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Possible Factors Associated with Anti-Allergic Agent Production

Shigeru Suna

Department of Medical Technology, Graduate School of Health Sciences, Kagawa Prefectural University of Health Sciences, Takamatsu, Kagawa, Japan

ABSTRACT

Background: Type 1 allergy is increasing worldwide, including Japan, where climate change is undergoing due to urbanization and global warming. Therefore, the production of anti-allergic agents that reflect demand should be increasing. It is also well known that climatic factors and air pollutants are closely related to allergic reactions. Therefore, the production of anti-allergic agents should be influenced by these factors.
Method: To clarify the factors associated with anti-allergic agent production, year-trend data of anti-allergic agent production, number of asthma patients among school children and environmental factors of Japanese urban areas such as relative humidity, ambient temperature and photochemical oxidant were analyzed utilizing multiple linear regression model.
Result: The anti-allergic agent production between 1991 and 2015 showed a linear increase trend. On the other hand, the number of asthma patients among school children has increased linearly from 1991 to 2010, but it has been observed that the number of asthma patients has begun to decline slightly due to the decrease in the number of entrants since 2010. The annual relative humidity tends to decrease, the annual ambient temperature tends to rise, and the annual photochemical oxidant concentration tends to increase. Stepwise linear regression analysis revealed that the number of asthma patients among school children and the annual relative humidity were significant independent variables.
Conclusion: A statistically significant decline in humidity in urban areas of Japan may increase the incidence of type 1 allergic reactions and lead to the promotion of anti-allergic agent production.

Key-words: Anti-allergic agent, Urbanization, Climate change, Type 1 allergy, Relative humidity

INTRODUCTION

In recent years, an increase in type 1 allergy has been pointed out worldwide. [1] In Japan, the prevalence of bronchial asthma at school age clearly rising year by year. [2, 3] These facts suggest that domestic demand for anti-allergic agents used prophylactically to control allergic reactions [4] is increasing. Most of anti-allergic agents produced in Japan are consumed domestically as prescription medicine. [5] Therefore, the secular tendency of anti-allergic agent production should reflect the trend of anti-allergic agent demand. Furthermore, since many studies have shown that environmental conditions such as relative humidity, ambient temperature and air pollutants are closely related to the allergic reaction of asthma, hay fever and eczema, [6-11] climate change [12] due to urbanization and global warming may affect to anti-allergic agents demand and eventually anti-allergic agent production.

The present study shows the possible factors associated with anti-allergic agent production in Japan where more than 90% of the total population live in urban areas [13] and allergic diseases are increasing and also urban heat island and global warming are undergoing. [14]

METHODS

The following information from 1991 to 2015 is a report published by government agencies, data obtained from the database of "e-Stat", or data calculated

from them. "e-Stat" is a portal site of Japanese government statistics.

Annual amount of anti-allergic agent production

Data since 2010 were from Statistics of Production by Pharmaceutical Industry conducted by Ministry of Health, Labour and Welfare (https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450151&result_page=1). Data before 2010 were from "KokuminEisei no doko", edition for 1991-2009: Kosei Tokei Kyokai (Health, Labour and Welfare Statistics Association).

Number of asthma patients among school children

The number of asthma patients was estimated from the prevalence of bronchial asthma and the number of children in elementary school (6-11years), lower secondary school (12-15years), and upper secondary school (16-18years). These data were obtained from School Health Survey (https://www.e-stat.go.jp/stat-search/database?page=1&toukei=00400002&tstat=000001011648&result_page=1) and School Basic Survey (https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00400001&kikan=00400&tstat=000001011528&result_page=1) conducted by Ministry of Education, Culture, Sports, Science and Technology.

Climatic conditions

The annual average values of relative humidity (%) and ambient temperature (℃) throughout the country were calculated from the values of the meteorological observatories in the central areas of the seven major metropolitan areas (Sapporo, Sendai, Tokyo, Nagoya, Osaka, Hiroshima, Fukuoka). The values were downloaded from the Japan Meteorological Agency (www.data.jma.go.jp/obd/stats/etrn/index.php?sess=6ef525a9cdef28cea634ce58ca736e68).

Air pollutants

In recent years, outdoor air pollutants such as sulfur oxides, nitrogen oxides, suspended particulate matter, etc. are on a downward trend due to exhaust gas regulation in Japan. Therefore, only the photochemical oxidant which tends to increase can be considered as a factor of an increase in allergic reaction. The annual average values of photochemical oxidant concentration were obtained from Ministry of the Environment, Government of Japan (http://www.env.go.jp/air/osen/index.html).

RESULTS

The trends in anti-allergic agent production, number of asthma patients in school children, relative humidity and ambient temperature between 1991 and 2015 are shown in Table 1. The anti-allergic agent production from 1991 to 2015 showed a linear increase trend. On the other hand, the number of asthma patients has increased linearly from 1991 to 2010, but it has been observed that the number of asthma patients among school children has begun to decline slightly due to the decrease in the number of entrants since 2010. The annual relative humidity tends to decrease, the annual ambient temperature tends to rise, and the annual photochemical oxidant concentration tends to increase. The number of asthma patients among school children, annual relative humidity, annual ambient temperature and annual photochemical oxidant concentration which are possible factors responsible for annual anti-allergic agent production were entered as independent variables in multiple regression analysis. The analytical results are shown in Table 2. The number of asthma patients among school children and the annual relative humidity are significant independent variables. The number of asthma patients among school children is positively, annual relative humidity is negatively associated with annual anti-allergic agent production. The Durbin–Watson statistic of 2.001 from the residual analysis was in the preferred range of 1.5-2.5, [15] suggesting no presence of the

autocorrelation. Also, a normal probability plot of the residuals showed a good linearity. [16]

Table 1: Anti-allergic agent production, number of asthma patients in school children, relative humidity and ambient temperature between 1991 and 2015.

Year	Anti-allergic agentproduction (million yen)	Number of asthma patients	Relative humidity (%)	Ambient temperature (℃)	Photochemical oxidant (ppm)
1991	152,488	192,600	68.7	15.5	0.039
1992	157,263	207,000	67.9	15.3	0.043
1993	165,966	201,700	67.9	14.7	0.041
1994	156,549	230,700	65.1	16.1	0.045
1995	185,764	235,700	66.0	15.2	0.044
1996	169,437	253,100	66.9	14.8	0.045
1997	177,565	255,500	67.4	15.5	0.044
1998	152,539	316,500	70.6	16.1	0.043
1999	182,180	362,800	67.9	15.8	0.044
2000	187,530	335,100	66.6	15.7	0.044
2001	250,342	339,800	65.1	15.4	0.045
2002	220,340	355,300	64.7	15.7	0.044
2003	248,823	374,800	67.6	15.3	0.045
2004	230,185	388,000	65.4	16.2	0.046
2005	233,466	424,100	65.4	15.3	0.047
2006	217,070	479,000	67.1	15.4	0.046
2007	229,234	493,400	64.0	16.1	0.048
2008	244,503	494,500	65.3	15.7	0.048
2009	239,445	490,700	64.4	15.7	0.048
2010	236,675	519,400	65.3	15.9	0.048
2011	263,709	514,600	65.7	15.6	0.044
2012	226,495	496,800	66.9	15.4	0.046
2013	258,017	493,000	65.9	15.8	0.047
2014	219,157	460,500	66.3	15.6	0.047
2015	233,739	461,800	67.6	16.0	0.048
Trend between 1991 and 2015	r=0.832 p<0.01	r=0.945 p<0.01	r=-0.392 p<0.05	r=0.366 p<0.05	r=0.790 p<0.01

Table 2: Stepwise multiple linear regression analysis of factors associated with anti-allergic agent production.

	Estimated regression coefficient, B	95% confidence interval		Partial regression coefficient, β	Cumulative R^2	*P*-value
		lower bound	upper bound			
Intercept	556328	161030	951627	-	-	0.008
Number of asthma patients	0.233	0.156	0.311	0.719	0.708	0.000
Relative humidity	-6534	-12271	-796	-0.272	0.767	0.027
Ambient temperature	-	-	-	-	-	0.127
Photochemical oxidant	-	-	-	-	-	0.442

DISCUSSION

The annual average value of relative humidity and ambient temperature is the average of the values observed in the center of the seven major metropolitan areas of Japan and the photochemical oxidant is also the average of the observation stations located nationwide mainly around seven major metropolitan areas, therefore these values may reflect the climatic condition of Japanese urban area. The relative humidity of 1991 - 2015 showed a decreasing trend, the ambient temperature and photochemical oxidant showed an increasing trend. From these results, it is speculated that urban areas of Japan are undergoing drying, warming14 and oxidant contamination. [17,18] Urbanization reduces green spaces and wetlands, [19-21] causing drying and heat island phenomena.

Multiple linear regression analysis revealed that the number of asthma patients is a significant positive independent variable and annual relative humidity is a significant negative independent variable. “0.708” of partial R2 indicating the contribution rate of the asthma patients to the variation in the anti-allergic agent production is remarkably

high, and it is speculated that the tendency of childhood bronchial asthma strongly influences anti-allergic agent production. Also, the cumulative R2 of "0.767" shows that the contribution of relative humidity to anti-allergic agent production is not negligible. Several reports have shown that the outdoor relative humidity and the prevalence of type 1 allergy, such as, asthma, hay fever and eczema show a negative correlation6-8. The low humidity condition enhances the dispersibility of pollen [22-25] and promotes transportation to urban areas. [26-28] Moreover, in urban areas it is possible that the re-scattering of allergens deposited on paved roads [29] and buildings may be repeated. Also, low humidity may lead to skin barrier dysfunction. [30,31] In contrast, the increase in hygroscopicity under high humidity conditions affects the settling rate of pollen and the transport of pollen, [23] and an increase in rainfall frequency may promote rain-out and wash-out. [32, 33] Also, higher humidity protects against eczema by improving skin barrier function. [34] However, in the case of thunderstorm, which occurs frequently in the urban area, the surrounding air containing airborne allergen particles is drawn into the thunderstorm cloud by updraft, condensed and spread by raindrop and downdraft. [35, 36] This may cause thunderstorms asthma. [37]

In conclusion, a statistically significant humidity declining trend in urban areas of Japan may increase the incidence of type 1 allergic reactions and lead to the promotion of anti-allergic agent production.

Since the current statistical analysis is based on data from the government, it is excellent in accuracy. However, this study has some limitations. The main limitation of this study was the lack of aero allergen information in urban areas. It is necessary to clarify the relationship between urbanization and allergen level. Secondly, present study has shown only association but not causality. Further study is needed to solve these problems.

Conflict of interest

The author reports no conflicts of interest in this work.

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