

東海大学大学院令和 5 年度博士論文

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

(アレルギー性鼻炎合併喘息患者を対象とした
ジフェンヒドラミン経皮的鼻翼塗布療法の
パイロットスタディ)

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1. Summary

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%. These figures suggest a close relationship between asthma and rhinitis, and improvement of rhinitis symptoms has been known to improve control of asthma. 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 are the mainstay of therapy, but they often cause adverse reactions, such as sedation or anticholinergic effects, and, in such cases, intra-nasal administration of the drug is recommended. Intranasal spray is widely used for this purpose but it is known to cause local mucosal irritation sometimes, such as epistaxis, nasal discomfort, and throat irritation, and to have a bad taste and would result in the discontinuation of the therapy. The less irritant topical therapy to the nasal mucosa is necessary in such instances but at the moment it is not available.

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. So far, topical administration of drugs to the skin mainly aims to control local pain arising from underlying muscles or joints, and for the purpose of control allergy, it has been limitedly used for superficial skin problems such as urticaria and hardly been used for deeper tissue from the skin.

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.

Ten patients with concomitant asthma and allergic rhinitis were recruited in the study. The dosing regimens of anti-allergy drugs, antihistamines, or steroids had to be stable for the 4 weeks before patients started the study. 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. Diphenhydramine cream 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 treatment period was followed by a 2-week washout period.

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 based on a questionnaire to the patient. The mean (SD) total quality of life (QOL) score according to the Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (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. 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 ($P = 0.47$). When the 2 drop-out cases were excluded from the analysis, the mean total QOL score of JRQLQ improved significantly (from 39.1 [20.1] to 13.3 [8.0]; $P = 0.0234$). 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 Self-assessment of Allergic Rhinitis and Asthma visual analogue scale score for rhinitis did not show significant changes during either the treatment or the washout period. 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. The median time to onset of improvement was shorter with intranasal ketotifen than with transdermal diphenhydramine (10 min vs 30 min, respectively; $P = 0.03$), but no difference was found in the duration of efficacy (4 hours vs 5 hours, respectively; $P = 0.72$). 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. No local adverse reactions to transdermal diphenhydramine were reported by any participants, whereas 4 patients had a history of irritability of the nasal cavity or epistaxis with intranasal drugs. Overall impression of the drug, including its efficacy and adverse effects were rated by patients on a scale of 0 to 100, with a higher score indicating a higher evaluation. The 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. These findings indicate that transdermal administration of diphenhydramine via the nasal ala might be effective in certain patients with low incidence of adverse effects. So far, topical administration of drugs to the skin mainly aims to control local pain or skin itchiness, but this study 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. The pilot studies on transdermal application of steroids and diphenhydramine have been performed for the trachea and conjunctiva. For cervical trachea, corticosteroid or diphenhydramine ointment was applied to the overlying skin 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. For conjunctiva, diphenhydramine ointment applied to the eyelids in patients with allergic conjunctivitis was effective in all 7 patients, including the 2 patients who discontinued the study due to side effects.

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.

In conclusion, this study is a pilot study with limited number of the patients without placebo control and 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.

2. Background and 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%, with 67.3% of Japanese patients with asthma being reported to have rhinitis. These figures suggest a close relationship between asthma and rhinitis, and improvement of rhinitis symptoms has been known to improve control of asthma. 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 are the mainstay of therapy, but they often cause adverse reactions, such as sedation or anticholinergic effects, and, in such cases, intra-nasal administration of the drug is recommended. Intranasal antihistamine or corticosteroid spray is widely used for this purpose but is often distasteful and sometimes causes local mucosal irritation sometimes, such as epistaxis, nasal discomfort, and throat irritation, resulting in the discontinuation of the therapy. The less irritant topical therapy to the nasal mucosa would be warranted.

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. Currently, topical administration of drugs to the skin mainly aims to control local pain arising from underlying muscles or joints, and for the purpose of control allergy, it has been limitedly used for superficial skin problems such as urticaria and hardly been used for deeper tissue from the skin.

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 as a supplemental therapy for under-controlled symptoms with less irritability to the intra-nasal mucosa.

3. Discussion

3.1 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.

3.2 Mechanisms

Direct delivery of nonsteroidal anti-inflammatory drugs through the skin to the subcutis and underlying muscles and to the synovial fluid 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. Anti-histamine agents are known to have anti-inflammatory and analgesic effects in osteoarthritis. Diphenhydramine ointment applied to the skin over osteoarthritis with pain revealed significant analgesic effect 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 or dexamethasone 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. 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.

3.3 Other allergic situations

In humans, pilot studies on transdermal application of steroids and diphenhydramine have been performed for the trachea and conjunctiva.

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. No adverse events were reported from the participants. Inhaled corticosteroid is the mainstay of the therapy for asthma. However, complete resolution of the symptoms cannot always be achieved by medication, and oropharyngeal side effects such as hoarseness or stomatitis sometimes develop and result in under-control of the disease due to restriction of the inhalation dose. The cervical trachea is a part of lower airway tract where the direct palpation is possible over the skin and represents approximately 40% of the whole trachea. In asthmatic patients, not only the bronchus but also the trachea is regarded as an inflammatory site. Thus, the treatment for tracheitis through direct distribution of the drug through the overlying skin could be considered as a choice with lower possibility of adverse effects, though it cannot cover whole length of trachea.

In the latter study, diphenhydramine ointment applied to the eyelids in patients with allergic conjunctivitis was effective in all 7 patients, including the 2 patients who discontinued the study due to side effects. Notably, except in 1 patient, rapid control of symptoms was noted after application of the cream and its duration of action was longer than that of eye drops. The reason for long-term sustained activity may be slow release of the drug from skin tissue. In contrast, a high local drug concentration is not maintained by eye drops because the drops overflow when the eyes are closed immediately after instillation or the drug is excreted via the lacrimal duct. Another point of advantage of eyelids ointment is its easiness of application of the drugs. It is difficult for elderly persons and those with upper limb problems to use eye drops, efficacy and compliance may be improved by topical application to the eyelids.

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.

3.4 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 contributed 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. Among these adverse effects, epistaxis is the most common effect with any intranasal drug, 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. 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.

3.5 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.

3.6 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. The optimum dose and safety of long-term use of transdermal diphenhydramine is unknown and should be explored in future studies, since the longer period of use of intranasal solutions, the higher rate of local side effects and thus the same concern should be taken into consideration in transdermal application to the nasal ala.

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.

The transdermal application of anti-allergic drugs should be investigated not only for rhinitis, but also for asthmatic cough and conjunctivitis as a supplemental therapy, and factors predicting positive responses should be analyzed in future studies.

4. 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.