

Assessment of antihistamines in the treatment of skin allergies

Hiroyuki Murota and Ichiro Katayama

Course of Integrated Medicine, Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan

Correspondence to: Hiroyuki Murota, MD, PhD, 2-2 Yamadaoka, Suita, Osaka 5650871, Japan
Tel: +81 668793031; fax: +81 668793039;
e-mail: h-murota@derma.med.osaka-u.ac.jp

Current Opinion in Allergy and Clinical Immunology 2011, 11:000–000

Purpose of review

Antihistamines, both old first-generation and new, are frequently prescribed to patients with allergic skin diseases. As the expected roles of antihistamines differ in each dermatosis, we should carefully consider the characteristics of each antihistamine prior to use. This review covers recent antihistamine topics, including novel pharmacological action, and enhancement of patient quality of life (QoL).

Recent findings

Nonsedative, second-generation antihistamines are recommended as first-line treatment for urticaria. For atopic dermatitis, most position papers doubt their efficacy of treatment due to insufficient evidence. However, recent articles revealed novel H1 receptor-independent properties for these agents, such as modulation of cytokine and chemokine production, tissue remodeling, and indicated its favorable effects on atopic dermatitis. Furthermore, several important benefits of second-generation antihistamines on the amelioration of atopic dermatitis symptoms, patient QoL and labor efficiency including loss of productivity and absenteeism from the workplace have been reported. In contrast, prescription of first-generation antihistamines for skin allergies should be avoided due to their bad risk/benefit ratio. Whereas they are not better in controlling itch, they also fail to improve patient labor efficiency unlike second-generation antihistamines.

Summary

Although antihistamine usefulness varies greatly, understanding the characteristics of each antihistamine will allow more personalized therapy for skin allergies.

Keywords

antihistamine, pharmacological property, quality of life, sedation, skin allergy

Curr Opin Allergy Clin Immunol 11:000–000
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1528-4050

Introduction

In many instances, chemical mediators such as histamine, which are derived from degranulated mast cells or basophils, act as triggers of inflammation. Released histamine acts on histamine receptor-expressing cells such as epithelial cells, fibroblasts, endothelial cells, antigen-presenting cells (e.g. Langerhans cells, dendritic cells, and macrophages), and nerve cells, and elicits inflammatory cell accumulation, vasodilation, and transvascular leakage of plasma, as well as provokes itch sensations [1].

Antihistamines are an excellent choice for controlling both early and late-phase skin allergy. They show promise for the treatment of skin allergy in which histamine H1 receptor-mediated signals are primarily implicated in its pathology (i.e. urticaria) and also ameliorate the late effects of allergic inflammation by modulating inflammatory factor production and tissue remodeling [2].

By contrast, there is concern about the possible adverse effects of antihistamines. Classical antihistamines can

cross the blood–brain barrier and cause widespread impairment of cognitive and psychomotor function via histamine H1 receptor antagonism. In addition, classic antihistamines, including older, first-generation antihistamines, have anticholinergic activity that can exacerbate pre-existing diseases, such as glaucoma, prostatic hyperplasia, and asthma.

It is speculated that physicians are able to provide appropriate treatment by exploiting the features of each antihistamine. Here we review the recent literature, discussing the characteristics and choices of antihistamines and reconsidering the best medications for patients with skin allergies.

Antihistamine in the treatment of urticaria: synopsis

First, identification and exclusion of potential causes (e.g. drugs, physical stimuli, inflammatory or infectious diseases, autoantibodies, dietary, etc.) should be considered in the management of urticaria [3–7]. As for symptomatic

therapy, antihistamines are believed to be a reliable therapeutic option [3–7] (Table 1). In the treatment of acute idiopathic (spontaneous) urticaria, the first-line use of nonsedative, second-generation antihistamines are strongly recommended, although the quality of evidence is low (Table 1) [3]. As acute idiopathic urticaria occurs in an unexpected fashion, high-quality evidence in placebo-controlled clinical trials is difficult to obtain. Meanwhile, in the treatment of chronic idiopathic urticaria and cold urticaria, nonsedative, second-generation antihistamines are recommended as a first-line treatment due to strong scientific evidence of their safety and efficacy [3]. In daily practice, some cases are resistant to typical doses of nonsedative, second-generation antihistamines on an empirical basis. In such cases, up dosing or a combination of antihistamines has been thought to provide clinical benefit (Table 1). Recent retrospective clinical analysis has revealed that up dosing of single, nonsedative, second-generation antihistamines has more pruritus suppressive effects than a combination of more than one antihistamine [8].

Antihistamine for the treatment of atopic dermatitis: synopsis

Table 2 summarizes the position of antihistamines in management of atopic dermatitis [9–15]. Histamine has been thought to partly contribute to the pathogenesis of the acute phase of atopic dermatitis but not to the chronic phase of atopic dermatitis. Because of this situation, many guidelines for the treatment of atopic dermatitis have found therapeutic value regarding improvement of itch and sleep disturbance by the central depressant action of older, first-generation antihistamines [9,10,13] (Table 2). The effects of H1 receptor antagonists on the symptomatic improvement of atopic dermatitis were underestimated because of a lack of supporting evidence [9,10,12,14]. Likewise, the soporific effect of sedating antihistamines on pruritus relief has also been introduced with extremely weak evidence [9–11,13]. Under such circumstances, Kawashima *et al.* [16] conducted randomized, multicenter, double-blind, placebo-controlled, parallel-group studies and demonstrated the efficacy of nonsedative, second-generation antihistamines in the treatment of itch in atopic dermatitis. According to the accumulation of evidence for the efficacy of newer second-generation antihistamines [17,18], the Japanese Dermatological Association recommends choosing lower sedative, second-generation antihistamines initially [15]. Thus, although further data are required, antihistamines with or without sedative action might reduce the intensity of itch in atopic dermatitis. On the basis of current knowledge, it seems warranted to use nonsedating antihistamines in pruritic atopic dermatitis since the response may differ individually.

Key points

- Recently discovered, novel pharmacological effects of more current nonsedative second-generation antihistamines are expected to ameliorate the underlying causes of skin allergies.
- In contrast, novel adverse effects of sedative first-generation antihistamines also have been recently reported.
- When antihistamines are prescribed, the highest priority should be given to improve patient's quality of life and workplace productivity.

Benefits of antihistamines in the treatment of skin allergies

Histamine affects various skin cells and exerts pleiotropic effects that lead to the pathological condition of atopic dermatitis. Recent studies have provided evidence of the novel functional characteristics of antihistamines that lead to the amelioration of the various symptoms of atopic dermatitis [19–25,26*,27–46] (Table 3).

Effects of antihistamines on itch

Itch is a major symptom in atopic dermatitis and is induced by specific, nonmyelinated C-fiber stimulation. The magnitude of itch is modulated by changes in stimulus frequency [47]. Additionally, increased epidermal nerve fiber density is frequently observed in atopic dermatitis skin lesions [47–49]. More recent second-generation antihistamines demonstrated decreases in epidermal nerve fiber densities via the decreased expression of nerve elongation factors (e.g. nerve growth factor, amphiregulin) and increased expression of axonal chemorepellant factors (e.g. semaphorin 3A) [26*]. Furthermore, several studies have referred particularly to the effects of certain antihistamines on decreasing nerve excitability (Table 3). Along with neuronal depolarization, neuropeptides such as substance P are released from nerve endings. Substance P elicits scratching behavior that is possibly mediated by its autocrine effects or by histamine through the degranulation of mast cells [50]. Previous studies [27,28,34] have discussed the novel functional characteristics of antihistamine to inhibit capsaicin-evoked neural excitation or substance P-induced mast cell degranulation.

Inflammatory blockade of antihistamines

Histamine has been implicated as a cause of inflammation and tissue remodeling in atopic dermatitis [2,51–53], primarily through H1 receptor activation [51]. Dermal fibroblasts, endothelial cells, Langerhans cells, and eosinophils are all involved in the pathogenesis of atopic dermatitis via the production of inflammatory mediators, adherence of inflammatory cells to endothelial cells, and alterations of dermal intercellular matrix components

Table 1 Position of antihistamines in the recommendations for urticaria management

Reference (type)	Type of urticaria	Recommendation	Sedative antihistamines	Nonsedative antihistamines	Comment
[3] (guideline)	Acute spontaneous urticaria Chronic spontaneous urticaria Cold urticaria	Start with a standard dose of a nonsedating H1 antihistamine	Should be avoided (except for special situations*)	Start with a standard dose as a first-line treatment	If standard dose does not achieve adequate symptom relief, increase the dose when the benefits outweigh the risks (*unprocurable in some situations)
[4] (guideline)	Chronic urticaria, angio-edema	Start with a standard dose of a nonsedating H1 antihistamine	Should be avoided	For adults Start with a standard dose as a first-line treatment	If patients do not achieve adequate symptom relief at a standard dose of nonsedative antihistamines, increase the dose when the benefits outweigh the risks
[5] (position paper)	Chronic urticaria	New low-sedative antihistamines represent first-line therapy	Alternatively, short-term use in the evening Consider if the symptoms are severe, associated angio-edema, and patients are anxious and disturbed at night	For children Preferred Recommended as a first-line therapy	There is presently no clear evidence that updosage or a combination of antihistamines provide significant clinical benefits
[6]	Acute urticaria/angio-edema	Comprises a cornerstone of therapy	May be considered when necessary to achieve optimal hive and pruritus relief	May be quite effective in controlling the urticarial process without side effects	Carefully build up the dose of older sedative antihistamines
	Chronic urticaria/with or without angio-edema	Remains the mainstay of symptomatic treatment Prophylactic administration	Sedative action may be desirable for reducing discomfort due to pruritus	Minimal risk of adverse effects	The decision to choose between first- and second-generation antihistamines should consider these differences
[7] (guideline)	Idiopathic urticaria	Consecutive administration provides benefit	Not stated	Not stated	Notice the possibility that treatment does more harm than good
	Urticaria inducible by particular stimuli	Consider prescription if the cause is unavoidable For cholinergic urticaria, antihistamines should be considered as basic treatment	Not stated	Not stated	Think elimination of a causative factor first
	Special type of urticaria	Prescribe based on the clinical situation	Not stated	Not stated	No special mention

* Unprocurable in some situations.

Table 2 Position of antihistamines in the recommendations for atopic dermatitis management

Reference (type)	Recommendation	Sedative antihistamines	Nonsedative antihistamines	Comment
[9] (recommendation)	Unclear	Adjunctive therapy to possibly reduce itching and improve sleep	Evidence of benefit is unconvincing	Evidence of benefit is unconvincing
[10] (review)	Dependent on the individual experiences of patients and physicians	Benefits from soporific effect	Clinical efficacy is unproven	Evidence of clinical efficacy is low
[11] (guideline)	Offer to patients with sleep disruption or allergic rhinoconjunctivitis and urticaria	Useful	Uncertain	There is benefit by the use of antihistamines in patients with other concurrent allergic diseases
[12] (consensus)	Useful as a short-term adjuvant to a topical treatment	Principally selected	Modest value	Lack of solid evidence of efficacy
[13] (guideline for children between 0 and 12 years of age)	Offer antihistamines depending on the situation	Offer if sleep disturbance is severe for the child (over 6 months of age) or their parents	Offer if severe itching or urticaria occurs	Prescription of sedative antihistamines should be considered for children over 6 months of age during acute flare
[14] (practice parameter)	Some patients may benefit for the relief of pruritus.	Offer at bedtime if the nocturnal pruritus persists	May be effective in relieving symptoms of atopic dermatitis	Majority of studies were flawed because of small sample size or poor study design
[15] (guideline)	Antihistamines are used for the purpose of suppressing pruritus and preventing exacerbation from scratching	Consider while observing both side effects and the suppression of pruritus	Recommended as initial choice	Previous studies have revealed efficacy [16–18]

(Table 3). Interestingly, it has been reported that antihistamines have favorable pharmacological properties on these aspects *in vitro* [2,29–34,39–46]. Keratinocytes are considered an immunocompetent cell type for the production of cytokines or other biological substances. Antihistamine-induced production of inflammatory cytokines or chemokines and inhibition of adhesion molecules and major histocompatibility complex class II expression have been experimentally verified in keratinocytes [19–25,39] (Table 3). Furthermore, mast cell-derived inflammatory cytokines and growth factor secretion by various stimuli are also involved in the pathogenesis of skin allergies and are inhibited by certain antihistamines [34–38,54] (Table 3).

Animal models

At present, animals with chronic dermatitis, which were developed by repeated topical application of haptens, are considered an experimental model of atopic dermatitis [55,56]. The effects of the oral administration of certain second-generation antihistamines have been verified using these animal models and were found as decreasing levels of inflammatory mediators, reduction in scratch behavior, and amelioration of skin barrier function [26*,29,57]. Interestingly, oral administration of olopatadine to animals in an atopic dermatitis model decreased the atopic dermatitis-induced increase in transepidermal water loss, the tissue concentrations of histamine, the expression of semaphorin 3A in the epidermis, and the serum titer of antigen-specific IgE [26*,29]. Thus, it was concluded that second-generation antihistamines might properly regulate not only abnormal immune reactions but also imbalances in skin homeostasis in atopic dermatitis.

From the patients' perspective

Regarding quality of life (QoL), labor efficiency, and loss of daily activities, skin allergy is widely perceived as a QoL-impairing disease [58*,59*,60]. Looking at the results of a questionnaire using validated measures, The Work Productivity Assessment Index (WPAI), which focused on patients with pruritus, overall work productivity impairment, overall classroom productivity impairment, and activity impairment were reduced approximately 40, 41, and 50%, respectively [59*]. As for atopic dermatitis/urticaria, the results for the evaluation of overall work impairment, overall classroom impairment, and daily activity impairment were reduced approximately 40/42, 41/63, and 50/38%, respectively [59*]. From these results, it appears that QoL in patients with skin allergies was severely affected, and clinicians should provide remedies to improve patient QoL, including the WPAI index.

For the choice of treatment, the differences between nonsedative versus sedative antihistamines have been

Table 3 Antihistamines affect many different types of cells

Target cells	Effect	Antihistamines
Keratinocyte	Downmodulation of proinflammatory cytokines (IL-1 α , TNF- α) Downmodulation of chemokines (IP-10, TARC, RANTES, Mig, I-TAC, MIF) Downmodulation of growth factor (VEGF) Downmodulation of adhesion molecule (ICAM-1) Downmodulation of MHC class II Upregulation of semaphorin 3A	Bepotastine [19], mizolastine [20], levocetirizine [21] #1 Bepotastine [19], epinastine [22], fexofenadine [23], loratadine [24], desloratadine [24], mizolastine [20], cetirizine [25] Mizolastine [20] Bepotastine [19], epinastine [22] Epinastine [22] Olopatadine [26 [•]] Olopatadine [26 [•]]
Nerve fiber	Downmodulation of number of epidermal nerve fiber Downmodulation of capsaicin-evoked calcium response Pretreatment with antihistamine prevented capsaicin-induced hyperalgesia	Dexbrompheniramine [27] Ketotifen [28]
Fibroblast	Upregulation of hyaluronic acid Downmodulation of histamine induced collagen synthesis and ICAM-1 expression Inhibition of nitric oxide induction by TNF α stimulation Inhibition of VEGF-induced proliferation	Olopatadine [29] Emedastine [30,31], diphenhydramine [30] Fexofenadine [32] carebastine [33]
Endothelial cell Inhibition of substance P-induced nitric oxide synthesis	Bepotastine [34]	
Mast cell (basophil)	Inhibition of histamine, angiogenic factors and cytokine secretion by various stimuli	Rupatadine [35], olopatadine [36] Epinastine [37] Bepotastine [34], desloratadine [38] Olopatadine [39], fexofenadine [40] Olopatadine [41] Levocetirizine [42] Desloratadine [43], epinastine [44], diphenhydramine [45], chlorpheniramine [45], fexofenadine [46]
Langerhans cell	Inhibition of degranulation by various stimuli Suppression of antigen-presenting ability Downmodulation of chemokines (TARCs)	
Eosinophil	Inhibition of adhesion Suppression of eosinophil survival	

#1, downmodulation of histamine-dependent expression. ICAM, intercellular adhesion molecule; MHC, major histocompatibility complex; TARC, thymus and activation-regulated chemokine; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

addressed [58[•],59[•]]. Regarding the WPAI index, it is obvious that nonsedative antihistamines produced greater overall improvements in productivity in patients with skin diseases than did sedative antihistamines (Fig. 1) [58[•],59[•]]. Nonsedative antihistamines significantly improved work productivity under almost all background conditions. A significant effect of sedative antihistamines was identified for the 'male' and 'eczema/dermatitis' categories, but no significant improvements were seen with sedative antihistamines for patients in other categories (Fig. 1) [58[•]]. In a comprehensive comparison of other evaluation items, both sedative and nonsedative antihistamines successfully provided significant relief of itch symptom, as well as improvement in impaired QoL (Skindex-16 measures; Fig. 2) [58[•]]. However, sedative antihistamines failed to reduce work productivity and daily activity impairments, despite their favorable effects on itch and QoL (Fig. 2) [57]. Impaired performance as an adverse effect of sedative antihistamines may be a major factor in these divergent results. Alternatively, nonsedative antihistamines significantly reduced overall work productivity and daily activity impairments (Fig. 2) [57]. Additionally, the extent of impairment in overall work productivity can be predicted by such QoL measures as the Skindex-16 measures. Nevertheless, clinicians should keep in mind that they

could overestimate the effect of sedative antihistamines to improve work productivity by relying solely on patient itch intensity and QoL values. For these reasons, nonsedative antihistamines have substantial value in the treatment of patients with skin allergies.

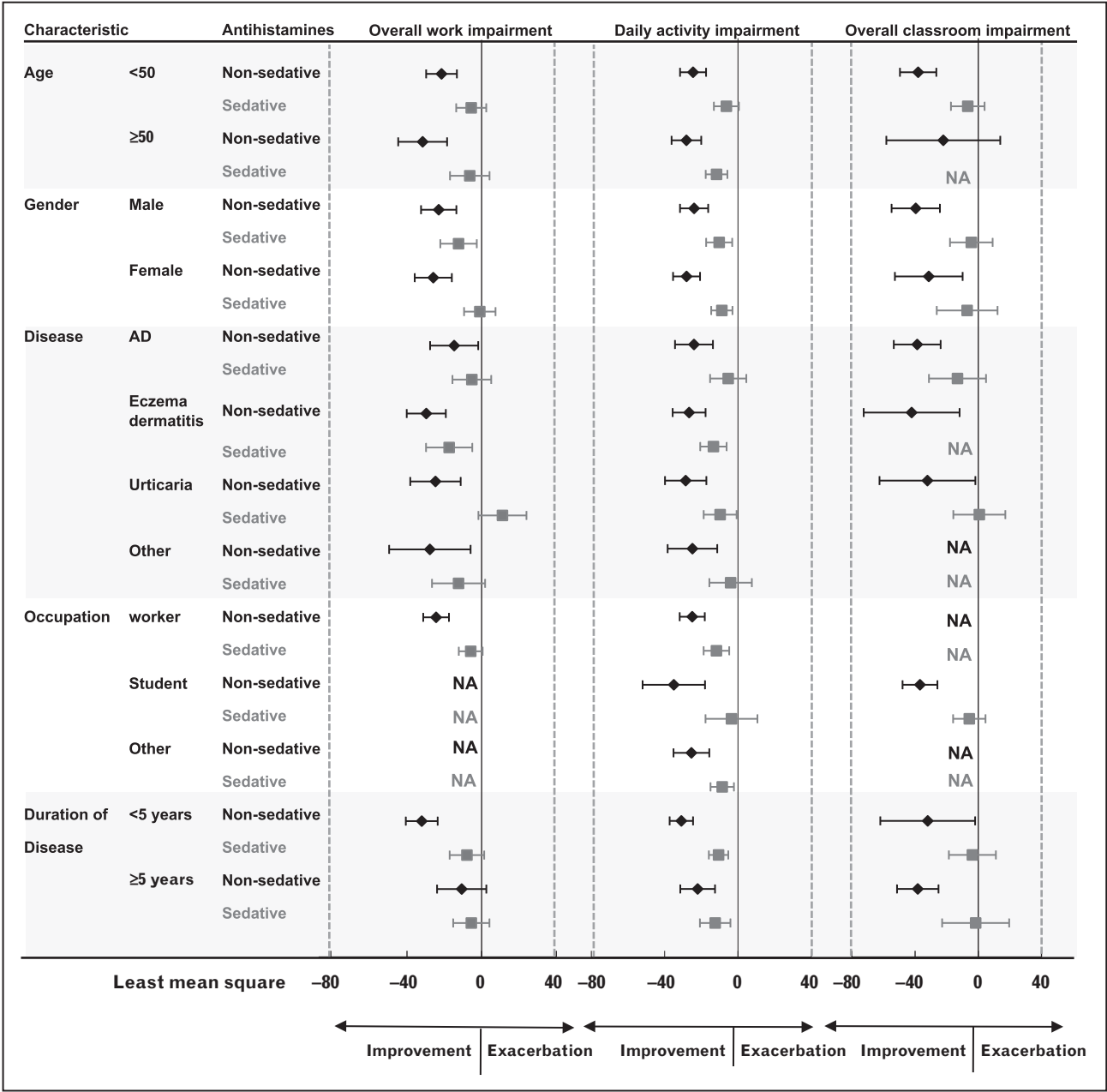
Disadvantages of antihistamines for the treatment of skin allergies

Adverse effects of antihistamine are found not only in the treatment of skin allergies but in all allergic diseases. As histamine is essential for some normal mammalian physiological functions, it is easy to assume that impairing histaminergic signaling might cause certain physical disorders [61^{••}].

Adverse effects of first-generation antihistamines on the central nervous system

Histamine is known to be important in waking mechanisms and cognitive functioning by affecting histaminergic neuronal systems in the mammalian brain [62,63,64^{••},65]. In these target areas, histamine modulates neuronal activity and excitability via histamine receptors, including the H1 receptor [65]. During wakefulness, histaminergic neurons discharge tonically and selectively. Administration of various substances that impair histaminergic

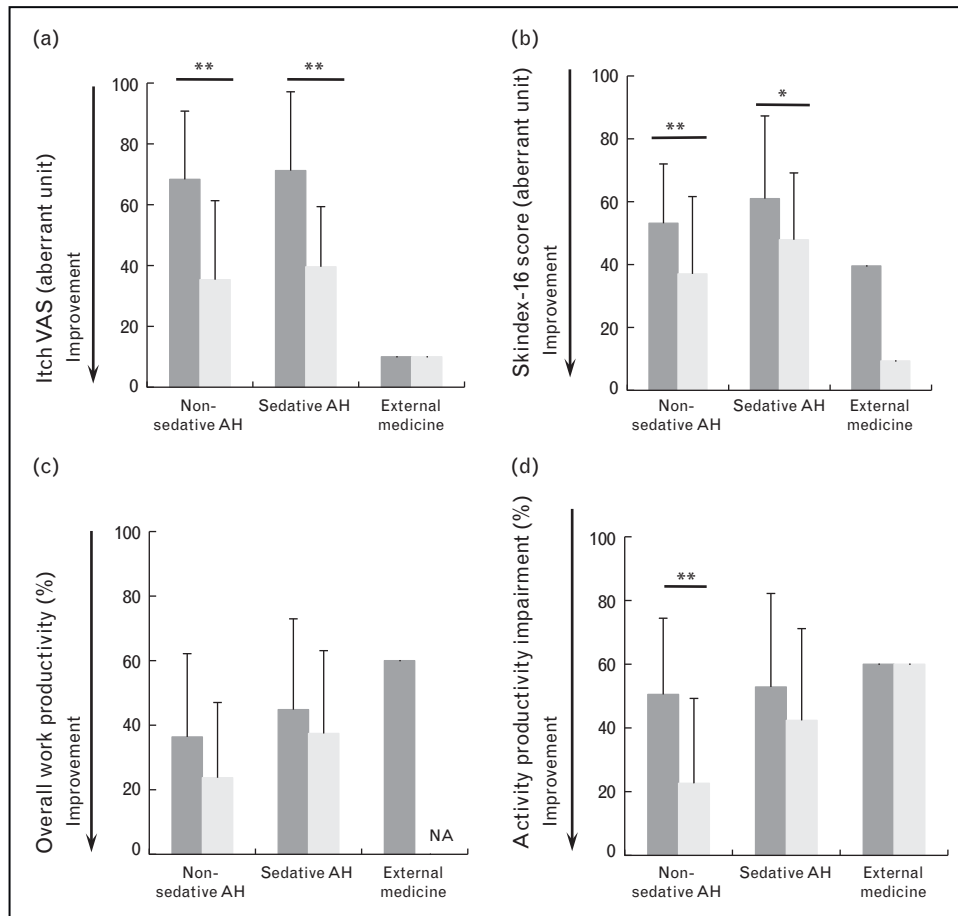
Figure 1 The impact of antihistamines on overall work productivity impairment, activity productivity impairment, and overall classroom productivity impairment per certain parameters of pruritic skin diseases



Changes in the evaluated value of certain parameters from baseline were adjusted with background factors and the initial value (a linear model). Results are shown in a forest plot. Black or red horizontal lines indicate 95% confidence intervals and the results of nonsedative and sedative antihistamines, respectively. The rhomboid or square dot on the center of the horizontal line indicates the point estimate. Significance is indicated by horizontal lines that do not overlap with the vertical line where the least mean square = 0. NA, not applicable. Reproduced with permission from the Japanese Society of Allergy [59].

transmission cause a significant decrease in wakefulness [66]. Likewise, many previous studies have focused on the impairment of cognitive function after antihistamine administration [64^{••},67,68]. In a review by van Ruitenbeek *et al.* [64^{••}] to determine which cognitive domains are most sensitive to antihistamines, cognitive functioning, such as driving, psychomotor skills, atten-

tion, and memories, were impaired by histaminergic hypofunction. Shamsi and Hindmarch [67] referred particularly to evidence of the harm of the 'sedation' of antihistamines on the safe performance of cognitive and psychomotor tasks of everyday life, and such excessive sedation in daytime increases the risk of accidents and reduces compliance, as well as the efficacy and utility of

Figure 2 The impact of antihistamines on patient outcomes in atopic dermatitis

The figure shows the impact of antihistamines on (a) itch visual analog scale, (b) Skindex-16 score, (c) overall work productivity impairment, and (d) daily activity productivity impairment seen in atopic dermatitis. The data of baseline assessment (dark gray bar) and posttreatment assessment (light gray bar) are shown as the mean $\pm$ SD. **Statistically significant improvement compared with the data of baseline assessment ($P < 0.001$), * $P < 0.01$. AH, antihistamines; NA, not applicable. Reproduced with permission from [58].

antihistamines. In certain guidelines or recommendations for the treatment of urticaria and atopic dermatitis, sedative antihistamines are recommended to be taken before bedtime to improve sleep. However, a caution has been raised about taking first-generation antihistamines before bedtime, because histaminergic hypofunction of the central nervous system may be maintained until the next morning [67,69]. This sedative action lasts longer than 12 h, whereas the antipruritic effects last only 4–6 h [3]. Yanai and Tashiro [68] confirmed the degree of sedative action of first-generation antihistamines by the visualization of cerebral H1 receptor occupancy of antihistamines using positron emission tomography with [^{11}C]-doxepin. As a significant correlation between cognitive function decline and brain H1 receptor occupancy was observed in chlorpheniramine [68,70], such imaging might be useful in predicting the adverse effects of sedative antihistamines. Furthermore, histamine and the H1 receptor are also known to regulate the level of food intake, body mass, and adiposity [71,72]; it has been

cautioned that H1 antihistamine users had a higher odds ratio for being overweight [73]. Thus, histamine is essential for maintenance of activities of daily living produced by histaminergic neural excitation, and we should keep in mind that antihistamines with high brain penetration, including older first-generation antihistamines, will impair the daily activities of patients.

Impairment of innate immune responses only by first-generation antihistamines

Infection is a major causal agent of skin allergies, including urticaria and atopic dermatitis [74–76]. St. Peter *et al.* [77] reported that prescription of diphenhydramine, a first-generation antihistamine, to children undergoing surgery for a perforated appendix significantly increased the risk of postoperative abscess, suggesting that first-generation antihistamines increase the susceptibility of infection. Metz *et al.* [78] validated the effects of diphenhydramine and desloratadine, a more recent nonsedating second-generation antihistamine, on innate

immunity using a mouse model of septic peritonitis. It is striking that administration of diphenhydramine impaired morbidity in septic peritonitis, whereas desloratadine has no such effect. Notably, a lack of influence on the morbidity of peritonitis model using H1 receptor-null mice clearly indicated that diphenhydramine affected morbidity through some other pathway apart from H1 receptor-mediated signaling [78^{••}]. Thus, although the detailed mechanism is unclear, older first-generation antihistamines potentially exacerbate skin allergies via increased risk of infection.

Conclusion

Antihistamines are well known therapeutic agents for improving the itch symptom or flare caused by the release of histamine from various types of cells, including mast cells and basophils. Actually, both older first-generation and more recent second-generation antihistamines reduce these symptoms successfully. However, the effects of these two types of antihistamine on daily living crucially differ from each other. From recent studies that evaluated patient QoL, we should focus on improving patients' activities involved in daily living, rather than merely decreasing symptoms of allergic diseases. From this perspective, second-generation antihistamines are recommended as a first-line treatment for skin allergies. In addition to H1 receptor antagonism, basic research on the function of second-generation antihistamines has revealed their unique properties, such as amelioration of ancillary symptoms found in skin allergies. Evaluation of reproducibility of such characteristics of these antihistamines in clinical practice should be performed in the future, and such information will contribute to improvements in both the status of antihistamines in the management of skin allergies and, most of all, patients' activity involved in daily living.

Acknowledgement

This work was supported by Health and Labour Sciences Research Grant of Japan.

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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