

Article Type: Letter to the Editor

TITLE PAGE

Letter to the Editor

Olopatadine, a non sedating H1 antihistamine, decreases the nocturnal scratching without affecting sleep Quality in atopic Dermatitis.

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Running head: Effects of antihistamine on nocturnal scratch and sleep quality in atopic dermatitis

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/exd.12630

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Abbreviations: AD, atopic dermatitis; VAS, visual analog scale; OH, Olopatadine hydrochloride; SPT, sleep period time

Keywords: antihistamine; scratching; sleep quality; atopic dermatitis; electroencephalogram

Background

Itching is the unpleasant sensation that compels the urgent desire to scratch. The act of scratching is a skin specific behavior incited by itching in several skin inflammatory disorders particularly in atopic dermatitis (AD). Scratching exacerbates the dermatitis process by promoting the expression of various chemical mediators in the skin, and thus it is the major therapeutic target in AD (1). Histamine from mast cells can stimulate nociceptors and is the best-known mediator of itch in humans. Blockade of histamine receptors, especially H1, and inhibition of mast cell degranulation are crucial for the therapeutic control of itch in human skin diseases. The effect of H1 antagonists in urticaria, a disease caused by mast cell-derived histamine, is well known.

Question addressed

The mechanism of AD-associated itch is complex and there is limited evidence on the effect of H1 antagonists on itching. Suppression of pruritus in AD by the H1-receptor antihistamine fexofenadine has been previously reported (2). However, itch has been evaluated by visual analog scale (VAS) without an objective measuring system.

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Experimental design

In the current study, we investigated the effect of an oral antihistamine on VAS and nocturnal scratching in patients with AD using a modified wristwatch-type scratching counting system detecting small scratching sounds from fingertip at wrists (Appendix S1) (3). We have also analyzed the sleep quality by simultaneous recording of electroencephalogram (Alice LE Diagnostic Sleep System, Philips Respironics, Murrysville, Pennsylvania).

Twenty volunteers with moderate to severe AD were enrolled and randomly divided into two groups in a double-blinded manner. Half of the subjects received the oral antihistamine, Olopatadine hydrochloride (OH: Allelock[®] 5 mg tablet, Kyowa Hakko Kirin, Tokyo, Japan), and the remaining half only placebo prepared in an identical capsule (Appendix S2, S3). OH is a second-generation non-sedating antihistamine that is used to treat allergic disorders including urticaria, rhinitis, and AD in Japan (4, 5). Measurement of scratching duration and electroencephalogram recordings were performed on day -2 and -1 and then the subjects started taking 5mg of oral OH or placebo twice daily from day 1 to 7. Measurement of scratching duration and electroencephalogram recordings was repeated on day 7. Using this system, although the subjects put the sensor on their wrist and head, they can freely move and scratch the skin unconsciously in bed. The scratching sound and brain activity were recorded from the time of light-off and analyzed from 23:00 to 6:00, and the ratio of scratching duration to sleep period time (SPT), abbreviated as scratching ratio, was calculated at every ten minutes.

Results

Recordings of the scratching ratio of the twenty AD patients on day -1 depict an undulating slope shortly after the first sleep, around 2 o'clock, and then early in the morning (Fig. 1a). The subjects' itching sensation, as evaluated by VAS, was decreased from day -1 to day 7 in the OH-treated group ($p < 0.05$ Wilcoxon signed rank test), but not in the placebo group (Fig. This article is protected by copyright. All rights reserved.

1b). Scratching from 23:00 to 6:00 was decreased in some treated subjects without significance, but not in the placebo group (Fig. 1c). The scratching ratio in treated group improved from 3:00 to 6:00 without significance (Fig. 1e) compared to the placebo group, but not that of from 0:00 to 3:00 (Fig. 1d).

On the electroencephalogram recording, we focused on the N3 stage that represents the deepest stage of sleep or slow-wave sleep. There were no differences in the N3 to SPT ratio between the treated and placebo groups from day -1 to day 7 (Fig. 2a). The arousal index, the frequency of awaking during SPT, also showed no difference by therapy (Fig. 2b). Other factors also showed no significant change (Fig. S1, S2).

Conclusions

Scratching physically impairs the epidermal keratinocytes and releases inflammatory cytokines (IL-1 β , IL-18, TNF- α) (6-8). The persistent release of IL-1 from injured keratinocytes causes arteriosclerosis, heart involvement and amyloidosis (9). Therefore, itch and scratch control is a required for AD therapy. The current study revealed effects of OH for itch by VAS evaluation, and scratching behavior of AD in part. The present scratch sound detection system has enough sensitivity to differentiate scratching of AD patients (3). AD is a disease with tissue remodeling and long history, and patients shows habitual scratching. Different from previous report (2), we performed no topical therapies in this study. However, OH successfully controlled itch, but scratching movement imperfectly. Discrepancy between the subjective judgment of itch and objective judgment of scratching is known in AD (Appendix S4). Suppression of scratching was suggested during 3:00 to 6:00am, but the variation of the scratching time was not small from 0:00 to 3:00 in the individuals, probably due to bigger changes in sleep depth at first sleep cycle. After becoming sleep depth stable, the response of OH might be more detectable and evident even in a limited number of the subjects. Drowsiness and impairment of sleep quality is a major concern for antihistamine

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therapy. In fact, old sedating antihistamines affect the quality of sleep including REM phases (Appendix S5, S6). Interestingly, no increase in the N3 to SPT ratio nor decrease in the time of sleep onset was observed using a second-generation non-sedating antihistamine.

As the current study enrolled a small number of subjects, further evaluation should be performed in a larger population to confirm these findings. In brief, this is the first study showing that a second-generation antihistamine has beneficial effects in itch and scratching behavior in AD patients without affecting sleep quality.

Acknowledgements

(Appendix S7)

Author contributions

KY, EM, YN, KU, ECG and HM designed the study, analyzed the data and wrote the paper.

KY, EM, YN, KU, TM, KUT, YO, KI, MK, KT, MO performed the experiments. KY and KU performed the statistical analysis.

Conflicts of interest

YN and HM have a patent (4162620) for the sound-based system that can detect movements in humans and experimental animals. KY, KU and HM received financial support from Kyowa-Hakko-Kirin for this project. KY, YO and HM has received honoraria for being a speaker for Kyowa-Hakko-Kirin.

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Figure legends

Figure 1. Scratching behavior in AD patients. (a) Recordings of scratching time from 20 AD patients on day -1 were collected every 10 minutes and calculated the scratching ratio by dividing actual scratching duration by 600 seconds (=10 minutes), revealing a undulating slope shortly after the first sleep, around 2 o'clock, and early in the morning. (b) The volunteers' itching sensation evaluated by VAS was significantly decreased from day -1 to day 7 in the OH treated group ($p=0.02$), but not in the placebo group ($p=0.56$). (c) The scratching ratio is calculated by dividing scratching duration on day -1 by that of day 7. Decreased scratching behavior was not observed during the whole night (from 23:00 to 6:00) in the group taking antihistamines. The ratio was not suppressed from 0:00 to 3:00 (d), but it was from 3:00 to 6:00 (e).

Figure 2. Electroencephalogram recordings in AD patients. (a) We investigated the possibility the antihistamine influences on the duration of deepest sleep stage or slow-wave sleep. The ratio of N3 to the sleep period time (SPT) was unchanged in the two groups. (b) Arousal index was also unchanged.

Figure 1.

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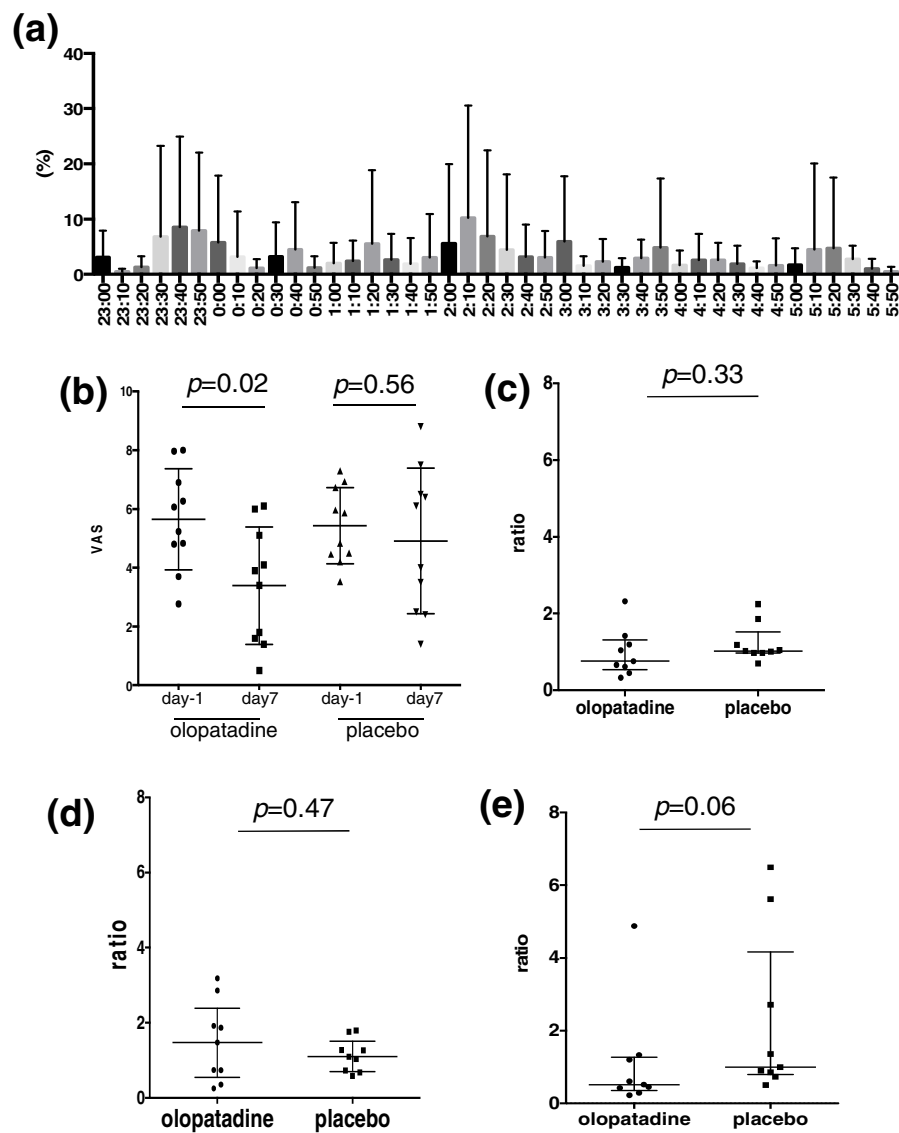


Figure 2.

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