p-value for trend.

42.9% and 57.1%, respectively. Such results indicated that Thai traditional tobacco farmers who were involved in intensive agriculture may have been exposed to pesticides from their activities in the cultivating season because before these farmers started growing tobacco plants in the areas, they had been growing vegetables, sticky rice, and other agricultural products. Besides this, Thai traditional tobacco cultivation always involves use of pesticides (e.g., organophosphate and carbamates) in early stages of the cultivation process in order to protect the roots of the tobacco plants with Carbofuran (Curater®). Also, methomyl, malathion, or pyrethroids may be sprayed onto the tobacco plants depending on infestation of insects. Also, the present study found that common symptoms of GTS were related to symptoms of pesticide exposure when farmers had AChE at a safe level, including nausea (7.1%) and vomiting (8.3%), while the symptom of GTS that was related to the symptom of pesticide exposure when farmers had PChE at a safe level was dizziness (38.1%). It is noteworthy that these results were different from the results of previous studies(Kachaiyaphum et al., 2010; Yassinet al., 2002) that the decrease in AChE and PChE levels was not statistically significantly associated with symptoms of pesticide exposure. However, it may be possible explain such association with the definition of GTS, including any general illness after exposure to tobacco leaves(Quandt et al., 2000) and use of specifically applied case definition of headache, nausea, dizziness, or vomiting during or after exposure to tobacco leaves as nicotine poisoning (Arcuryet al., 2003). Furthermore, even when the farmers have a safe level of AChE and PChE, abnormal symptoms may still occur after exposure to a low dose of pesticides exposure and changes in cholinesterase inhibition that may cause similar symptoms with different mechanisms. It is also possible that previously depressed acetylcholinesterase levels may have occurred before enrollment (Ciesielski et al., 1994). It is also possible that symptoms such as nausea, vomiting, headache, and dizziness may result from organo-phosphorous insecticide exposure when organo-phosphorous insecticides are applied(Arcury et al., 2008).

However, it is worth noting that chemical pesticides will not be applied during harvest of Thai traditional tobacco plants, and the definition of GTS refers to a group of symptoms that occur after working with tobacco plants without any previous application of pesticides. Therefore, it is possible to interpret that the safe levels of AChE and PChE are associated with nicotine poisoning as well.

LIMITATIONS

Some limitations of this study should be noted. This study was a cross-sectional research study, and it is acknowledged that uncertainty in time relationship could interpretation of this type of study. Moreover, the validity of data collection depended partly on characteristics of both the interviewer and study participants.

In fact, characteristics of the participants including their ability to recall the data and their willingness to answer the questions asked by the interviewer may have an influence on the validity of the study results. Therefore, during data collection, the researchers intended to overcome such a limitation by providing clear explanation to the farmers before data collection commenced.

CONCLUSION

The study results revealed that the process of Thai traditional tobacco cultivation which involves contact with nicotine and pesticides through dermal exposure is a major risk of GTS.The present study is considered the first of its kind to find out the association between symptoms of GTS and symptoms of the levels of AChE and PChE that occur after exposure to pesticides among Thai traditional tobacco farmers in Nan Province, Thailand. The results have indicated that the safe levels of AChE and PChE are associated with symptoms of low dose pesticide exposure and could possibly explain an association between the safe level of AChE and PChE and nicotine poisoning. Based on such results, it is recommended that a health education program is needed to disseminate knowledge and information regarding health risksof exposure to nicotine and pesticides to raise awareness of Thai traditional tobacco farmers. Also, further studies should be conducted to shed more light on long-term effects of exposure to both nicotine and pesticides among Thai traditional tobacco farmers.

ACKNOWLEDGEMENT

The authors would like to thank Thai Fogarty ITREOH Center (Grant Number. 1D43 TW007849 Fogarty International Center-National Institute of Health) and NIEHS sponsored Center Grant #P30ES005022 for research financial support. The ACHE and PCHE test kit and supplies were supported by the Ratchadapisek Sompoch Endowment Fund (2014), Chulalongkorn University (CU-57-078-AS). The College of Public Health Sciences, Chulalongkorn University, Bangkok, Thailand is also gratefully acknowledged.

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