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Florida Red Tide Toxins (Brevetoxins) and Longitudinal Respiratory Effects in Asthmatics

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Abstract

Having demonstrated significant and persistent adverse changes in pulmonary function for asthmatics after 1 hour exposure to brevetoxins in Florida red tide (*Karenia brevis* bloom)

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Conflict of Interests

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aerosols, we assessed the possible longer term health effects in asthmatics from intermittent environmental exposure to brevetoxins over 7 years. 125 asthmatic subjects were assessed for their pulmonary function and reported symptoms before and after 1 hour of environmental exposure to Florida red tide aerosols for upto 11 studies over seven years. As a group, the asthmatics came to the studies with normal standardized percent predicted pulmonary function values. The 38 asthmatics who participated in only one exposure study were more reactive compared to the 36 asthmatics who participated in ≥4 exposure studies. The 36 asthmatics participating in ≥4 exposure studies demonstrated no significant change in their standardized percent predicted pre-exposure pulmonary function over the 7 years of the study. These results indicate that stable asthmatics living in areas with intermittent Florida red tides do not exhibit chronic respiratory effects from intermittent environmental exposure to aerosolized brevetoxins over a 7 year period.

Keywords

Asthma; harmful algal bloom (HAB); *Karenia brevis*; longitudinal health study

1. Introduction

Research has demonstrated that the aerosolized brevetoxins from the harmful algal bloom (HAB) organism, *Karenia brevis (K. brevis)* can cause acute, sub-acute, and possibly chronic respiratory effects in humans and in laboratory animals (Fleming et al., 2005a; Fleming et al., 2011; Kirkpatrick et al., 2004a; Zaias et al., in press). During Florida red tide events, recreational beach goers measured before and after a visit to the beach and healthy lifeguards measured before and after their work shifts demonstrated significant changes in their report of respiratory symptoms, but not significant changes in their pulmonary function (Backer et al., 2003; Backer et al., 2005). Asthmatics ≥12 years of age demonstrated statistically significant increases in self-reported symptoms and decreased lung function after only 1 hour of aerosolized brevetoxin exposure at the beach; the symptoms and further decreases in pulmonary function continue for several days after their beach exposure (Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009; Kirkpatrick et al., 2011). Significantly increased admissions for respiratory illnesses among coastal residents were seen during a Florida red tide bloom compared with a period without blooms (Hoagland et al., 2009; Kirkpatrick et al., 2010; Kirkpatrick et al., 2006; Quirino et al., 2004). Research using the sheep model of asthma demonstrated acute and sub-acute respiratory effects in both asthmatic and non asthmatic sheep exposed to levels of aerosolized brevetoxins similar to those experienced by humans at the beach during a Florida red tide bloom; possible immunologic effects have also been documented in rodents and sheep exposed chronically to aerosolized brevetoxins (Abraham et al., 2006; Abraham et al., 2005a; Abraham et al., 2005b; Abraham et al., 2009; Benson et al., 2005; Zaias et al., 2004; Zaias et al., in press).

We evaluated the possible long term respiratory health effects of repeated aerosolized brevetoxin exposure in a cohort of asthmatics over 7 years.

2. Methods

Over the past decade, an interdisciplinary research team has evaluated aerosolized *K. brevis* red tide brevetoxin exposures, and their possible acute and chronic health effects in humans and animals (Fleming et al., 2005a; Fleming et al. 2011). These studies were approved by Florida Dept of Health (H1198) and University of Miami (HSRO19990282) institutional review boards.

As described previously in detail (Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009), asthmatic participants were defined as: a) self-reported diagnosis by a physician; b) ≥12 years old; c) smoked for ≤10 years; d) able to walk ≥30 minutes on the beach; and e) resident of the Sarasota (Florida) area for ≥6 months. For each study, participants spent ≥1 hour at the beach in areas with coordinated environmental monitoring. Participants could return at any time from the beach if they felt symptomatic; all participants were encouraged to use any personal asthma medications as needed throughout the study period.

Detailed information was collected for all subjects in a baseline questionnaire. Each asthmatic in this study participated in at least one evaluation during an active *K. brevis* bloom (exposure period), and during a period without a bloom (non-exposure period). Both evaluations included pre/post-beach: questionnaires, nasal swab sampling, and spirometry (FEV_1, $FEF_{25–75}$, PEF, and FVC) as previously described (Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009; NIOSH, 1997). All study participants had ≥3 reproducible spirograms before and after visiting the beach; only data conforming to the standard guidelines for collection and interpretation of spirometry measurements were accepted (ATS, 1995). The pre/post-beach questionnaires collected information on recent medical history, asthma medication use, symptoms, and possible confounders. The use of asthma medications within 12 hours before going to the beach was used as a surrogate for increased asthma severity and lack of disease control. Coastal residence was defined as residence <1 mile of a barrier island or Sarasota Bay.

As previously described, extensive environmental and personal monitoring in all field studies was conducted (Cheng et al., 2005a; Cheng et al., 2005b; Cheng et al., 2005c; Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009; NIOSH, 1997; Naar et al., 2002; Pierce et al., 2003; Pierce et al., 2005). Based on the environmental monitoring criterion of cell counts for *K. brevis* >100,000 cells/L in water, and brevetoxins detected by ELISA and/or LCMS in both water and air, 5 studies (March’03, February’05, March’05, September’06, and December’09), were considered to have exposure to red tide toxins. Six non-exposure studies (January’03, May’04, October’04, June’06, September’07, and May’08) were also carried out.

2.1. Statistical Methods

All analyses were performed using SAS, version 9.2. Distributions of variables were examined for outliers and skewed data. Both t-test and mixed modeling were employed for examining differences in the groups for the dependent variables (e.g. pulmonary function tests, and symptom score). Two indices of goodness of fit, Akaike’s information criterion (AIC) and Bayesian information criterion (BIC), were examined to determine the appropriate covariance structure when applying mixed modeling. The covariance structure chosen was unstructured.

The first question assessed was: did the exposure to brevetoxin over the 7 years result in the participants having lower pulmonary functions in their pre-walk measures? After examining this question without considering any covariates, we then evaluated the pre-exposure pulmonary function values with the following variables: 1) exposure or not, 2) time since entrance in the first study for each person, and 3) the potential interaction between time and exposure. Using mixed modeling, the analyses focused on the pre-exposure percent predicted values for FEV_1 and PEF over all 11 studies; these values were adjusted using national standards (Hankinson et al., 1999). In addition, based on our prior research, the residence of the participant as well as their use of medications might influence the predicted pulmonary function values, so these two variables were examined next. The mixing modeling analyses were rerun using each variable separately in the model.

The next question was whether or not the participants who reacted strongly after their first beach walk when there was a red tide would not participate in other exposure studies? Two groups were identified: Group 1 participants dropped out of the study after participating in only one of the 5 exposure studies, whereas Group 2 participants came to ≥4 exposure studies. Using the first exposure study for each individual, the difference in their pre-beach walk pulmonary function value from the post-exposure value was calculated, and then the means of the differences were compared between the two groups. The mean differences in the pre-exposure symptom score and the post-exposure score were also compared for the 2 groups. The variables, coastal residence and asthma medication use, were also examined.

The third hypothesis was to determine if Group 2 subjects who participated in ≥4 studies had differences in lung function over time given multiple exposures to Florida red tide? Again we used the mixed modeling of the pre-exposure percent predicted values for their FEV_1 and PEF over all 11 studies, and included the prior variables of interest and the interaction of time and exposure.

3. Results

Over the 7 years, 125 asthmatics ≥12 years of age participated in the study's cohort for at least 1 exposure study, with an average of 5+/−3.2 field studies/person (Table 1). Mean age on enrollment was 40.5+/−20.0 yrs; they were predominantly white (95%) and female (61%). Using baseline information, most were diagnosed with asthma many years ago (26.5+/−25.5 yrs). The majority (52.4%) used asthma medications, and the majority (70%) lived inland. Only 15% had been hospitalized for respiratory causes in the year prior to study enrollment.

3.1. Environmental Exposure

To evaluate whether or not participants showed any significant health effects from environmental exposure to the aerosolized brevetoxins prior to coming to the beach for a field study, we examined the percent predicted pre-exposure FEV_1 and PEF for all participants over the 7 years of 11 studies (Hankinson et al., 1999). In general, the mean FEV_1 and PEF were within normal clinical range of ≥80% for all studies (Table 2) (Clausen et al., 1989; Hankinson et al., 1999). Although statistically significant changes were observed in FEV_1 (p=0.001) and PEF (p=0.0008), these changes were not associated with exposure; nor was there any interaction between time and exposure. The mean predicted FEV_1 and PEF at baseline were 86.5% and 99% respectively, whereas for the last field study, the mean predicted FEV_1 were 84.3% and 97% respectively; these were small differences and within normal limits. In a model with the variable medication use included (along with the factors of exposure, time, and the interaction of exposure and time), statistically significant changes in FEV_1 (p=0.001) and PEF (p=0.0005) were observed over time, but not by exposure; nor were there any interactions between time and exposure (p=0.63 and p=0.76, respectively). Evaluating the variable residence, statistically significant changes in FEV_1 (p=0.002) and PEF (p=0.0009) were observed over time, but not by exposure; nor was there any interaction between time and exposure (p=0.66 and p=0.86, respectively).

3.2. Study subpopulations

The 38 persons (Group 1) who were in only 1 exposure study participated in fewer total studies than the 36 people (Group 2) who participated in ≥4 exposure studies (p=0.001) (Table 1). The Group 1 participants were more likely to have been hospitalized for respiratory causes in the year prior to enrollment (10 [29%] vs 1 [3%]; p=0.002) and to use

asthma medications (24 [67%] vs 15 [42%]; p=0.03). The two groups did not differ with respect to the proportions of who lived near the coast (p=0.21).

The means of the differences for FEV_1, PEF, and $FEF_{25–75}$ were positive for both Group 1 and Group 2 (i.e. the values before beach exposure were larger than the values afterwards), and a depression of respiratory function from the 1 hour of beach exposure occurred for both groups. Group 1 had higher means for FEV_1, PEF, and $FEF_{25–75}$ than Group 2; thus, the negative effects on respiratory function of the 1 hour of beach was greater for Group 1 than Group 2. The means of the differences for FEV_1 (Group 1:78.9 vs Group 2:21.9; p=0.05) and for $FEF_{25–75}$ (190.8 vs 54.1; p=0.03), but not the PEF (371.6 vs 176.7; p=0.21), were statistically significant. For those who took no medications, the means of the differences for FEV_1 (84.6 vs 12.9; p=0.05) and $FEF_{25–75}$ (253.8 vs 39.1; p=0.01), but not PEF (340.0 vs −8.1; p=0.13), were statistically significant; again the effect of the 1 hour of beach exposure was greater for Group 1 than Group 2. For those who took asthma medications, none of the means of the differences for FEV_1 (Group 1:75.8 vs Group 2: 34.7; p=0.39), PEF (388.8 vs 435.3; p=0.84) and $FEF_{25–75}$ (156.7 vs 75.3; p=0.39) were statistically significant; however, the directions of the results were similar with FEV_1 and $FEF_{25–75}$ of Group 1 being greater than Group 2.

The mean symptom scores before and after the 1 hour beach exposure for Group 1 were 2.02+/−1.9 and 2.9+/−1.9 (mean difference −0.86+/−2.1), respectively; whereas Group 2 had mean symptom scores of 1.6+/−1.8 and 2.4+/−1.8 (mean difference= −0.76+/−2.5), respectively. No statistically significant difference (p= 0.85) were observed between Group 1 and 2 regarding changes in symptom scores. Nevertheless, Group 1 asthmatics arrived at the beach with higher symptom scores, and experienced an increase in their symptoms after 1 hour of beach exposure. For those who took no medications, the difference in the mean difference of the symptom score (−1.1+/−1.9 vs 1.2+/−2.5; p=0.88) was not statistically significant. Similar results were seen for those who took asthma medications, with no statistical significance in the mean difference of the symptom scores for Group 1 as compared to Group 2 (−0.8+/−2.2 vs −0.1+/−2.5; p=0.42).

3.3. Longitudinal effects: Group 2

To look at the longitudinal effect of repeated aerosolized brevetoxin exposure over time, the same mixed modeling analyses were performed on predicted pulmonary function before exposure, but only for the Group 2 participants. The percent predicted FEV_1 values went from 80% (January 2003) to 82% (December 2009); the percent predicted PEF values from 92% (January 2003) to 94% (December 2009) (Table 2). In the model of FEV_1 incorporating the covariates exposure and time, for asthma medication use there was a statistically significant change in FEV_1 over time (p=0.01), but not by exposure (p=0.49); nor was there any interaction between time and exposure (p=0.92). Therefore, although there were changes in the preexposure percent predicted pulmonary function over time by different covariates, in general these changes were not related to exposure.

4. Discussion

These analyses summarize the data from a cohort of asthmatics followed over 7 years with assessments before and after 1 hour of brevetoxin exposure at the beach, during exposure and non-exposure periods. The results suggest no significant effect from their initial exposure to Florida red tide on subsequent pre-exposure measures of pulmonary function for the entire cohort nor for most of the subgroups. However, certain subpopulations (i.e., less controlled asthmatics and those who lived inland) appeared to show changes in pulmonary function over time as they continued to participate on our studies (Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009).

The subpopulation of subjects who participated in only 1 exposure study reacted significantly more to the 1 hour of brevetoxin exposures than another those subjects who participated in at least ≥4 exposure studies. Based on the standardized percent predicted pulmonary function values, these latter individuals did not appear to have differences over time in their preexposure pulmonary function (with the exception of the less controlled asthmatics). Therefore, at least for the relatively stable asthmatics able to participate in ≥4 exposure studies, the results suggest that the participants did not have significant longitudinal respiratory effects from repeated exposures to brevetoxins over seven years. These results are consistent with prior research demonstrating that pulmonary function decreases with age in both asthmatics and non asthmatics. The naturally occurring amount of change is similar for chronic asthmatics and non asthmatics; however, new onset or unstable asthmatics experience greater pulmonary function change over time (Ulrik et al., 1994).

These findings have important implications for persons with asthma and possibly other respiratory diseases who live or visit areas with aerosolized brevetoxin exposures. Even well controlled asthmatics and their healthcare providers need to be aware that only 1 hour of exposure to Florida red tide aerosols can cause increased symptoms and decreased respiratory function lasting for at least several days after exposure. We recommend persons with underlying respiratory disease (and their healthcare providers, emergency medical facilities and public health officials) be aware of the onshore activity of Florida red tide blooms, and avoid visiting coastal areas with strong onshore winds during onshore blooms (Fleming et al., 2011). This appears to be particularly important for poorly controlled asthmatics, and those with relatively little regular brevetoxin exposure (e.g. who live inland or visitors). Furthermore, although the use of common asthma medications have been shown to be efficacious in preventing and mitigating the respiratory response to brevetoxins in the sheep model (Abraham et al., 2006; Abraham et al., 2005a; Abraham et al., 2005b; Abraham et al., 2009), since these medications can be dangerous if over-used (Jonas et al., 2008), it is important that asthmatics avoid the brevetoxin exposure rather than treat the symptoms of an ongoing exposure. Our research also provides support for ongoing efforts in environmental monitoring and outreach and education to keep persons with underlying lung disease, healthcare providers, and public health officials informed about the possibility of onshore Florida red tide activity (Fleming et al., 2007; Kirkpatrick et al 2004b; Kirkpatrick et al 2008; Nierenberg et al., 2009; Nierenberg et al., et al 2011; Stumpf et al., 2009). Finally, at least in well controlled chronic asthmatics, it appears that long term intermittent exposures to brevetoxins does not increase the typical rate of decrease in lung function over time.

4.1. Limitations

Due to wind and other environmental conditions, as well the patchiness of the *K brevis* blooms, brevetoxin aerosols exposure levels vary significantly by both time and space, even within the same exposure study (Cheng et al., 2005a; Cheng et al., 2005b; Cheng et al., 2005c; Fleming et al., 2005b; Fleming et al., 2007; Fleming et al., 2009; NIOSH, 1997; Naar et al., 2002; Pierce et al., 2003; Pierce et al., 2005). Participants could also have experienced environmental exposure to these aerosols before and after exposure field studies if they lived, worked, and/or played in coastal areas with onshore blooms (although our analyses suggest there was no major environmental exposure for the majority of the cohort since overall the pre-exposure percent predicted pulmonary function tests were within normal standardized ranges). The study cohort was open; this lead to the development of several different subpopulations within the cohort (e.g. Group 1 and Group 2). Although our analyses are suggestive that intermittent brevetoxin exposure in asthmatics does not lead to long term chronic respiratory effects, we were unable to evaluate the longitudinal effects of this exposure for the more reactive Group1 population. Due to the relatively small number

of study participants, we cannot completely exclude possible longitudinal effects from brevetoxin exposure even in Group 2 asthmatics (e.g., among the poorly controlled asthmatics).

HIGHLIGHTS

- Brevetoxins from Florida red tide (*Karenia brevis* bloom) can be aerosolized
- Aerosolized brevetoxins can cause acute and subacute effects in asthmatics
- Unstable asthmatics are particularly susceptible to aerosolized brevetoxin exposures
- After 7 years of brevetoxin exposure, stable asthmatics have no chronic effects

Abbreviations

PbTx	Brevetoxins
ELISA	Enzyme linked immunosorbent assay
HAB	Harmful algal bloom
K. brevis	*Karenia brevis*
LCMS	Liquid chromatography mass spectroscopy
mg/m^3	milligram per meter cubed
ug/L	microgram per liter
ng/m^3	nanogram per meter cubed
FEV$_1$	forced expiratory volume in 1 second
FEF$_{25–75}$	forced expiratory flow 25% – 75%
PEF	peak expiratory flow
FVC	forced vital capacity

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Table 1

Demographics of entire study cohort (n=125); and Group 1 vs Group 2

Variable	All Asthmatics	Group 1	Group 2	P value*
N	**125**	**38**	**36**	
Age at entry ± Standard Deviation (Range in yrs)	40.5+/− 20.0 (12–73)	41.4+/−19.4 (12–73)	39.3+/−20.6 (12–66)	0.65
Female (%)	76 (61%)	25 (66%)	19 (53%)	0.25
White (%)	118 (95%)	32 (89%)	35 (97%)	0.18
Hispanic (%)	−3 (2.4%)	1 (3%)	0	0.50
Years with diagnosis ±SD (Range in yrs)	26.5+/−25.5 (0–88)	26.2+/−25.8 (0–88)	26.4+/−26.5 (1–88)	0.98
Positive History of symptoms with Florida Red Tide exposure (%)	110 (87%)	28 (85%)	24 (82%)	0.80
Current smoker (%)	8 (7.5%)	2 (6%)	2 (6%)	0.70
Hospitalized ≥1 in past year from Respiratory Causes (%)	18 (14.9%)	10 (29%)	1 (3%)	**0.002**
Used medications[a] within 12 hours before first study exposure (%)**	66 (52.4%)	24 (67%)	15 (42%)	**0.03**
Living >1 mile from Coast (%)**	78 (69.9%)	21 (55%)	26 (72%)	0.13
Mean number of studies participated ±SD (Range in yrs)	5.7+/−3.0 (1–11)	2.6+/−0.9 (1–5)	9.2+/−1.4 (6–11)	**0.001**

* Significance testing by ttest (or Fishers) or by Chi square;

** Asthma medications predominantly beta2 agonists.

Table 2

Pre-exposure mean percent predicted pre-exposure FEV_1 and PEF for all participants and for Group 2 Participants over entire 7 years by study and by exposure status

Exposure Status	Date	All participants		Group 2 participants	
		N	mean percent (%) predicted +/− Standard Deviation*	N	mean percent (%) predicted +/− Standard Deviation*
FEV_1					
Unexposed	**Jan 2003**	68	86.5+/−16.8	30	80.3+/−15.6
	May 2004	66	88.6+/−12.4	31	82.4+/−17.4
	Oct 20O4	71	85.5+/−17.2	31	82.2+/−17.6
	Jun 2006	62	86.2+/−17.0	32	84.3+/−16.7
	Sept 2007	62	83.2+/−20.6	27	83.9+/−15.7
	May 2008	73	79.8+/−20.2	30	79.7+/−16.3
Exposed	**March 2003**	58	84.9+/−17.0	26	79.5+/−16.5
	Feb 2003	79	84.5+/−18.2	33	84.8+/−16.3
	March 2003	79	84.3+/−19.2	35	84.7+/−16.7
	Sept 2006	47	80.9+/−18.7	34	82.6+/−16.3
	December 2009	55	84.3+/−18.5	23	82.5+/−16.9
PEF					
Unexposed	**Jan 2003**	68	99.0+/−17.9	30	92.4+/−17.6
	May 2004	66	102.4+/−21.6	31	92.5+/−22.6
	Oct 20O4	71	97.1+/−21.1	31	94.3+/−20.2
	Jun 2006	62	97.2+/−19.6	32	91.5+/−17.8
	Sept 2007	62	94.9+/−23.7	27	94.8+/−17.3
	May 2008	73	91.5+/−23.2	30	89.9+/−19.4
	March 2003	58	97.4+/−20.1	26	91.4+/−19.3
Exposed	**Feb 2003**	79	98.1+/−22.3	33	97.3+/−18.4
	March 2003	79	98.1+/−22.9	35	96.8+/−19.1
	Sept 2006	47	92.9+/−19.9	34	94.7+/−17.1

Exposure Status	Date	All participants		Group 2 participants	
		N	mean percent (%) predicted +/− Standard Deviation*	N	mean percent (%) predicted +/− Standard Deviation*
	December 2009	55	96.6+/−22.2	23	94.3+/−21.5

*Percent predicted FEV_1 standardized by age, gender, race, height, and weight (Hankinson et al. 1999); Group 2= participants in ≥4 exposure studies