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ORIGINAL RESEARCH

Association Between Inappropriate Use of Over-The-Counter Drugs for Allergic Rhinitis and Side Effects on the Central Nervous system—a Cross-Sectional Survey

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Purpose: Antihistamine over-the-counter (OTC) drugs for allergic rhinitis are widely used and cause central nervous system side effects. Most available data on anti-allergic drugs are on controlled usage. It is necessary to investigate the occurrence of side effects in the context of self-medication to avoid inappropriate use. We aimed to clarify the association between the usage of OTC anti-allergic drugs and central nervous system side effects.

Patients and Methods: An online, anonymous, cross-sectional study was conducted using a structured questionnaire. People who had used OTC anti-allergic drugs in the year prior to the study were recruited. To assess the association between inappropriate drug use and the occurrence of side effects, a binary logistics regression analysis was performed according to three dosage forms (oral only, nasal only, and oral and nasal combined use).

Results: Somnolence was experienced by 59.1% of the participants using the OTC drug for allergic rhinitis. Using logistic regression analysis, "drug use exceeding the upper limit" was seen to be associated with side effects in only oral (Somnolence: OR = 1.41, 95% CI = 1.17–1.70; Dull head: OR=1.41, 95% CI = 1.16–1.70; Loss of concentration: OR = 1.25, 95% CI = 1.04–1.49) and oral and nasal combined use groups (Somnolence: OR = 1.33, 95% CI = 1.04–1.71; Dull head: OR = 1.47, 95% CI = 1.15–1.89; Loss of concentration: OR = 1.51, 95% CI = 1.19–1.91). Furthermore, "expired drug use" was associated with side effects in the nasal spray-only group (Somnolence: OR = 1.31, 95% CI = 1.07–1.60; Dull head: OR =1.25, 95% CI = 1.02–1.53; Loss of concentration: OR = 1.24, 95% CI = 1.00–1.54).

Conclusion: Inappropriate use was common among users of OTC allergic rhinitis drugs. Differences in side effects depending on the dosage form used were observed.

Keywords: antihistamines, adherence, oral medicine, nasal spray, somnolence

Introduction

Japanese people suffering from allergic rhinitis are familiar with drugs for allergic rhinitis and are often purchased at drug stores. In Japan, the prevalence of allergic rhinitis caused by cedar pollen is about 40%, and the prevalence of perennial allergic rhinitis is approximately 23%.[1–3] Self-care is common in an environment where effective medicines are readily available, such as over-the-counter (OTC) medicines. Self-care has the potential benefits of effective treatment, reducing medical pressure by reducing the number of doctor visits, reducing medical costs, and improving the independence of patients as they manage their own health.[4–6]

There are also disadvantages to self-care, such as delayed visits to medical institutions and mistakes in self-diagnosis. In addition, the use of medicines without expert guidance increases the risk of misuse, abuse, overdose, side effects, and interaction with other medicines and supplements.[4–6] In many cases, OTC drug purchasers visit the store anonymously and not continuously, and thus appropriate use and monitoring of side effects are inadequately conducted compared to those during the use of prescription drugs. Previous studies have reported that many OTC drugs are used at inappropriate doses.[7–9] In addition, it has

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been clarified that medicines that require the use of devices such as nasal drops and inhalers are more likely to be used inappropriately than are oral medicines, and sufficient explanation of how to use them is essential.[10–12] As described above, although there are concerns about the usage of OTC drugs requiring the use of specialized devices, the actual situation remains unknown.

As of March 2021, there were 158 types of oral medicines and 65 types of nasal drops that were sold as OTC anti-allergic drugs in Japan.[13] Among these, medicines that require pharmacist instruction and can only be sold by pharmacists were one type each for oral use and nasal drops, while all the rest were Class 2 medicines.[13] Most of the allergic rhinitis nasal drops sold in Japan are classified as Class 2 drugs,[14] and can be sold online or by registered sellers.

The main ingredient present in most types of OTC anti-allergic drugs sold in Japan is chlorpheniramine maleate, which is a first generation antihistamine.[13] Antihistamine allergic rhinitis drugs, including the first generation drugs, are known to have side effects that affect the central nervous system, such as somnolence, mood changes, anxiety, dizziness, and sleep disturbance.[3,15–17] Side effects of the central nervous system are mainly observed when using oral medications, and it is considered that the occurrence is suppressed with dosage forms that show local effects such as nasal drops.[16,18,19] Although there is some evidence regarding the side effects of antihistamines and other anti-allergic drugs, most are data for controlled usage.[20,21] Therefore, it is necessary to investigate the real-world situation regarding side effects in the context of self-medication where various inappropriate uses may be expected. Especially, as mentioned above, drugs requiring the use of devices are often inappropriately used.

The purpose of this study was to clarify the relationship between the usage of OTC anti-allergic drugs and the occurrence of central nervous system side effects.

Materials and Methods

Study Design and Participants

An online, anonymous, cross-sectional study was conducted using a structured questionnaire. The survey period was March 8th to 9th 2021. The criteria for selecting subjects were as follows: people living in Japan, over 20 years old, and who had used drugs for allergic rhinitis (for purposes such as hay fever) in the form of oral medication or/and nasal drops (spray) by themselves within the past year. A questionnaire was distributed to 120,861 monitors registered with an Internet research company (Cross Marketing Co., Ltd.), and a total of 1800 males and females of all age groups who met the selection criteria were recruited. The recruitment was stopped when the target number of each sex and age was achieved.

Sample Size

G-power, an online sample size calculator, was used to determine the sample size.[22] Based on this, a sample size of 1443 was required (Set α error 0.01 and β error 0.95).

Contents of Questionnaire

The contents of the questionnaire included the characteristics of respondents (sex, age), the symptoms of allergic rhinitis, the use of oral and nasal drops purchased at drug stores in the past year, combination medications, central nervous system symptoms that occurred during the use of medicines (symptoms suspected as side effects), and items related to inappropriate use of medicines. The severity classification of allergic rhinitis was conducted based on a self-assessment questionnaire of the symptoms of allergic rhinitis.[3]

For the symptoms that occurred while using the drug, we selected 3 symptoms related to somnolence and impaired performance by referring to the side effects described in "Allergic Rhinitis Guideline 2020"[3] and used the Likert scale for scoring: 1, often; 2, sometimes; 3, rarely; 4, never.

Five items regarding inappropriate use of medicines were created under the supervision of research members with clinical experience as pharmacists and with reference to measurement items used in previous studies.[23–25] The Likert scale was used for scoring as follows: 1, strongly agree; 2, agree; 3, disagree; 4, strongly disagree.

Analysis

Respondents were categorized into three groups according to their usage status of allergic rhinitis medication over the past year: oral medication-only, nasal spray-only, and oral and nasal spray combination. Sex, age, and severity of allergic rhinitis among the three groups were compared using a chi-square test. In addition, inappropriate use of medicines and symptoms experienced while using allergic rhinitis treatments were also compared among the three groups using the chi-square test.

Logistics regression analysis (step wise) was performed to investigate the association between inappropriate drug use and side effects. The presence or absence of side effects was used as the dependent variable. The independent variable was a measurement item for medication usage. Sex, age, severity of allergic rhinitis, anti-allergic drugs prescribed in hospitals, and use of sleeping medicine and cold medicine purchased at drug stores were used as adjustment variables. Cronbach's alpha coefficient, which indicates internal consistency, was 0.78 for the measurement item for medication usage.

The statistical software SPSS Statistics 27 (SPSS Inc., Chicago, IL, USA) was used for analyses. A $p < 0.05$ was considered statistically significant.

Ethical Consideration

The survey protocol adhered to the ethical guidelines for medical and health research involving human subjects in line with the Declaration of Helsinki and was approved by the ethical review board of Nihon University's School of Pharmacy (approval number: 20–016). Consent was obtained from respondents before proceeding to the survey response page.

Results

After the questionnaire was delivered, 1800 responses, which was the target number of responses, were collected in two days. Respondents who took allergic rhinitis medications over the past year were categorized into those who took only oral medications, those who took nasal drops only, and those who took both oral and nasal drops. Table 1 presents the background of the respondents in each of the three groups. Of the 1800 people, 927 (51.5%) were male and 873 (48.5%) were female. The severity of allergic rhinitis was most severe or severe in 809 (44.9%) and moderate or low in 991 (55.0%). No sex differences were present between the three groups, but there was a difference in age and severity.

The most common symptom experienced while using OTC allergic rhinitis medication was somnolence, with 1063 (59.1%) participants responding "often" or "sometimes." The next most common symptom was a dull head, with 949 (52.7%) participants responding.

Table 1 Characteristics of the Respondents in Each Dosage Form Group

		Total n = 1800	**Oral n = 915**	**Nasal n = 502**	**Oral+Nasal n = 383**	**P***
		n (%)				
Sex	Male	927 (51.5)	458 (50.1)	276 (55.0)	193 (50.4)	0.186
	Female	873 (48.5)	457 (49.9)	226 (45.0)	190 (49.6)	
Age	20s	325 (18.1)	170 (18.6)	71 (14.1)	84 (21.9)	<0.001
	30s	363 (20.2)	187 (20.4)	75 (14.9)	101 (26.4)	
	40s	369 (20.5)	201 (22.0)	97 (19.3)	71 (18.5)	
	50s	299 (16.6)	150 (16.4)	92 (18.3)	57 (14.9)	
	60s	249 (13.8)	121 (13.2)	82 (16.3)	46 (12.0)	
	Over 70s	195 (10.8)	86 (9.4)	85 (16.9)	24 (6.3)	
Severity of allergic rhinitis	Asymptomatic	9 (0.5)	8 (0.9)	1 (0.2)	0 (0)	<0.001
	Mild symptom	332 (18.4)	168 (18.4)	118 (23.5)	46 (12.0)	
	Moderate symptom	650 (36.1)	312 (34.1)	196 (39.0)	142 (37.1)	
	Severe symptom	472 (26.2)	244 (26.7)	125 (24.9)	103 (26.9)	
	Most severe symptom	337 (18.7)	183 (20.0)	62 (12.4)	92 (24.0)	

Note: *χ2test.

Table 2 Frequency of the Three Selected Symptoms That Were Related to the Somnolence and Impaired Performance (Symptoms Suspected as Central Nervous System Side Effects) Experienced While Using Over-The-Counter Medicines in Each Dosage Form Group

		Often	Sometimes	Rarely	Never	P*
		n (%)				
Somnolence	Oral	176 (19.2)	394 (43.1)	208 (22.7)	137 (15.0)	<0.001
	Nasal	60 (12.0)	160 (31.9)	138 (27.5)	144 (28.7)	
	Oral+Nasal	98 (25.6)	175 (45.7)	64 (16.7)	46 (12.0)	
Dull head	Oral	125 (13.7)	352 (38.5)	265 (29.0)	173 (18.9)	<0.001
	Nasal	52 (10.4)	168 (33.5)	131 (26.1)	151 (30.1)	
	Oral+Nasal	91 (23.8)	161 (42.0)	81 (21.1)	50 (13.1)	
Loss of concentration	Oral	96 (10.5)	293 (32.0)	262 (28.6)	264 (28.9)	<0.001
	Nasal	41 (8.2)	137 (27.3)	136 (27.1)	188 (37.5)	
	Oral+Nasal	68 (17.8)	158 (41.3)	89 (23.2)	68 (17.8)	

Note: *χ^2test.

Table 2 presents the symptoms (symptoms suspected as central nervous system side effects) experienced while using OTC medicines in each group. There were significant differences among the three groups in terms of the experience of all three symptoms.

Regarding inappropriate use of medicines, the most common response was "I may continue to use the same medicine for a long time (1 month or more) without the symptoms subsiding (indiscriminate use), "a total of 726 people (31.2%) responded "strongly agree" or "agree". Moreover, 708 (31.0%) participants responded that" I may use according to my own symptoms rather than the usage described in the instruction (self-regulation use)", 670 (30.3%) participants responded, "I may use expired medicines (expired medicine use)", and 544 (30.2%) responded, "when the symptoms are severe, the dose may exceed the upper limit stated in the instruction manual (use exceeding the upper limit)."

Table 3 presents the inappropriate drug use for each group. There were significant differences among the three groups in all items of inappropriate use of medicines. Table 4 presents the relationship between drug usage and side effects in each group.

Medication use exceeding the upper limit was associated with all side effects in the oral medication-only group (Somnolence: Odds Ratio (OR) = 1.41, 95% Confidence Interval (95% CI) = 1.17–1.70; Dull head: OR=1.41, 95% CI = 1.16–1.70; Loss of concentration: OR = 1.25, 95% CI = 1.04–1.49) and the both oral and nasal spray group (Somnolence: OR = 1.33, 95% CI = 1.04–1.71; Dull head: OR =1.47, 95% CI = 1.15–1.89; Loss of concentration: OR = 1.51, 95% CI = 1.19–1.91). Self-regulatory use was associated with all side effects in the oral medication-only group (Somnolence: OR = 1.22, 95% CI = 1.02–1.45; Dull head: OR=1.36, 95% CI = 1.14–1.62; Loss of concentration: OR = 1.39, 95% CI = 1.16–1.66). The use of expired drugs was associated with side effects only in the nasal spray group (Somnolence: OR = 1.31, 95% CI = 1.07–1.60; Dull head: OR = 1.25, 95% CI = 1.02–1.53; Loss of concentration: OR = 1.24, 95% CI = 1.00–1.54).

Discussion

This cross-sectional study revealed the association between inappropriate use of OTC allergic rhinitis drugs and the occurrence of side effects affecting the central nervous system. More than 30% of OTC allergic rhinitis drug users were found to be using the drugs indiscriminately, self-adjusting the dose, using expired drugs, or using the drug beyond the upper limit. Moreover, improper use of OTC anti-allergic drugs is common. In addition, the results of multivariate analysis revealed an association between inappropriate use and the occurrence of side effects, but differences depending on the dosage form used were observed.

The nasal spray-only group had a lower rate of allergic rhinitis symptom classification than the oral only or oral and nasal spray group. As the severity increases, the use of oral medications increases, and the patients suffering from the most severe symptoms are more likely to use both oral medications and nasal drops. Therefore, nasal drops were used by patients with relatively mild symptoms. In addition, older respondents tended to use only nasal drops. Many of the anti-allergic drugs sold as OTC drugs in Japan have antihistamine effects, and these drugs are on the Beers list that requires

Table 3 Inappropriate Drug Use in Each Dosage Form Group

		Strongly Agree	Agree	Disagree	Strongly Disagree	P*
		n (%)				
When my symptoms are severe, the dose may exceed the upper limit stated in the instruction.	Oral	40 (4.4)	158 (17.3)	260 (28.4)	457 (49.9)	<0.001
	Nasal	29 (5.8)	132 (26.3)	164 (32.7)	177 (35.3)	
	Oral +Nasal	56 (15.6)	135 (35.2)	118 (30.8)	71 (18.5)	
I may use according to my own symptoms rather than the usage described in the instruction manual.	Oral	51 (5.6)	254 (27.8)	346 (37.8)	264 (28.9)	<0.001
	Nasal	40 (8.0)	169 (33.7)	171 (34.1)	122 (24.3)	
	Oral +Nasal	59 (15.4)	135 (35.2)	118 (30.8)	71 (18.5)	
I may use expired medicines.	Oral	53 (5.8)	243 (26.6)	304 (33.2)	315 (34.4)	<0.001
	Nasal	29 (5.8)	164 (32.7)	139 (27.7)	170 (33.9)	
	Oral +Nasal	42 (11.0)	139 (36.3)	108 (28.2)	94 (24.5)	
I may continue to use the same medicine for a long time (1 month or more) without the symptoms subsiding.	Oral	62 (6.8)	275 (30.1)	353 (38.6)	225 (24.6)	<0.001
	Nasal	42 (8.4)	158 (31.5)	184 (36.7)	118 (23.5)	
	Oral +Nasal	61 (15.9)	128 (33.4)	134 (35.0)	60 (15.7)	
Sometimes I use medicines without much understanding of how to use them.	Oral	30 (3.3)	190 (20.8)	414 (45.2)	281 (30.7)	<0.001
	Nasal	21 (4.2)	112 (22.3)	209 (41.6)	160 (31.9)	
	Oral +Nasal	35 (9.1)	96 (25.1)	164 (42.8)	88 (23.0)	

Note: *χ^2test.

caution when administered to the elderly.[26] One of the reasons may be that it is recommended for elderly people to use nasal drops that show local effects in order to minimize side effects.

Fewer respondents experienced all the side effects investigated in the nasal spray-only group than in the oral only group. The reason may be related to the fact that those who take only nasal drops are more likely to have mild illnesses than those who take oral medicine. Furthermore, it is generally thought that nasal drops have a low incidence of systemic side effects owing to their local mechanisms of action.[18,19]

Somnolence was the most common symptom observed in this study and is known as a peculiar side effect of anti-allergic drugs. In this survey, 60% of respondents experienced somnolence while using medicines. In addition, more than half of the respondents said that they might experience a dull head while using medicines. Many of the OTC anti-allergic drugs sold in Japan contain first- and second-generation antihistamines, which reiterates the need to alert people to side effects such as drowsiness and impaired performance.

The reliability of the index of inappropriate use of the drug used in this study was judged to be generally acceptable because the Cronbach's α coefficient was 0.78. Many studies have been conducted on the evaluation of inappropriate use of medicines, most of which are for chronic diseases caused by prescription drugs.[27–29] Regarding the use of OTC drugs, attention should be paid to overdose and self-regulation use, as well as missing doses as measured in traditional adherence studies. Therefore, an OTC-specific index was needed. This study is considered to be significant in terms of developing indicators of inappropriate use based on the usage status of OTC drugs.

More than 30% of the respondents in this study used the drug beyond the upper limit. The use of OTC drugs over the upper limit has been reported in other studies,[30] and further guidance from pharmacists should be advocated. Excessive use of oral medications was associated with the development of all side effects examined in this study. On the other hand, although the rate of inappropriate use exceeding the upper limit was higher in the nasal spray-only group than that in the oral drug-only group, the results of multivariate analysis revealed no association between this form of inappropriate use

Table 4 Association Between Inappropriate Use of Medicines and the Occurrence of the Three Selected Symptoms That Were Related to the Somnolence and Impaired Performance (Symptoms Suspected as Central Nervous System Side Effects) Experienced While Using Over-The-Counter Medicines in Each Dosage Form Group (Binary Logistic Analysis, Step-Wise Method)

	Oral		Nasal		Oral+Nasal	
	OR*	95% CI	OR*	95% CI	OR*	95% CI
Somnolence						
When my symptoms are severe, the dose may exceed the upper limit stated in the instruction.	1.41	1.17–1.70			1.33	1.04–1.71
I may use according to my own symptoms rather than the usage described in the instruction manual.	1.22	1.02–1.45				
I may use expired medicines.			1.31	1.07–1.60		
I may continue to use the same medicine for a long time (1 month or more) without the symptoms subsiding.						
Sometimes I use medicines without much understanding of how to use them					1.56	1.15–2.12
Dull head						
When my symptoms are severe, the dose may exceed the upper limit stated in the instruction.	1.41	1.16–1.70			1.47	1.15–1.89
I may use according to my own symptoms rather than the usage described in the instruction manual.	1.36	1.14–1.62				
I may use expired medicines.			1.25	1.02–1.53		
I may continue to use the same medicine for a long time (1 month or more) without the symptoms subsiding.					1.36	1.03–1.80
Sometimes I use medicines without much understanding of how to use them	1.24	1.02–1.51				
Loss of concentration						
When my symptoms are severe, the dose may exceed the upper limit stated in the instruction.	1.25	1.04–1.49			1.51	1.19–1.91
I may use according to my own symptoms rather than the usage described in the instruction manual.	1.39	1.16–1.66				
I may use expired medicines.			1.24	1.00–1.54		
I may continue to use the same medicine for a long time (1 month or more) without the symptoms subsiding.	1.29	1.09–1.53			1.45	1.12–1.89
Sometimes I use medicines without much understanding of how to use them			1.43	1.13–1.82		

Notes: *Adjusted age, sex, severity of allergic rhinitis, combined medicine use (prescribed allergic rhinitis medicine (oral, nasal), OTC sleeping medicine, cold medicine).
Abbreviation: OTC, over the counter.

and side effects in the nasal spray-only group. As shown in previous studies, the locally specific effects of nasal drops are thought to reduce the side effects on the central nervous system.[16,18,19]

It has been clarified that the adherence and proper use guidelines for drugs that require the use of devices such as nasal drops are different from those for oral drugs.[11] In this study, the nasal drop-only group experienced side effects associated with the use of expired drugs. It is unclear why the use of expired nasal drops is directly related to the development of side effects. In previous studies, about half of the users thought that nasal drops that had been opened for more than one month should not be used.[31] It is considered unfavorable from a hygiene point of view to use nasal drops that have been opened for a long period of time.

The strength of this study is that it can be generalized as nationwide data were collected. This study has several limitations. First, since this study is a cross-sectional study, it was not possible to clarify the causal relationship between the usage of OTC drugs and the occurrence of side effects. Second, we investigated the use and side effects of medicines over the past year, but we cannot deny the possibility of recall bias. However, since this survey was conducted at the peak of cedar pollinosis, many respondents were just using medicines when responding to the questionnaire, and it seems that

the recall bias may have been minimized. Third, in this study, the assessment of inappropriate drug use was through self-reporting using a questionnaire. Therefore, there remains a possibility of differences from actual usage conditions. However, it is generally believed that face-to-face surveys are often conducive to socially desirable behaviors,[32,33] and the online survey adopted in this study is thought to minimize socially desirable bias. Finally, socio-economic factors could not be considered because we did not collect data on the respondents' income and educational background.

It was suggested that the inappropriate use of anti-allergic drugs in self-medication situations differs according to the dosage form of the drug, and that they are associated with the occurrence of side effects. Pharmacists and other healthcare professionals must recognize the inappropriate usage trends that differ for each dosage form and provide guidance that is appropriate for the dosage form used.

Conclusion

Inappropriate use, such as exceeding the upper limit of the drug or using an expired drug, has become common among users of OTC allergic rhinitis drugs. The results of multivariate analysis in this study revealed a positive relationship between inappropriate use of OTC drugs and the occurrence of side effects, but differences depending on the dosage form used existed. It is necessary to strengthen guidance on OTC anti-allergy drugs to oral drug purchasers regarding indiscriminate use and exceeding the upper limit of the drug and to nasal spray purchasers regarding expiration dates.

Author Contributions

All authors made a significant contribution to the work reported in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and have agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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