A Pilot Study of Transdermal Application of Diphenhydramine to the Nasal Ala in Patients with Allergic Rhinitis and Asthma

Mitsuhiro KAMIMURA[*1], Toshiya INUI[*1], Atsuto MOURI[*1], Hiroaki TODO[*2], Kenji SUGIBAYASHI[*2] and Koichiro ASANO[*3]

[*1]*Department of Respiratory Medicine, National Hospital Organization Disaster Medical Center*
[*2]*Faculty of Pharmaceutical Science, Josai University*
[*3]*Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine*

(Received November 26, 2021; Accepted August 1, 2022)

Background: To date, topical allergic rhinitis drugs must be applied intranasally. We studied the efficacy, safety, and impact on co-existing asthma symptoms of transdermal delivery of diphenhydramine through the nasal ala.
Methods: We enrolled outpatients with symptomatic allergic rhinitis and asthma who were on stable medication for at least 4 weeks. Patients applied diphenhydramine ointment, 0.07 g measured with weighing spoon (0.7 mg diphenhydramine), to the nasal ala twice a day for 2 weeks, followed by 2 weeks' washout. Effects were assessed with the Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) and Self-assessment of Allergic Rhinitis and Asthma (SACRA) and Asthma Control Test (ACT) questionnaires.
Results: Ten patients participated in the study. Two patients experienced acute exacerbation of asthma during the intervention phase, but no other adverse effects occurred. Self-assessments indicated efficacy in treating nasal symptoms in 5 patients. No significant changes in scores were seen, although mean total JRQLQ score showed a numerical improvement (from 34.3 [21.0] to 14.4 [8.8]; P = 0.0547). Asthma symptoms improved subjectively in 2 patients.
Conclusions: The efficacy of transdermal application of diphenhydramine on the nasal ala for treating allergic rhinitis was not conclusive, but appears to be effective in certain patients.

Keywords: topical therapy, intranasal administration, adverse reaction, QOL, drug delivery

INTRODUCTION

In general, 80% or more of patients with allergic asthma have concomitant rhinitis, whereas the prevalence of asthma among patients with rhinitis ranges widely from 20% to 60% [1], with 67.3% of Japanese patients with asthma being reported to have rhinitis [2]. These figures suggest a close relationship between asthma and rhinitis, and improvement of rhinitis symptoms has been known to improve control of asthma [1]. Various therapies are available for rhinitis, such as oral administration of anti-allergic drugs or antihistamines and intranasal administration of corticosteroids, anti-allergic drugs, or antihistamines. Systemic administration of antihistamine drugs including transdermal emedastine [3] are the mainstay of therapy, but they often cause adverse reactions, such as sedation or anticholinergic effects [4], and, in such cases, intra-nasal administration of the drug is recommended [5].

Transdermal application of drugs is known to show efficacy in treating symptoms arising from deeper organs or tissues, such as alleviation of joint pain by intra-articular infiltration of medication after the application of a poultice or nonsteroidal anti-inflammatory cream or ointment to the overlying skin [6, 7]. Because the site of inflammation is close to the nasal ala in patients with rhinitis, we hypothesized that transdermal treatment could also be effective in rhinitis. Therefore, we performed a pilot study to investigate the efficacy and safety of application of a cream containing the antihistamine diphenhydramine to the nasal ala of patients with allergic rhinitis and asthma.

METHODS

Participants

Among outpatients who visited the respiratory department at our institute from February to May, 2018, we recruited patients with asthma aged over 18 years old who presented with allergic rhinitis due to Japanese cedar pollinosis. The dosing regimens of anti-allergy drugs, antihistamines, or steroids had to be stable for the 4 weeks before patients started the study. Exclusion criteria included starting anti-allergy drugs, antihistamines, or inhaled or oral corticosteroids within 4 weeks of study initiation; presence of a skin disease around the nasal ala; pregnancy or breastfeeding in women; and being considered ineligible by the investigators.

The study was approved by the ethics committee of the National Hospital Organization Disaster Medical Center and performed in accordance with the principles of the Declaration of Helsinki. Written informed

Mitsuhiro KAMIMURA, Department of Respiratory Medicine, National Hospital Organization Disaster Medical Center, 3256 Midoricho, Tachikawa, Tokyo 190-0014, Japan Tel: +81-42-526-5511 Fax: +81-42-526-5535 E-mail: tdmckamimura@yahoo.co.jp

Table 1 Demographic data of all study participants and of those in whom transdermal diphenhydramine was effective in controlling nasal symptoms

	All patients	Transdermal diphenhydramine effective
n	10	5
Age*	61 (53–74)	54 (53–72)
Male, n (%)	2 (20)	0 (0)
Sensitized allergen		
Japanese cedar, n (%)	8 (80)	4 (80)
House dust mites, n (%)	5 (50)	3 (60)
Cat dander, n (%)	2 (20)	1 (20)
Symptoms		
JRQLQ score*	29 (18–55)	27 (7–59)
ACT score*	18 (16–22)	18 (17–23)
SACRA questionnaire VAS score for rhinitis*	5 (2–8)	4 (2–5)
SACRA questionnaire VAS score for asthma*	3 (1–5)	3 (2–5)
Pulmonary functions		
FEV_1, % predicted*	92 (84–106)	96 (87–120)
FEV_1/FVC*	78 (67–80)	79 (78–84)
FeNO*	29 (22–45)	28 (18–45)
Treatment		
GINA treatment step 2/3/4/5, n	1/0/0/9	0/0/0/5
Inhaled corticosteroids, dose in μg **	1600 (1000−2000)	1600 (1000−2000)
Intranasal corticosteroid, used as needed, n (%)	8 (80)	5 (100)
Intranasal antihistamines, used as needed, n (%)	10 (100)	5 (100)
Antileukotriene drugs, n (%)	8 (80)	4 (80)
Oral antihistamine drugs, n (%)	5 (50)	2 (40)
Efficacy of transdermal diphenhydramine on asthma symptoms		
Effective, n (%)	2 (20)	2 (40)
Not effective, n (%)	6 (60)	1 (20)
N/A***, n (%)	2 (20)	2 (40)

* Median and interquartile range

** The doses were converted into equivalent doses of budesonide

*** NA: not assessed because no asthma symptoms were present at the time of enrollment

ACT, asthma control test; GINA, Global Initiative for Asthma; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fraction of exhaled nitic oxide; JRQLQ, Japanese Allergic Rhinitis Standard Quality of Life Questionnaire; SACRA, Self-assessment of Allergic Rhinitis and Asthma; VAS: visual analog scale

consent was obtained from all participants. The protocol was registered in the University Hospital Medical Information Network clinical trials registry (registration number, UMIN000031455; date of registration, Feb 23, 2018).

Study design

Diphenhydramine cream (1%, Kowa Co. Ltd., Nagoya, Japan) at a dose of 0.07 g measured with weighing spoon provided to the participants (approximately 0.7 mg of diphenhydramine) was applied to the bilateral nasal ala twice daily for 2 weeks. The pharmacists at our institute showed the study participants how much of the drug to use and where to apply it. The treatment period was followed by a 2-week washout period. Quality of life (QOL) was assessed with the Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) of the Japanese Society of Allergology [8]; asthma and allergic rhinitis, with the Self-assessment of Allergic Rhinitis and Asthma (SACRA) [9]; and asthma symptoms, with the Asthma Control Test (ACT). Assessments were performed 3 times: at the start and end of treatment and at the end of the washout period. To obtain objective data, at the same 3 time points a pulmonary function test (PFT) was performed and exhaled nitric oxide (FeNO) was measured.

At the end of the study, patients were asked about the following: effectiveness of transdermal diphenhydramine on nasal and asthma symptoms (effective, mildly effective, not effective); adverse effects; time to onset of improvement after topical application of the drug; duration of efficacy of the drug; and overall impression of the drug, including its efficacy and adverse effects, which were rated by patients on a scale of 0 to 100, with a higher score indicating a higher evaluation. Patients were also asked to assess these aspects of other intranasal solutions (corticosteroids, antihistamines), if they had a history of their use.

Statistical analysis

Data are presented as median and interquartile range (IQR) for continuous variables and as number and percentage for categorical variables. The significance of differences in the results of the questionnaires, PFT, and FeNO between the start of treatment and the end of treatment and between the end of treatment and the end of the washout period were assessed

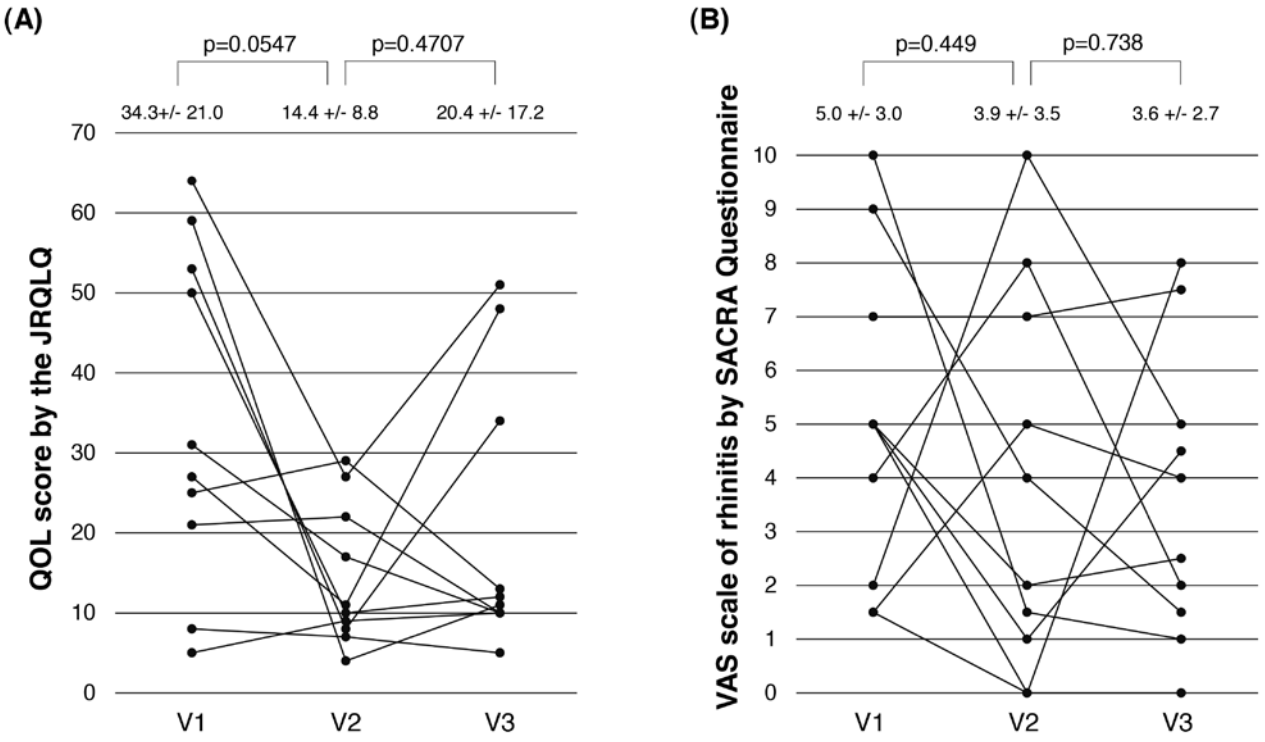

Fig. 1 Changes in nasal symptoms from before to after transdermal diphenhydramine treatment
Transdermal diphenhydramine was applied for 2 weeks in 10 patients with seasonal allergic rhinitis and asthma. Nasal symptoms were evaluated by the Japanese Allergic Rhinitis Standard Quality of Life Questionnaire score (A) and the Self-assessment of Allergic Rhinitis and Asthma Questionnaire visual analog scale for rhinitis (B) before and after treatment and after a 2-week washout period. Analyses were performed by the Wilcoxon signed rank test. JRQLQ, Japanese Allergic Rhinitis Standard Quality of Life Questionnaire; SACRA, Self-assessment of Allergic Rhinitis and Asthma Questionnaire; V1, before treatment; V2, after treatment; V3, after the 2-week washout period; VAS, visual analog scale

with the Wilcoxon signed rank test, with $P < 0.05$ indicating statistical significance. Statistical analyses were performed with JMP for Windows, version 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Ten patients were enrolled (8 women, 2 men; median age, 61 years [IQR, 53–74 years]). Patient characteristics are shown in Table 1. Participants were being treated for asthma according to the Global Initiative for Asthma [10] treatment steps, and the severity of asthma ranged from 2 (mild persistent) to 5 (severe). All patients except one was receiving an oral antihistamine or antileukotriene or both. Eight patients had a history of intranasal corticosteroid treatment, and all 10 patients had a history of intranasal ketotifen use. According to the patients' subjective assessments, intranasal ketotifen was clearly effective in all 10 patients, and intranasal corticosteroid was clearly effective in 5 patients but not effective in 3.

Effects on nasal symptoms

The subjective evaluation of the effects of transdermal diphenhydramine on nasal symptoms showed that it was effective in 5 patients, mildly effective in 3 patients, and not effective in 2 patients. The mean (SD) total QOL score according to the JRQLQ mean score showed a numerical improvement (from 34.3 [21.0] to 14.4 [8.8]; $P = 0.0547$), but did not reach statistical significance (Fig. 1A). No significant change of the score was observed by withdrawal of the treatment: 14.4 (8.8) at V2 and 20.4 (17.2) at V3 ($P = 0.47$). In the patients for whom transdermal diphenhydramine was effective or mildly effective in treating nasal symptoms, withdrawal of the treatment tended to worsen the symptoms during the washout period ($P = 0.094$). The SACRA VAS score for rhinitis did not show significant changes during either the treatment or the washout period (Fig. 1B).

In those patients in whom transdermal diphenhydramine was effective or mildly effective ($n = 8$), the time to onset of improvement and the duration of efficacy were compared between intranasal ketotifen and transdermal diphenhydramine (Fig. 2, $n = 7$; 1 patient could not determine the time to onset of improvement or the duration of efficacy). The median time to onset of improvement was shorter with intranasal ketotifen than with transdermal diphenhydramine (Fig. 2A, 10 min vs 30 min, respectively; $P = 0.03$), but no difference was found in the duration of efficacy (Fig. 2B, 4 hours vs 5 hours, respectively; $P = 0.72$).

Effects on asthma symptoms

Treatment with transdermal diphenhydramine improved asthma symptoms in 2 patients (nasal symptoms and postnasal drip also improved in these patients), whereas asthma symptoms did not improve

Table 2 Adverse reactions to topical medication for allergic rhinitis

	IN-CS (n = 8)	IN-AH (n = 10)	TD-DH (n = 10)
Nasal pain, n (%)	4 (50.0)	4 (40.0)	0 (0.0)
Epistaxis, n (%)	1 (12.5)	1 (10.0)	0 (0.0)
Nasal discharge, n (%)	1 (12.5)	0 (0.0)	0 (0.0)
Throat pain, n (%)	1 (12.5)	1 (10.0)	0 (0.0)
Lacrimation, n (%)	0 (0.0)	1 (10.0)	0 (0.0)
Asthma exacerbation, n (%)	0 (0.0)	0 (0.0)	2 (20.0)

IN-CS, intranasal corticosteroid
IN-AH, intranasal antihistamine
TD-DH, transdermal diphenhydramine

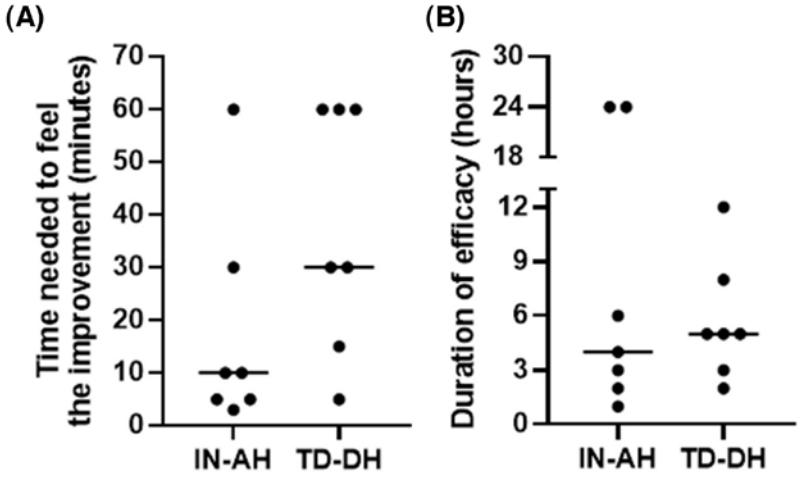

Fig. 2 Time to onset of improvement and the duration of efficacy with topical application of antihistamine drugs
Time to onset of improvement (A) and duration of efficacy (B) during treatment with intranasal ketotifen (IN-AH) or transdermal diphenhydramine (TD-DH) was evaluated in patients in whom the transdermal treatment was either effective or mildly effective (n = 7; 1 patient could not determine the time to onset of improvement or the duration of efficacy). Bars represent the median values. P = 0.03 for Fig. 2A, P = 0.72 for Fig. 2B.

in 6 patients, 2 of whom developed an exacerbation of their asthma during the treatment period. The remaining 2 patients were not aware of any asthma symptoms at the time of enrollment and therefore could not be included in the evaluation. The mean (SD) SACRA VAS score for asthma changed from 3.1 (2.4) at the start of treatment to 3.7 (4.0) (P = 0.88) at the end of treatment and 3.6 (2.8) (P = 0.63) after the washout period; neither of these comparisons was significant. The mean (SD) ACT score changed from 18.3 (4.5) at the start of treatment to 17.6 (5.9) (P = 0.84) by the end of treatment and 17.4 (5.8) (P = 0.91) after the washout period; neither of these comparisons was significant. No significant changes were observed in the PFT or FeNO (data not shown).

Safety outcomes

Two patients experienced an exacerbation of their asthma. No local adverse reactions to transdermal diphenhydramine were reported by any participants, but nasal pain and epistaxis were reported by 4 and 1 patients, respectively, after use of intranasal solutions (Table 2).

Patients' overall impressions of treatment

The overall impression of treatment with intranasal corticosteroids, intranasal ketotifen, and transdermal diphenhydramine was rated as high (score of 70 or greater) by 50%, 90%, and 50% of the patients, respectively. The overall impression of intranasal corticosteroids was rated as low (score of 20 or lower) by 3 patients, and that of transdermal diphenhydramine was rated as low by 1 patient. Fig. 3 gives an overview of the patients' overall impression of the 3 treatments.

DISCUSSION

Main findings

Transdermal administration of diphenhydramine via the nasal ala was studied in 10 patients who had persistent symptoms despite their usual treatment for allergic rhinitis. The 2-week treatment was well tolerated without any local adverse effects. The treatment was effective in treating nasal symptoms in 5 patients and mildly effective in 3. This efficacy rate is lower than that of intranasal antihistamine, which had an efficacy rate of 100%; however, when transdermal diphenhydramine was effective, the onset and duration of its action were comparable to those of the nasal formulations. The effects of transdermal diphenhydramine on asthma control were limited, although asthma symptoms (as well as nasal symptoms and postnasal drip) improved in 2 patients.

Mechanisms

Direct delivery of nonsteroidal anti-inflammatory drugs through the skin to the subcutis and underly-

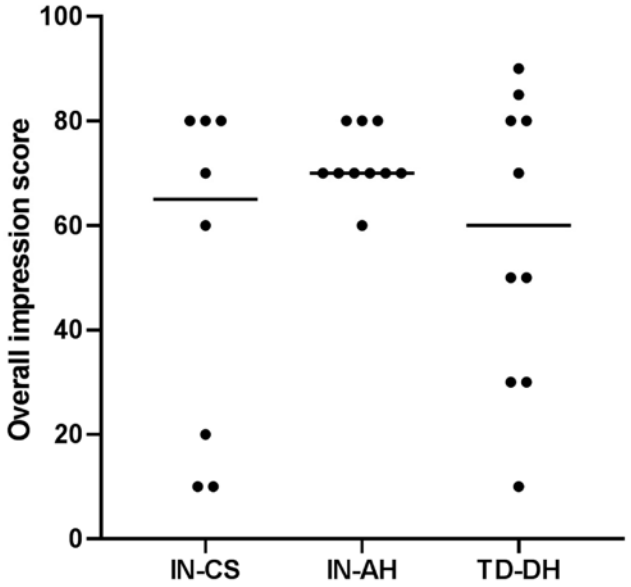

Fig. 3 Overall impression of topical pharmacological treatments as evaluated by patients
Patients rated the overall impression of intranasal corticosteroids (IN-CS, n = 8), intranasal ketotifen (IN-AH, n = 10), and transdermal diphenhydramine (TD-DH, n = 10). Bars represent median values.

ing muscles [11, 12] and to the synovial fluid [6, 7] has been reported. Also, after topical application the concentration of corticosteroids in the subcutaneous tissue under the application site was reported to be higher than the plasma concentration [13, 14]. Antihistamine agents are known to have anti-inflammatory [15] and analgesic effects in osteoarthritis [16, 17]. Diphenhydramine ointment applied to the skin over osteoarthritis with pain revealed significant analgesic effect [17] and the fact suggests that diphenhydramine also has the potential to penetrate into deep tissue from the skin. So far, topical administration of drugs to the skin mainly aims to control local pain or skin itchiness, but we tried to expand its use to control allergic rhinitis.

Allergic reactions to environmental allergens occur mainly in the eyes and upper and lower respiratory tract, including the conjunctiva, nasal vestibule, and cervical trachea located immediately under the skin; thus, transdermal application might potentially be feasible for controlling allergic symptoms. In allergic conjunctivitis, application of ketotifen fumarate [18] or dexamethasone [19] to the eyelids in rabbits increased the drug concentration on the ocular surface. In a rat model of tracheitis, prednisolone sodium succinate application to the skin over the cervical trachea resulted in a higher drug concentration at the tracheal surface than in the plasma [13]. These findings indicate that a clinically relevant concentration of drugs may migrate from the skin of the nasal ala to the nasal mucosa. Another possible way to administer diphenhydramine and suppress nasal symptoms could be inhalation of vaporized diphenhydramine via the nostrils; however, this approach may not be feasible because the boiling point of diphenhydramine is 162°C, so it would not become a vapor at room or body temperature. In humans, pilot studies on transdermal application of steroids and diphenhydramine have been performed for the trachea [20] and conjunctiva [21]. In the former study, corticosteroid or diphenhydramine ointment was applied to the cervical trachea in patients with asthma-related cough, and symptoms improved in 11 out of 28 patients with the corticosteroid and in 5 out of 14 with diphenhydramine [20]. In the latter study, diphenhydramine ointment applied to the eyelids in patients with allergic conjunctivitis was effective in 5 out of 7 patients [21]. Taken together with the results of this study, the findings indicate that the response rate of transdermal therapy for these organs appears to be lower than that of conventional therapies; however, the finding that some patients have a positive response supports the use of this drug administration route for supplemental therapy in patients with allergic diseases whose symptoms are insufficiently controlled or who experience adverse effects from conventional therapies.

Adverse reactions

Two patients experienced exacerbation of their asthma, one because of an acute upper respiratory infection and the other for an unknown reason. Thus, the likelihood that the study drug directly contribution to the adverse reactions appears to be low.

Topical use of an intranasal antihistamine or corticosteroid spray is known to cause local mucosal irritation, such as epistaxis, nasal discomfort, and throat irritation, and to have a bad taste [22–24]. Among these adverse effects, epistaxis is the most common effect with any intranasal drug [24], and a longer duration of drug treatment is associated with a higher incidence, e.g., 3.2% for 2 weeks' use of intranasal antihistamine and 19% to 25% for 12 months' use, and 17% to 23% for 12 months' use of intranasal steroid [24]. In contrast, participants in our study reported no local adverse effects of transdermal therapy, and 4 patients who had a history of irritability of the nasal cavity or epistaxis with intranasal drugs rated their overall

impression of the transdermal diphenhydramine as higher than that of nasal solutions. Transdermal application avoids direct stimulation of the nasal mucous membrane, so fewer local adverse effects could be expected.

Limitations

This study had several limitations. Evaluation of treatment efficacy was subjective, the number of patients recruited was small, and treatment was not blinded. A constant level of disease activity could not be ensured because of the seasonal and variable nature of the target disease. Patient QOL tended to improve during treatment, but it did not worsen during the washout period after drug withdrawal. However, in some patients the impact of drug withdrawal could not be evaluated because the washout period overlapped with the final phase of the pollen season.

Because the study lacked a control group, the extent of a placebo effect cannot be estimated. Also, a systemic effect of transdermal diphenhydramine could not be ruled out. However, the likelihood of systemic effects is assumed to be quite low because the dose of transdermal diphenhydramine was 0.7 mg each time; this dose is far lower than the usual dose of oral diphenhydramine hydrochloride, which is administered as 2 to 3 daily doses of 30 to 50 mg each.

Future research implications

Based on the results of this pilot study, a future clinical trial should target at the patients with allergic rhinitis using JRQLQ score as the primary endpoint; the sample size required for the placebo-controlled study with 95% confidence level and 80% power is estimated to be at least 17 patients each for placebo and diphenhydramine group, calculated by Sample Size Calculator [25]. The optimum dose and safety of long-term use of transdermal diphenhydramine is unknown and should be explored in future studies. Because the area of the nasal ala is small compared with the large area of the total nasal cavity, further investigation of the mechanism of effect of this drug, which was similar to that of intranasal formulations, is warranted. However, animal experiments are not feasible because no animal has a similar nasal anatomy to that of humans. The impact of the surface area of the nasal ala on efficacy should also be estimated because the surface area can differ greatly between individual patients and between ethnic groups [26].

Conclusion

The efficacy of transdermal application of diphenhydramine on the nasal ala for treating allergic rhinitis was not conclusive, but appears to be effective in certain patients. The treatment should be considered as a new supplemental therapy for allergic rhinitis, especially in patients who develop local irritations from intranasal solutions. Further investigation on its efficacy, safety, and effects on concomitant asthma is warranted in larger study populations and longer-lasting studies.

ACKNOWLEDGMENTS

We thank Mrs. Eri Kurauchi, Mr. Ryuichiro Nemoto, and Mr. Kozo Watanabe from the Department of Pharmacy at the National Hospital Organization Disaster Medical Center for giving instructions to the participants and providing assistance with this study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in this study.

REFERENCES

1) Scadding G, Walker S. Poor asthma control?--then look up the nose. The importance of co-morbid rhinitis in patients with asthma. Prim Care Respir J. 2012; 21(2): 222–8.
2) Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, *et al*. Prevalence and impact o f rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. J. Allergy. 2011; 66(10): 1287–95.
3) Okubo K, Uchida E, Terahara T, Akiyama K, Kobayashi S, Tanaka Y. Efficacy and safety of the emedastine patch, a novel transdermal drug delivery system for allergic rhinitis: Phase III, multicenter, randomized, double-blinded, placebo-controlled, parallel-group comparative study in patients with seasonal allergic rhinitis. Allergol Int. 2018; 67(3): 371–379.
4) Meltzer EO. Evaluation of the Optimal Oral Antihistamine for Patients With Allergic Rhinitis. Mayo Clin Proc. 2005; 80(9): 1170–6.
5) Berger WE, Meltzer EO. Intranasal spray medications for maintenance therapy of allergic rhinitis. Am J Rhinol Allergy. 2015; 29(4): 273–82.
6) Efe T, Sagnak E, Roessler PP, Getgood A, Patzer T, Fuchs-Winkelmann S, *et al* Penetration of topical diclofenac sodium 4% spray gel into the synovial tissue and synovial fluid of the knee: a randomised clinical trial. Knee Surg Sports Traumatol Arthrosc 2014; 22: 345–350.
7) Seefried L, Blyth M, Maheshwari R, McDonnell SM, Frappin G, *et al*. Penetration of topical diclofenac into synovial tissue and fluid of osteoarthritic knees: a multicenter, randomized, placebo-controlled, pharmacokinetic study. Ther Adv Musculoskelet Dis. 2020; 12: 1759720X20943088. Published online 2020 Aug 29.
8) Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, *et al*. Japanese guidelines for allergic rhinitis 2017. Allergol Int. 2017; 66(2): 205–19.
9) Yasuo M, Kitaguchi Y, Komatsu Y, Hama M, Koizumi T, Agatsuma T, *et al*. Self-assessment of Allergic Rhinitis and Asthma (SACRA) Questionnaire-based Allergic Rhinitis Treatment Improves Asthma Control in Asthmatic Patients with Allergic Rhinitis. Intern Med. 2017; 56(1): 31–9.
10) Global Initiative for Asthma. Global Strategy for Management of and Prevention. 2018. www.ginasthma.org.
11) Sugibayashi K, Yanagimoto G, Hayashi T, Seki T, Juni K, Morimoto Y. Analysis of skin disposition of flurbiprofen after topical application in hairless rats. J Control Release 1999; 62: 201–8.
12) Hasegawa T, Kawazome A, Yanagimoto G, Hayashi T, Seki T, Akimoto M, *et al*. Analysis of skin disposition of flurbiprofen after topical application using dual agar gel discs-inserted rats. Biol Pharm Bull. 2007 Nov; 30(11): 2135–40.
13) Ishii H, Suzuki T, Todo H, Kamimura M, Sugibayashi K. Iontophoresis-facilitated delivery of prednisolone through throat skin to the trachea after topical application of its succinate salt. Pharm Res 2011; 28(4): 839–47.
14) Hashimoto N, Nakamichi N, Yamazaki E, Oikawa M, Masuo Y, Schinkel AH, *et al*. P-Glycoprotein in skin contributes to transdermal absorption of topical corticosteroids. Int J Pharm. 2017 Apr 15; 521(1–2): 365–373.
15) Shirinsky I, Shirinsky V. H1-antihistamines are associated with lower prevalence of radiographic knee osteoarthritis: a cross-sectional analysis of the Osteoarthritis Initiative data. Arthritis Res Ther. 2018 Jun 7; 20(1): 116. doi: 10.1186/s13075–018–1619–7.
16) Apiliogullari S, Keles B, Apiliogullari B, Balasar M, Yilmaz H, Duman A. Comparison of diphenhydramine and lidocaine for prevention of pain after injection of propofol: a double-blind, placebo-controlled, randomized study. Eur J Anaesthesiol. 2007 Mar; 24(3): 235–8.

17) Fujita T, Ohue M, Fujii Y, Jotoku T, Miyauchi A, Takagi Y, *et al*. Prompt analgesic effect of antihistaminic diphenhydramine ointment on bone-joint-muscle pain as assessed by skin impedance. Pharmacology. 2013; 92(3–4): 158–66.
18) Kimura C, Tojo K. Development of a stick-type transdermal eyelid delivery system of ketotifen fumarate for ophthalmic diseases. Chem Pharm Bull (Tokyo). 2007; 55(7): 1002–5.
19) Boddu SH, Gupta H, Bonam SP. Preclinical evaluation of a ricinoleic acid poloxamer gel system for transdermal eyelid delivery. Int J Pharm. 2014; 470(1–2): 158–61.
20) Kamimura M, Mouri A, Takayama K, Mizutani T, Hamamoto Y, Iikura M, *et al*. Transdermal application of steroid to cervical trachea for the cough in patients with bronchial asthma and cough variant asthma. --- A Pilot Study. J Allergy Ther 2013; 4: 5. doi: 10.4172/2155-6121.1000152.
21) Kamimura M, Ohnishi T, Terada H, Mouri A, Naoi T, Todo H, *et al*. Application of diphenydramine ointment to the eyelids for allergic conjunctivitis. Iberoam J Med. 2021; 3(1): 44–50.
22) Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011; 32(3): 213–20.
23) Berger WE, Ratner PH, Casale TB, Meltzer EO, Wall GM. Safety and efficacy of olopatadine hydrochloride nasal spray 0.6% in pediatric subjects with allergic rhinitis. Allergy Asthma Proc. 2009; 30(6): 612–23.
24) Roland PS, Marple BF, Wall GM. Olopatadine nasal spray for the treatment of allergic rhinitis. Expert Rev Clin Immunol. 2010; 6(2): 197–204.
25) Sample Size Calculator. Determines the minimum number of subjects for adequate study power. https://clincalc.com/stats/samplesize.aspx
26) Funayama E, Yamamoto Y, Furukawa H, Murao N, Shichinohe R, Yamao T, *et al*. Full-Thickness Entire Nasal Alar Reconstruction Using a Forehead Flap in Asians: No Cartilaginous Infrastructural Lining Is Necessary. J Craniofac Surg. 2017; 28(3): 734–7.