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THE EFFECTS OF AEROSOLIZED BREVETOXIN EXPOSURE ON THE HUMAN RESPIRATORY SYSTEM

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INTRODUCTION

Karenia brevis is a marine dinoflagellate responsible for red tides that form almost annually in late summer and autumn in the Gulf of Mexico and the Caribbean, and can be carried on ocean currents to the east coast of the United States as far north as North Carolina. *K. brevis* produces potent toxins called brevetoxins which contain a number of different components including hemolytic, cardiotoxic, and neurotoxic compounds (Kirkpatrick, 2004). The effects of neurotoxic shellfish poisoning as a result of consuming whole, contaminated fish or bivalves which concentrate the toxins in their tissues (Sellner et al., 2003) are seen in many marine animals, and these toxins were responsible for a large die-off of dolphins in 2004 (Naar et al., 2007). Because people in the United States do not generally consume fish in their entirety, deaths due to neurotoxic shellfish poisoning from the consumption of fish are rarely documented in people in this country (Naar et al., 2007).

Even if they are not consumed, brevetoxins can have detrimental effects on the health of marine animals and humans. These toxins, particularly PbTx-3, can be aerosolized when the fragile organism is broken open in the crashing waves near the shoreline and can be carried inland on wind and attached to salt particles, causing respiratory irritation when inhaled. The mechanism by which brevetoxin exerts its effect on the respiratory system is believed to be the result of the opening of voltage gated sodium channels on nerve cell membranes. Brevetoxin induces contraction of the lower airway smooth muscle by stimulation of the cholinergic nerve fiber sodium channels with acetylcholine release. Additional pathways, such as mast cell degranulation, are also thought to play a role in respiratory dysfunction. As a result of exposure, individuals have reported an acute onset of conjunctival irritation, cattarrhal exudates, rhinorrhea, nonproductive cough, bronchoconstriction, and other symptoms such as dizziness, tunnel vision, and skin rashes. Furthermore, some researchers have postulated that in addition to these acute effects of brevetoxin exposure, chronic effects such as chronic neuro-intoxication, hemolytic anemia, and/or immunologic compromise may also occur in humans and has been documented in chronically exposed manatees (Kirkpatrick, 2004).

While much information has been collected about the effects of brevetoxin ingestion in contaminated seafood, there has been very little research conducted and little is known about the effects of these toxins when inhaled in aerosols (Backer et al., 2003). The effects of brevetoxins are of great public health concern because not only are harmful algal blooms increasing in frequency and duration of occurrence, they are also expanding their area of distribution (Sellner et al., 2003; Kirkpatrick, 2004). Since a significant proportion of the world's population live within 75 miles of an ocean coast and this density of human coastal populations is increasing daily, particularly in subtropical and tropical areas (Fleming et al., 2006), this puts many people at risk for suffering from respiratory ailments, particularly those individuals that have already been diagnosed with respiratory disease such as asthma.

The purpose of this research paper is to review literature on the epidemiologic relationship between aerosolized brevetoxin exposure during red tide events in Florida and the development of respiratory related ailments, particularly in those individuals that may be at increased risk due to preexisting respiratory conditions such as asthma, chronic obstructive pulmonary disease, smoking, and degenerative disease in the elderly.

REVIEW OF LITERATURE

Four prospective cohort studies were conducted in Florida to examine the effects of aerosolized brevetoxin exposure on pulmonary function. The first two studies examined healthy individuals exposed at Florida beaches, and the second two studies examined visitors to these beaches that had been previously diagnosed with asthma by a physician.

The first prospective cohort study by Backer et al. (2003) was conducted during two separate Florida red tide events to assess whether beach-goers exposed to aerosolized brevetoxins reported adverse health symptoms and experienced measurable changes in lung function (spirometry) tests after spending time on the beach. The studies took place at two different beaches, one in Sarasota on the Gulf coast of Florida in February 1999, and one in Jacksonville on the northeast coast of Florida in October 1999. A total of 129 subjects were evaluated. The subjects at the Sarasota beach were unlikely to be exposed because the red tide remained offshore and there was little wind. The subjects in Jacksonville were likely to be exposed because strong onshore winds were present and capable of carrying aerosolized toxins onto the beach. During both studies, questionnaires were administered (including questions about demographics, pulmonary health history, amount of time spent on the beach, medications, information about potential confounders, and various symptoms), nose and throat swabs were collected to evaluate potential biological markers of exposure (infiltration of inflammatory cells, presence of epithelial cells, and immunohistochemical analysis of brevetoxin within cells), and pulmonary function tests by spirometry were conducted. These evaluations were conducted on visitors both before and after they spent time on the beach. Environmental samples were also collected to determine the concentration of *Karenia brevis* cells in seawater and the ambient air.

Of the study participants, 38% admitted to having allergies, 5.4% had been diagnosed with asthma by a physician, 10% had suffered from some kind of pulmonary disease including emphysema or bronchitis, 31% were current smokers and 22.5% were former smokers. Compared with those with low exposure to brevetoxins, those with medium or high exposure reported more symptoms associated with both upper respiratory irritation (e.g. eye irritation, nasal congestion, throat irritation, and cough) and lower respiratory irritation (e.g. chest tightness, wheezing, shortness of breath). Since few subjects from the nonexposed group reported increased respiratory symptoms, it is highly unlikely that exposure to sea spray and sand alone were responsible for the significant changes seen in the exposed group. There were no clinically important changes in the spirometry parameters in any of the groups.

In Jacksonville, nose and throat swabs were collected from 41 highly exposed and

51 moderately exposed study participants before and after they spent time on the beach. On the high exposure day, 2.5% had a marked increase, 5% had moderate increases, and 42% had mild increases in inflammatory response after exposure. On the moderate exposure day, no one had a marked increase, 10% had moderate increases, and 29% had mild increases in inflammatory response after exposure. A total of 49% and 39% of people sampled on the high and moderate exposure days, respectively, had an increase in inflammation in the nose and/or throat swab sample. The predominant inflammatory response was acute to subacute, and primarily neutrophils were observed in the samples. Twenty swab samples were immunohistochemically examined for the presence of brevetoxin: 65% of pre- and post-exposure samples were negative, 10% were negative in the pre-exposure and positive in the post-exposure samples, and 25% were negative in the pre-exposure and equivocal in the post-exposure samples.

There were a number of variables in this study that may have had an effect on the results. For instance, the different times of the year (February vs. October) made it likely that other variables may be present; nasal swabs were only taken from individuals at the Jacksonville beach and it is likely that the swabbing itself was irritating enough to cause an inflammatory response; Jacksonville was hotter and less humid than Sarasota during the studies; offshore winds in Sarasota changed to onshore later in the afternoon but the levels of detectable brevetoxins in the air was low; participants spent anywhere from ten minutes to eight hours at the beach and the averages for the time spent on the beach differed with the degree of exposure to brevetoxins; and not everyone successfully completed the spirometry tests. Aside from these factors, though, this was the first study of its kind to compare the effects of aerosolized brevtoxins on the respiratory system, and it provided a good baseline for future studies to further analyze the effects of these toxins.

The second prospective cohort study conducted by Backer et al. (2005) looked at 28 full-time healthy lifeguards on various beaches in Florida that are occasionally affected by red tide. Subjects were subjected to spirometric pulmonary function tests and symptom surveys which included questions about upper respiratory symptoms (i.e., eye and throat irritation, nasal congestion, cough) and lower respiratory symptoms (i.e., chest tightness, wheezing, shortness of breath) both before and after working a 6-8 hour shift both during times of red tide (exposure) and not (unexposed). Environmental samples of sea water and air were analyzed for the presence and levels of brevetoxins and compared with subject results to confirm exposed/unexposed status.

The lifeguards were first interviewed using a questionnaire comprising questions about demographics and pulmonary health history. These factors were then taken into consideration when reviewing the results to rule out confounding factors. Exposure status was determined separately for each individual lifeguard by day and by beach. This was based on air sample analysis which corresponded with the air that the individual lifeguards were exposed to since the instruments used to measure the brevetoxin levels were located on the lifeguard towers near the lifeguards' breathing zones. This also helped to rule out inconsistencies in the experimental design (wind speed and direction, etc.). Because this study utilized self-reported symptom data, the possibility for the study to suffer from reporting bias was apparent. The actual exposure status of the participants, though, was not known by the participants or the researchers at the time of evaluation, and only became clear later when the environmental sample analysis was completed.

Compared with nonexposure periods, the healthy lifeguards in the study reported more upper airway but not lower airway discomfort during the red tide exposure periods. There were statistically significant effects on some spirometry test parameters during exposure to brevetoxins, but the changes were small and not clinically significant. This study, therefore, suggested that, for healthy people, exposure to low levels of brevetoxins in the air during Florida red tides is associated with temporary discomfort in the form of respiratory irritation but is not associated with acute adverse effects on pulmonary function.

This study used a fairly small sample size of healthy subjects. This is a difficult study to control because subjects are exposed to natural environmental conditions which cannot always be held constant. Overall the researchers did a nice job of interpreting the results individually to avoid generalizations that may have not taken into consideration the personal exposure of each lifeguard based on environmental variables. Also, it is apparent that improvements were made in this study compared to the first one previously discussed. The levels of brevetoxins present in the air were not as high as they can sometimes get during red tide events, and it is interesting to note that even during low levels of exposure by healthy individuals, respiratory irritation and discomfort is experienced.

The third prospective cohort study conducted by Fleming et al. (2005) is very similar to the two conducted by Backer et al., only this time fifty nine subjects with physician-diagnosed asthma were evaluated for one hour before and after recreationally visiting the beach on days with (exposed) and without (nonexposed) Florida red tide. In addition to the spirometric pulmonary function tests and symptom surveys, the subjects also had swabs taken from their nose and throat. This time participants were significantly more likely to report respiratory symptoms after brevetoxin exposure and demonstrated small but statistically significant decreases in forced expiratory volume in one second, forced expiratory flow between 25-75%, and peak expiratory flow after exposure. This was particularly true of individuals regularly using asthma medications. Similar evaluations during nonexposure periods did not differ.

This study used similar techniques to the ones above to avoid confounding factors and bias. Because there was a broader age range of subjects evaluated in this study, age groups were evaluated as tertiles. Subjects were allowed to use their prescribed asthma medications during the study, and this use was also taken into consideration during the study analysis. The nose and throat swabs were an addition to the second study and were used to evaluate the presence of inflammatory cells and protein transudation as a result of the increased permeability of cell membranes due to the inflammatory process. These swabs helped eliminate bias further since it was an additional objective test that the subject did not have control over (as opposed to the symptom surveys). A larger sample size may have shown even larger differences between pre-and post-exposure to brevetoxins.

A fourth prospective cohort study by Fleming et al. (2008), very similar to the one just discussed, also researched the effects of aerosolized red tide toxins on patients with asthma. Ninety seven asthmatic subjects were evaluated by questionnaires, nasal swabs, and spirometry after one hour at the beach both during times of red tide (exposure) and without (nonexposure).

A baseline questionnaire was administered to collect information on possible confounding factors, such as smoking, medication use, place of residence, etc. Participants were examined separately in subpopulations by medication use prior to the study period and by their geographic location of residence. Each participant underwent at least three reproducible spirograms before and after visiting the beach to avoid the possibility of an error with the readings. During this study more precise equipment and diagnostics had been developed, including an individual personal sampler for aerosolized toxins which measures 12 L/min instead of the previous 2 L/min. There was also a new ELISA developed to determine the presence of brevetoxins in the air samples.

The mean spirometry values after one hour of exposure were uniformly decreased in comparison with values during nonexposure periods. Symptoms, predominantly chest tightness, for both the medication and residence groups were statistically different during exposure periods, whereas no significant differences were found during nonexposure periods. These symptoms were particularly great in participants who did not use medications prior to their beach visit. Participants with more severe asthma demonstrated more uniform and greater differences in spirometry values and started with lower preexposure baseline values. In the study population, participants living inland that did not use medication had higher preexposure baseline spirometry values than the other three subpopulations. The authors suspected that persons living inland may be less exposed on a regular basis to the aerosols of an active *K. brevis* bloom, even though these aerosols have been measured more than one mile inshore from the coast. The participants residing in coastal areas had a preexposure spirometry measurement less than that of persons residing inland, suggesting that coastal residents are exposed on a chronic basis before the one hour beach exposure, thus reacting less to the beach exposure during the experimental period.

Experiments involving environmental exposures can be difficult to regulate, as a large number of variables may be present. Aside from the bronchoconstricting toxins produced by *K. brevis,* the organism also produces a natural inhibitor to the toxins known as brevenol. Brevenol was also measured during these experiments, but it is not known how great of an effect this substance has on counteracting the toxins present in the aerosols. This study did a very good job at looking at many variables and confounding factors to rule out inconsistencies in the design. Because each subject served as their own control, this study seems reliable based on the data that was reported.

A retrospective cohort study was conducted by Kirkpatrick, et al. (2006) to compare the rates of emergency room (ER) visits to the Sarasota Memorial Hospital (SMH) between two time periods; October 1 – December 31, 2001 when there was a red tide and October 1 – December 31, 2002 when there was no red tide period in Sarasota, Florida. SMH is the largest acute care facility in Sarasota County and serves 63.3% of this county's population; it is also the closest facility to the coastline. The authors received access to anonymous medical data provided by the Decision Support Services at SMH. The Phytoplankton Ecology Program at Mote Marine Laboratory provided data on the red tide cell counts.

ER admission data were collected from the same months in 2001 (red tide period) and 2002 (non-red tide period) to minimize the effects of variation from respiratory exacerbations or reactions from seasonal exposures, such as pollen, molds, or dander. Since Sarasota has a seasonal population, the same three month period was used to adjust for the fluxes in the population as most seasonal residents have the same visitation pattern year after year. The study data consisted of the ER admission diagnosis with the international classification of diseases (ICD) diagnosis classification for respiratory disease and all other ICD diagnoses, the patient age, the residence zip code, and the date of admission. The residence zip code was used to break up the subjects into two groups: coastal residents and inland residents. The following mutually exclusive respiratory disease primary diagnoses were selected for the study: pneumonia, bronchitis, asthma, and upper airway disease. These four respiratory diagnoses accounted for 91-92% of all respiratory diagnoses of ER admissions reported during the study months. All other diagnoses were grouped as “all other primary diagnoses”.

The overall number of ER admissions during the 2001 and 2002 periods were similar, as were the ages, gender distribution, and race distribution of the ER patients. Of the respiratory diagnoses, pneumonia, bronchitis, asthma, and upper airway disease comprised 92% of respiratory related ER admissions in 2001 and 91% in 2002. When ER admission rates were adjusted for age, the overall admission rates for all diagnoses were similar for the red tide period and the non-red tide period. When the respiratory ER admission rates were adjusted based on residence (coastal: < 1.6 km of shore; inland: >1.6 km of shore), though, residents living in the coastal area had a statistically significantly increased ER admission rate compared to the inland residents during the red tide period. However, when examined by subcategory of diagnosis, there was a non-significant increase in the admission rate for coastal residents during the red tide period compared to their admission rates during the non-red tide period.

During the red tide period, there was a small increase in the risk of having an ER admission for any respiratory diagnosis for coastal residents when compared with the risk for inland residents. There was also an increased risk for ER admission for pneumonia and upper airway disease during the red tide period for coastal residents compared to inland residents. These increases, though, were not statistically significant. Interestingly, during the non-red tide period, the inland residents had an increase in ER admissions for respiratory diagnosis compared to coastal residents. The authors speculated that other inland environmental triggers for respiratory symptoms may have been the cause for this.

Since the data in the study demonstrated increased rates of more chronic respiratory illnesses such as bronchitis and pneumonia for people living in coastal areas during red tide blooms, this may be reason to suspect that brevetoxins have a more lasting effect on the respiratory system than the transient response associated with aerosolized toxins. These chronic effects would be consistent with findings in manatees and laboratory rodents. The authors suggest that although the cause of respiratory disease may be infectious in nature, chronic exposure to aerosolized brevetoxins may be responsible for immunosuppression that is sufficient to cause the increased rates of pneumonia and bronchitis seen in this study.

There were a number of limitations with this study. For instance, no individual exposure information was collected for this analysis, and therefore the study only reports an association of exposure with the time periods selected. Repeated admissions by the same patient could not be identified and removed, nor could latency periods or underlying predisposing health conditions be determined. No other health assessments were made to explore other patterns that might have affected the increase in specific respiratory admissions in 2001, such as an early influenza season. The zip codes reported as place of residence do not necessarily identify the actual location of Florida red tide exposure, nor do they document that exposure actually occurred. Florida population for the year 2000 was used; however, age rate ratios based on the years 2001 and 2002 were used with a 95% confidence interval. It is not clear whether analysis accounted for the possible increase in the population in 2002 compared with 2001 which may have affected the number of admissions to the ER. P values were greater than 0.05, and thus not statistically significant in most cases. Sample sizes were small and the confidence intervals were wide indicating a considerable amount of variability in the data.

Overall, this study was a good preliminary analysis to determine the possible link between brevetoxin exposure and chronic respiratory ailments. However, more specific studies would need to be conducted to make any definitive conclusions regarding this link.

SUMMARY AND CONCLUSIONS

The research being conducted on the effects of aerosolized brevetoxin exposure and respiratory irritation and dysfunction in people is still in the developing stages. All of the epidemiological studies conducted so far have been done by the same group of researchers. Nonetheless, the negative effects of such exposures are apparent. Experimental research conducted by Abraham (2005a, 2005b) on asthmatic sheep as models for human disease have clearly shown a relationship between brevetoxins and respiratory dysfunction. There are numerous reports by beach-goers and coastal residents, though most are anecdotal, of irritation to the respiratory tract and difficulty breathing during times of red tide (Fleming, Backer, Baden, 2005). Due to the nature of the exposures to these toxins, and the numerous variables that environmental conditions can have on exposures, such as wind speed and direction, wave activity, and humidity, controlling for these variables during systematic studies is difficult. As more and more research is conducted on this subject, though, a more precise link between exposure to brevetoxins and the effects this has on respiration will surely be identified, especially if larger groups of subjects are utilized to obtain more statistically significant results. This will have a great impact on the public health of coastal and inland areas of Florida, and more appropriate control measures for the protection of public health, particularly for individuals already suffering from respiratory ailments, can be implemented.

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