

Efficacy of a 5-HT_{1A} receptor agonist in atopic dermatitis

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Summary

Background. Atopic dermatitis (AD) can be aggravated by mental stress. We recently showed that pretreatment with tandospirone citrate (TC), a serotonin (5-HT) agonist for the 5-HT_{1A} receptor subtype, significantly inhibits stress-induced degranulation of mouse dermal mast cells.

Aims. To evaluate the efficacy of TC in treatment of AD.

Methods. Changes in anxiety levels, depression symptoms and the clinical severity of AD after administration of TC were examined. Data were collected for 20 patients with AD who received TC 30 mg/day for 4 weeks and 17 patients with AD who did not receive the drug. Profile of Mood States (POMS) scores were used to measure several types of mental stress. Severity of AD was evaluated using the SCORAD Index, and the patients' level of stress and sleeping status were evaluated using visual analogue scales.

Results. Before TC administration, all scores were markedly different in the 37 patients compared with 37 normal healthy controls matched for age and gender. POMS scores for tension–anxiety (T-A) and the SCORAD Index decreased significantly in patients who received TC, but did not change significantly in the untreated patients. The two groups had significantly different treatment responses based on changes in T-A scores. There was a significant correlation between changes in the T-A score and SCORAD Index.

Conclusion. These data suggest that anxiolytic drugs such as 5-HT_{1A} agonists are useful in the clinical management of stress-associated aggravation of AD. Inhibition of stress-induced mast cell degranulation may be one of the mechanisms underlying the clinical efficacy.

Introduction

Atopic dermatitis (AD) is a chronic recurrent skin disease. The chief symptoms are persistent itching and eczema. Mental stress in patients with AD is thought to increase itching and scratching, which then aggravate skin symptoms,¹ and this process may produce new stress, leading to a vicious cycle. The mental state of patients with AD has been investigated previously with

psychological tests, and the results have shown that patients with AD have significantly more anxiety and depression than healthy people,^{2,3} and that the extent of these conditions has a positive correlation with the severity of itching⁴ and the lesional skin area.² It has also been shown that standard AD treatment improves emotional stress and skin symptoms.⁵

Psychological interventions may play a key role in AD treatment, but few studies have investigated the effects of such interventions. Linnet *et al.*⁶ found that psychotherapy in patients with AD with a high anxiety level is likely to improve their psychological and dermatological status, and Hashizume *et al.*⁷ found that tandospirone citrate (TC), a serotonin (5-hydroxytryptamine, 5-HT)-1A receptor (5-HT_{1A}R) agonist,⁸ has an effect on the anxiety score of the State Trait Anxiety Inventory

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(STAI) score in patients with AD and has a parallel effect in improving itching. We have shown that mental stress and foot-shock stress enhance degranulation of skin mast cells in a mouse model of stress^{9,10} and that TC inhibits this degranulation.¹¹ In the current study, improvements in skin symptoms and insomnia corresponding to changes in psychological profile were assessed in patients with AD during TC administration.

Methods

Study design

The study was conducted as a randomized controlled trial in subjects who were inpatients or outpatients at our department. The details of the study were explained to the patients in accordance with the rules of the ethics committee of Nippon Medical School, and informed consent was obtained from all patients.

In total, 37 subjects (24 men, 13 women; mean age 28.3 years, range: 18–37) were enrolled in the study. The subjects were randomized using the envelope method into two groups. In the treatment (TC) group, 20 patients (14 men, 6 women; mean age 29.6 years) were given a 10-mg TC tablet orally three times a day for 4 weeks. The other 17 patients (10 men, 7 women, mean age 26.9 years), who formed the untreated group, were not given TC. Mental state was analysed by the Profile of Mood States (POMS) and a visual analogue scale (VAS) for awareness of stress and insomnia. Skin status was assessed by the SCORing Atopic Dermatitis (SCORAD) Index at the start of the study and 4 weeks later in both groups. Patients with marked depressive symptoms or a history of depression were excluded. If patients were already using oral antihistamines or topical corticosteroids, they were allowed to continue with them. Benzodiazepine anxiolytics, antidepressants and antipsychotics were prohibited because of their possible influence on the evaluation.

Analysis of mood states, severity of atopic dermatitis and awareness of mental stress and insomnia

The mood states for the previous 3 days were assessed using the Japanese edition¹² of the POMS,¹³ which comprises 65 questions that are answered by the subject, based on self-assessment. The questions are separated into six scales: tension–anxiety (T-A), depression–dejection (D), anger–hostility (A-H), fatigue (F), confusion (C) and vigour (V). The POMS scores for the six scales were determined for all 37 patients with AD (AD group). Standard scores for the six scales for 37 healthy controls

(imaginary subjects) were estimated using a mood profile conversion table with separate gender and age rankings, which is based on analysis of a large number of healthy volunteers.¹² POMS scores were compared between the two groups.

The AD conditions of each patient were assessed by two doctors using the SCORAD Index¹⁴ at the start and on completion of the study. A VAS was used to assess mental stress and insomnia. Subjects indicated their level of mental stress on a scale bar from 1 (no sense of stress) to 10 (intolerable sense of stress) at the start of the study and at completion (4 weeks later). Similarly, the subjects indicated their level of insomnia for the previous 3 days on a VAS from 1 (slept very well) to 10 (could not sleep at all).

Statistical analysis

POMS scores were compared between patients with AD and the healthy controls using the Student *t*-test. Comparisons of changes from baseline values and intergroup comparisons of changes in each score between the TC and untreated groups were performed by one-way ANOVA. Spearman rank correlation coefficients were calculated between changes in clinical severity and mental parameters, and the correlations were analysed by the Shapiro–Wilk test. $P < 0.05$ was considered significant.

Results

Mood profile of patients with atopic dermatitis

POMS scores for the T-A ($P < 0.01$), D ($P < 0.01$) and F ($P < 0.001$) scales were significantly higher and that for the V scale was significantly lower ($P < 0.05$) in the AD group compared with the respective standardized scores estimated from a mood profile conversion table with separate gender and age rankings compiled for a large number of healthy controls.¹² A tendency for higher POMS scores for the A-H (NS) and C ($P = 0.05$) scales was seen in the AD group (Fig. 1).

Changes in Profile of Mood States scores after tandospirone citrate administration

There were no significant differences in mean POMS score, SCORAD Index or VAS score between the TC and untreated groups at the start of the study. There was a significant decrease in mean POMS score (T-A scale) for the 20 patients with AD who received TC 30 mg/day (TC group: change -2 , $P < 0.05$), but a non-significant

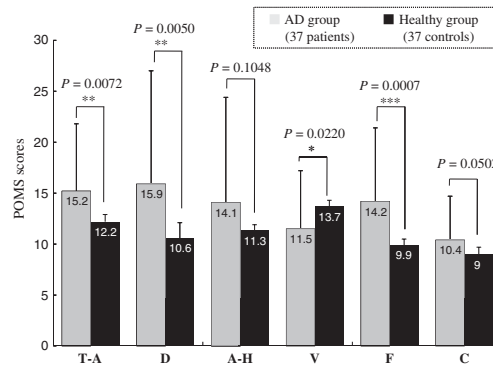


Figure 1 Profile of Mood States (POMS) scores for patients with atopic dermatitis (AD) and healthy controls. The scores for tension–anxiety (T-A), depression–dejection (D) and fatigue (F) were significantly higher in the 37 patients with AD than in the 37 normal healthy controls matched for age and gender. Similarly, the score for vigour (V) was much lower in patients with AD. Those for anger–hostility (A-H) and confusion (C) were higher in patients with AD, but the difference was not significant. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

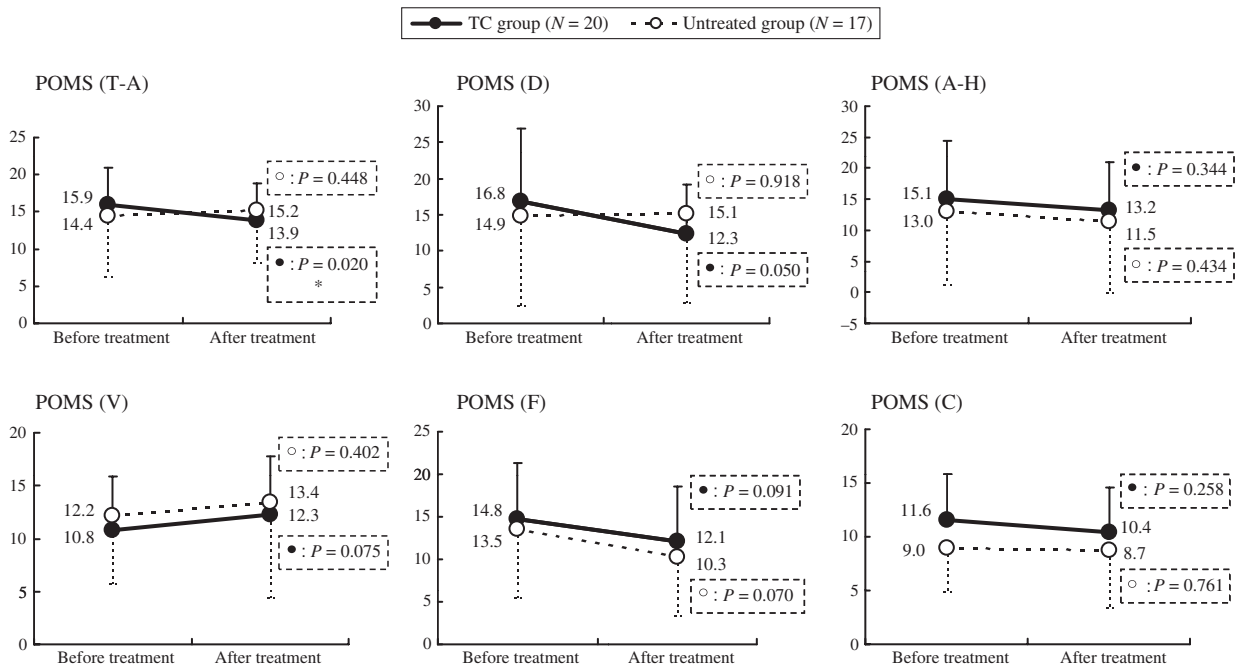


Figure 2 Changes in Profile of Mood States (POMS) scores for patients with atopic dermatitis (AD) after treatment with tandospirone citrate (TC) for 4 weeks. Twenty patients received TC 30 mg/day for 4 weeks (TC group) and 17 did not receive the drug (untreated group). POMS scores for tension–anxiety (T-A) and depression–dejection (D) decreased markedly in the TC group after treatment, whereas the untreated group did not show significant changes. POMS scores for vigour (V) and fatigue (F) found a tendency to change in the TC group, but the difference was not significant. Other psychological symptoms (anger–hostility: A-H and confusion: C) did not change significantly in either group. * $P < 0.05$.

increase in the 17 patients who did not receive TC (untreated group: change + 0.2). The change in the TC group was less than that in the untreated group ($P < 0.05$). The TC group had a tendency towards improvement in the D, V and F scales, but without statistical significance, and the A-H and C scales had almost no change from before to after administration (Fig. 2).

Changes in SCORAD Index and visual analogue scales after tandospirone citrate administration

There was a significant decrease in the SCORAD Index after 4 weeks for the TC group (before treatment 49.6, after treatment 36.4, change -13.2 ; $P < 0.001$), but not in the untreated group (before treatment 44.5, after treatment 37.9, change -6.6 ; NS). The change in the

TC group was greater, but the difference between the two groups was not significant. The VAS scores for awareness of mental stress showed a tendency to decrease in the TC group after 4 weeks (before treatment 5.95, after treatment 4.54, change -1.41 ; NS), but did not change in the untreated group (before treatment 5.11, after treatment 5.09, change -0.02 ; NS); the differences between the two groups were not significant. The VAS scores for insomnia also showed a tendency to improve in the TC group after 4 weeks (before treatment 5.04, after treatment 3.90, change -1.14 ; NS), but there was almost no change in the untreated group (before treatment 3.52, after treatment 3.16, change -0.36 ; NS), and the difference between the two groups was not significant.

Association between changes in clinical severity and mental parameters after tandospirone citrate administration

Changes in the SCORAD Index after TC administration significantly correlated with changes in the POMS scores for the T-A scale ($r = 0.50$; $P < 0.05$), but not with those for the D scale ($r = 0.31$; NS) or other mental parameters over the course of treatment.

Discussion

When stress responses present as behavioural responses, fight, flight and subordination are engaged in the mood and emotions of anger and frustration, fear and anxiety, and depression, respectively.¹⁵ The POMS includes almost all the emotions and moods that are induced by a stress response, and therefore can be used for assessment of various stresses.¹³ Stress response induces emotional changes such as reduced activity, frustration, fatigue and anxiety, and further stress finally leads to depression.

The results of the current study show that patients with AD have less vigour than healthy people and are likely to feel fatigued, to have marked anxiety and tension, and to experience severe depression. These findings suggest that patients with AD have chronic long-term stress. Several studies using other psychological tests have found similar results, and these characteristics are considered to reflect the common psychological and mental profile of patients with AD.^{2,3} Clinically, mental stress is seen as an aggravating factor in skin disorders including AD. Neuroimmunological and neuroendocrinological studies have shown that the central stress response system is closely related to the local stress response system in skin.¹⁶ Specifically,

activation of neurohormones by mental stress occurs largely via the hypothalamic–pituitary–adrenal axis, with subsequent upregulation of key stress hormones such as corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone and glucocorticoids. Immune responses are profoundly altered via these stress-related hormones and by additional stress response mediators such as neuropeptides or neurotrophins, and mast cells in skin are one of the most important participants in these responses.¹⁶ Stressors also stimulate the sympathetic nervous system, releasing norepinephrine and favouring a tilt toward a T-helper 2 immune response and distortion of the regulatory immune mechanism, resulting in protracted atopic allergy.¹⁷

The effects of stress suggest that psychological intervention is likely to be useful as a part of AD treatment. Our goal was to relieve mental stress in patients with AD and to concurrently improve skin condition by treatment with TC, an effective 5-HT_{1A} agonist that has been used as an antidepressant and anxiolytic agent.¹⁸ TC was given to patients with AD at a normal dose (30 mg/day) for 4 weeks, which resulted in significant improvement of anxiety and depression, concurrent reduction of stress and insomnia, and marked improvement of clinical severity assessed using the SCORAD Index. There was a significant correlation between changes in the SCORAD Index and those in POMS scores for T-A. This suggests that treatment with TC may have improved skin symptoms of patients with AD, partially through a psychological intervention. However, intergroup difference in the SCORAD Index between the TC group and the untreated group was definite but not significant, which may be due to the limited sample size for statistical analysis. Therefore, large-scale trials with an adequate sample size for statistical assessment are necessary for further studies.

Serotonergic neurones are distributed in the midline region of the brain and the raphe nuclei, and project their axons over wide regions of the brain. These neurones are reported to have a particular presence in the septohippocampal system and are involved in development of anxiety.⁸ TC acts on postsynaptic 5-HT_{1A} receptors in the limbic system, and exhibits a selective anxiolytic effect by inhibiting the increase in serotonergic nerve activity.

There are two possible mechanisms for the effects of TC on skin. The first is secondary inhibition of skin inflammation through TC-mediated regulation of the stress response in the brain. Studies in mouse and rat have shown that a variety of types of stress induce mast-cell degranulation mediated by neuropeptides and neurotransmitters including substance P (SP),

neurotensin (NT), calcitonin gene-related peptide (CGRP) and CRH.^{9,10,19,20} We have recently shown that pretreatment with TC significantly inhibits stress-induced degranulation of mouse dermal mast cells,¹¹ and these findings suggest that improvement of skin symptoms by TC in patients with AD is associated with inhibition of degranulation of skin mast cells. A placebo effect on mental stress is also possible, and may have improved the negative emotions of the patients, thus both this and the drug actions of TC may have contributed to the clinical improvement.

The precise mechanism of the influence of inhibition of central nerve activity on the peripheral mast cell response is not fully understood, but direct or indirect blockage of production of neuropeptide mediators and neurotransmitters in the central nervous system may be important in improvement of emotional disturbance.¹⁹

The other possible mechanism for the effect of TC is through local action in skin. 5-HT is synthesized by keratinocytes, melanocytes, Merkel cells and fibroblasts.^{21,22} A variety of 5-HT receptors, including 5-HT_{1A}R, is expressed on these cells and may be involved in skin inflammation and cell proliferation. Release of histamine from a human mast-cell line is reduced by 8-hydroxy-2-di-n-propylamino-tetralin, a 5-HT_{1A}R agonist,²¹ and buspirone, another 5-HT_{1A}R agonist, diminishes the severity of contact allergy in animals.²³ Therefore, TC may have a direct agonistic effect on receptors on dermal mast cells and other inflammatory cells. However, the sites of action of TC require further study.

AD and psoriasis are exacerbated by mental stress, and our clinical findings are consistent with an abnormal distribution of dermal nerves and enhanced degranulation of mast cells.^{24,25} Our findings suggest that anxiolytic agents may be an alternative treatment strategy for stress-aggravated skin diseases.

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