

ORIGINAL ARTICLE

Evaluation of the antihistamine effects of olopatadine and levocetirizine during a 24-h period: A double-blind, randomized, cross-over, placebo-controlled comparison in skin responses induced by histamine iontophoresis

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ABSTRACT

The antihistamine effects of olopatadine and levocetirizine, in standard-dose application described in their information (5 mg twice a day for olopatadine; 5 mg once daily for levocetirizine), were examined from 11.5 to 24 h after application. The test was designed in a double-blind, randomized, cross-over, placebo-controlled study of 12 healthy volunteers on histamine-induced flare and wheal response using an iontophoresis technique. The suppressive effect of olopatadine on the wheals induced by a 0.1-mA histamine iontophoresis lasted for 24 h after dosing. Both drugs inhibited flare induced by histamine iontophoresis almost completely until 24 h after the first administration. Suppression of the 0.2-mA-induced wheal response by levocetirizine, taken once daily, decreased with time, although 0.1-mA-induced flare was almost completely suppressed by the drug. Olopatadine completely suppressed even the wheal response induced by a 0.2-mA histamine iontophoresis. Compared with the placebo, the two drugs significantly suppressed the subjective itching assessed by visual analog scale at all intervals. There were no significant differences in subjective drowsiness and objective cognitive function between drug- and placebo-treated subjects. These results demonstrate that olopatadine seems to be more potent than levocetirizine when administrated in a standard dose. In conclusion, mild to moderate urticaria could be controlled by standard application as described in their information. On the other hand, severe urticaria could be managed by a standard application of olopatadine, but levocetirizine may need an additional dose to control severe urticaria.

Key words: antihistamines, flare, histamine iontophoresis, levocetirizine, olopatadine, wheal.

INTRODUCTION

In urticaria, histamine acting on H_1 receptors, induces local vasodilatation and edema to cause the wheal and stimulates sensory nerves to cause pruritus and the surrounding neurogenic flare. Because these histamine-related symptoms provoke the urge to scratch, often impairing the quality of life (QOL), measures to suppress and control these symptoms are required.¹ It would be expected that H_1 antihistamines should be very effective in relieving the symptoms of urticaria. It is well known that first-generation antihistamines, such as chlorpheniramine and diphenhydramine, while relieving allergic symptoms, cause central nervous system-related side-effects such as sedation and impaired psychomotor performance. Second-generation antihistamines were developed to reduce these adverse effects.² Third-generation H_1 antihistamines are the active enantiomer or metabolite derivatives of second-generation

drugs intended to have increased efficacy with fewer adverse drug reactions.³

Olopatadine hydrochloride (olopatadine), one of the second-generation non-sedating antihistamines, is used for urticaria, rhinitis and atopic dermatitis in Japan as an oral application and is also used for allergic conjunctivitis worldwide as a topical application.^{4,5} It also has an inhibitory effect on the release of inflammatory lipid mediators, such as leukotriene and thromboxane, from human polymorphonuclear leukocytes and eosinophils.⁶ It was proven to be more potent and stable with regard to its antihistaminic effects in skin responses compared to other commonly used second-generation antihistamines in a double-blind, randomized controlled study.⁷

Levocetirizine hydrochloride (levocetirizine) is a third-generation, long-acting, selective peripheral histamine H_1 receptor antagonist. Levocetirizine is the active R-enantiomer of the racemate cetirizine. Although the clinical implications of the

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enantiomer purification of the cetirizine molecule are still not entirely well understood, levocetirizine is the active part of the molecule which carries most of the affinity and selectivity for the H₁ receptor. The binding configuration of the dextrocetirizine molecule, that is, the inactive enantiomer, is not optimal for it to have meaningful antihistaminic activity and is, therefore, not useful as a drug.⁸

Olopatadine and levocetirizine have proven efficacies in the treatment of chronic spontaneous urticaria,^{6,8} but levocetirizine was just approved in Japan in 2011 without any clinical trials in Japan. So, we would like to know the effectiveness of these two drugs in urticaria. While the best way to compare the clinical efficacy of both drugs is to perform head-to-head studies, these are expensive and have ethical and logistical problems. Iontophoresis is a non-invasive method of histamine application used to induce an inflammatory skin response (wheal/flare). It is reliable and useful to compare the antihistamine effects of different drugs,^{7,9} even in a relatively small-sized study. In this study, we examined the antihistamine effects of the two drugs, in healthy subjects using the iontophoresis technique in accordance with the current manufacturer's recommended doses described in their information. Our aim in this study was to observe the suppression of histamine-induced skin responses at late phase (from 11.5 to 24 h after the first dose), with iontophoresis of different currents (0.1 and 0.2 mA), which represents mild or severe wheals/flare. Moreover, the effects of the two drugs on drowsiness, objective cognitive function and suppression of itching were also examined as secondary end-point.

METHODS

Subjects

A total of 12 healthy adult volunteers (eight men and four women) aged 22–55 years (mean, 39.3 ± 10.3) participated in the study. Subjects were excluded if they had taken any antihistamines or corticosteroid (oral/topical) within 7 days prior to participation. The study was approved by the Medical Ethics Committee, School of Medicine, Aichi Medical University (approval no. 11-088). Written informed consents were collected from all subjects prior to participation.

Study design

The study was performed in a double-blind, randomized, cross-over and placebo-controlled manner. Testing for each treatment was separated by a washout interval of at least 7 days. The study design and evaluation with histamine iontophoresis is shown in Figure 1. Subjects received active or placebo treatment at 21.00 hours and at 09.00 hours the following morning. A pantethine 30 mg formulation (pantetheine) was used as a placebo. The dosing schedule was as follows: olopatadine 5 mg twice daily and levocetirizine 5 mg once daily. For levocetirizine, the first dose was active and the second placebo. To maintain blindness, olopatadine hydrochloride, levocetirizine and pantethine were put into commercially available opaque gelatin capsules by a controller who was not involved in the wheal/flare measurement, drowsiness or cognitive function

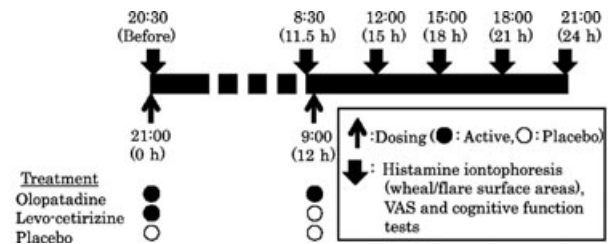


Figure 1. Study design. Each subject was given three kinds of treatment. Each treatment was separated by a washout interval of at least 7 days. Measurement of the wheal/flare areas induced by histamine iontophoresis, assessment of itching, drowsiness (visual analog scale, VAS) and objective cognitive function (typing test) were performed before administration and at 11.5, 15, 18, 21 and 24 h after administration.

tests. The capsules were swallowed along with water. The controller assigned the treatment and kept the key code undisclosed until the study was complete.

Histamine-induced wheal/flare response

Histamine prepared as a 1% solution was administered on the volar surfaces of the forearms using an iontophoreser (UI-2060; BS Medical, Tokyo, Japan).⁷ The electrode had a tip diameter of 10.0 mm. Current was applied for 60 s at 0.1 mA to the right arm and at 0.2 mA to the left. Iontophoresis was performed at 0 h (before dosing) and 11.5, 15, 18, 21 and 24 h after the first dose was given. Fifteen minutes after induction, wheal/flare areas were traced onto a thin transparent plastic sheet, and the area was measured using Image J software (National Institutes of Health, Bethesda, MD, USA).

Effects on itching and drowsiness

Subjective itching and drowsiness was evaluated by visual analog scale (VAS). Assessments were undertaken at 0 h (before dosing) and 11.5, 15, 18, 21 and 24 h after the first dose. The VAS was graded from 0 (no drowsiness) to 100 (excessive drowsiness).

Effects on objective cognitive function

The effects on objective cognitive function were assessed based on typing speed and accuracy using typing training software, MIKA TYPE.⁷ Assessments were undertaken at 0 h (before dosing) and 11.5, 15, 18, 21 and 24 h after the first dose. At each assessment, the numbers of characters typed and errors made per minute were recorded in triplicate and the mean values representing typing speed and accuracy were used for analysis.

Statistical analysis

Homoscedasticity between groups was tested by Levene's method. Non-parametric statistics (Steel-Dwass, Excel Statistics; SSRI, Tokyo, Japan) was used to assess the statistical differences between the three study groups – placebo, olopatadine and levocetirizine – and $P < 0.05$ was accepted as a statistically significant difference. Numerical data are shown as

mean $\pm$ standard error of the mean (SEM). All statistical analysis, except Steel–Dwass test, was done using SPSS software (SPSS, Chicago, IL, USA).

RESULTS

Skin responses (0.1 mA)

Suppression of the 0.1-mA iontophoresis-induced wheals was compared between the drugs and the placebo (Fig. 2a). Compared with the placebo, levocetirizine and olopatadine significantly suppressed the wheals at all time points (from 11.5 to 24 h after the first dose). Olopatadine completely suppressed the wheals from 15 to 24 h. Wheal suppression by levocetirizine began to decline at 18 h, resulting in a significant difference from olopatadine in wheal area after 21 and 24 h.

Compared with the placebo, olopatadine and levocetirizine significantly suppressed the flares up to 24 h (Fig. 2b).

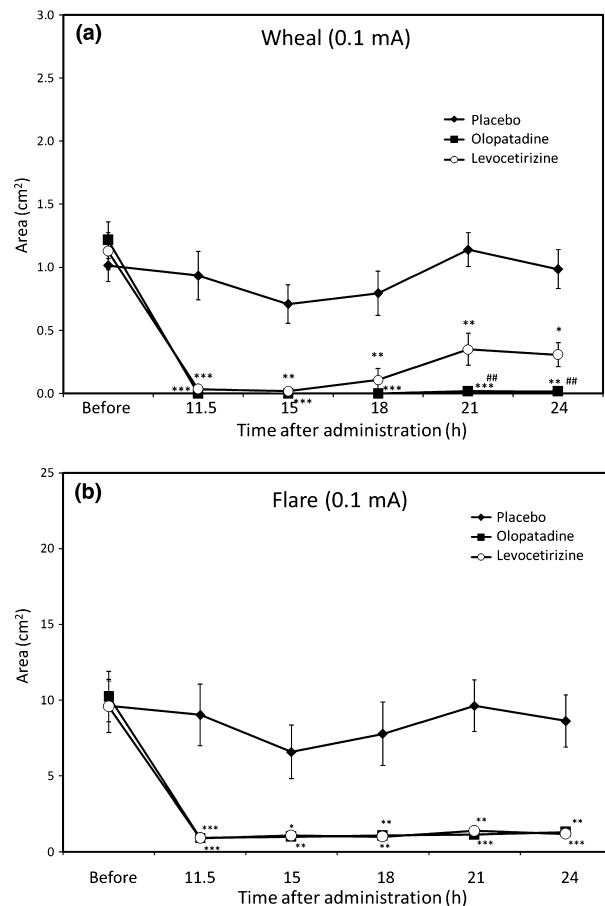


Figure 2. Suppression of 0.1-mA iontophoresis-induced wheals (a) and flares (b) by antihistamines ($n = 12$). Data are presented as mean $\pm$ standard error. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs placebo; # $P < 0.05$, ## $P < 0.01$ vs levocetirizine.

Skin responses (0.2 mA)

Suppression of the 0.2-mA iontophoresis-induced wheals was also compared between the administered drugs and the placebo (Fig. 3a). Compared with the placebo, olopatadine and levocetirizine significantly suppressed the wheals after 11.5 h. Although the histamine load had been increased with the 0.2 mA current, olopatadine completely suppressed the wheals from 15 to 24 h after the first dose with 0.2-mA induction. Wheal suppression by levocetirizine began to decline at 18 h, showing a significant difference from olopatadine from 21 to 24 h.

Compared with the placebo, the two drugs significantly suppressed the flares at all intervals (Fig. 3b). Significant difference was not shown in each administered drug.

Itching

The subjective itch intensity was assessed on a VAS. The itch score at 0 h before medication was almost the same (35.2–40.6). Compared with the placebo, the two drugs significantly

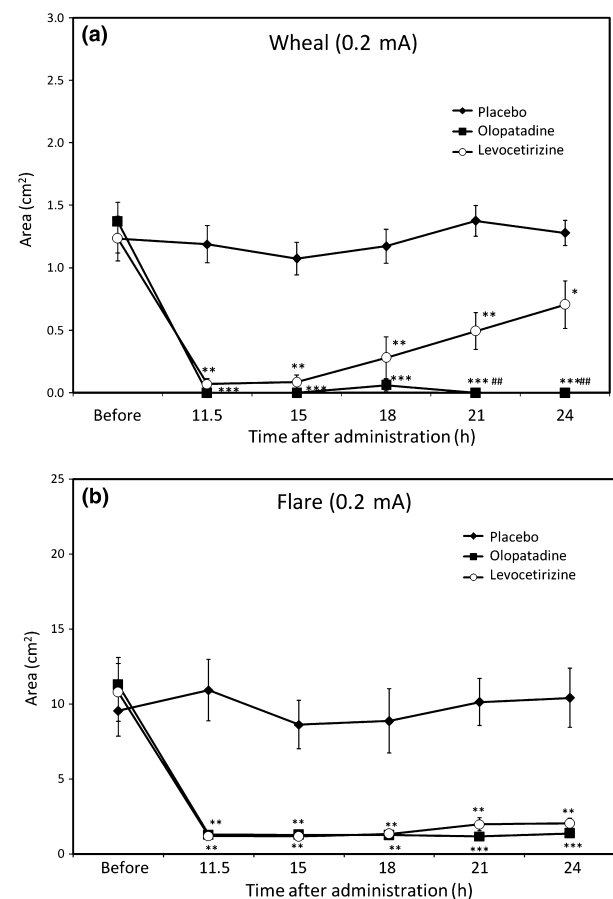


Figure 3. Suppression of 0.2-mA iontophoresis-induced wheals (a) and flares (b) by antihistamines ($n = 12$). Data are presented as mean $\pm$ standard error. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs placebo. ns, not significant.

suppressed the subjective itching assessed by VAS at all intervals (Fig. 4a). Significant difference was not shown between the two drugs, but reduction of itching by olopatadine was greater than that of levocetirizine (Fig. 4a).

Drowsiness

As shown in Figure 4(b), subjective drowsiness assessed by VAS at specified times showed no significant differences between the placebo and the two administered drugs.

Objective cognitive function (typing test)

Effects on objective cognitive function were assessed by typing speed and accuracy. No significant differences were noted in typing speed (characters typed per minute) between drugs and placebo at any time (Fig. 5a). As for typing accuracy (errors made per minute), there were also no significant differences between the drugs and the placebo at any time (Fig. 5b).

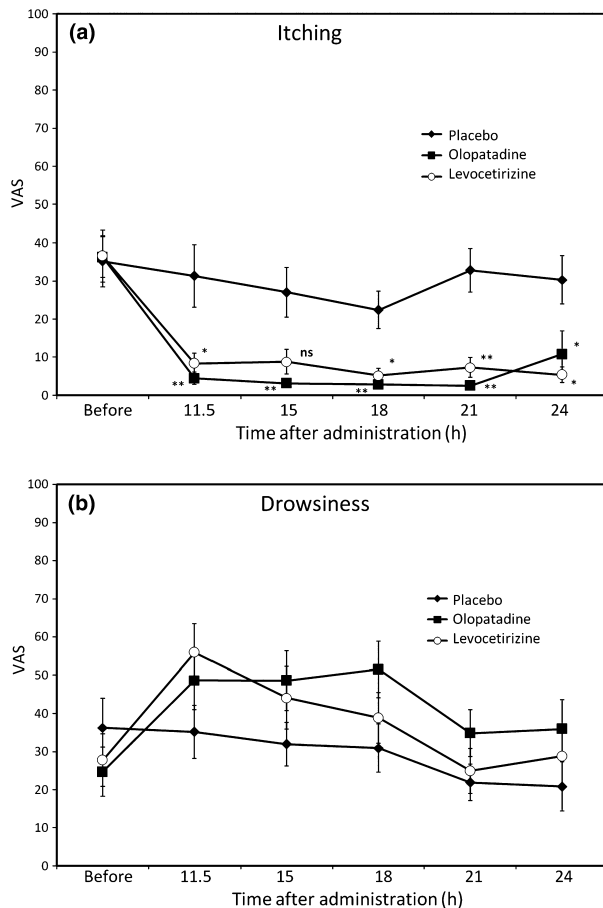


Figure 4. Visual analog scale (VAS) values of subjective itching (a) and drowsiness (b). Itching or drowsiness was evaluated with VAS scores: 0 (no symptoms) to 100 (excessive symptoms) in 12 subjects. Data are presented as mean $\pm$ standard error.

DISCUSSION

Urticaria, especially chronic spontaneous urticaria (CSU), is a difficult condition to treat. It is known to cause severe disability and impair a person's QOL, due to the interruption of sleep, fatigue, social isolation, energy loss and emotional/sexual difficulties.¹⁰ Though the second-generation antihistamines have been proved effective against acute and chronic urticaria, it remains a vexing problem as it often responds incompletely to treatment, and patients remain uncomfortable and perturbed by the chronic pruritus. So, it is important for the antihistamine drugs against chronic urticaria to have strong efficacy and sustainability, as well as mild adverse effects.²

In this study, olopatadine and levocetirizine were examined for the efficacy and duration of their antihistamine effects when administered in accordance with the manufacturer's recommended doses (the once daily formulation levocetirizine and the twice daily formulations olopatadine) by a double-blind, randomized, cross-over and placebo-controlled method. The efficacy of antihistamine effect was assessed by measuring the histamine-induced wheal and flare areas. The duration of the

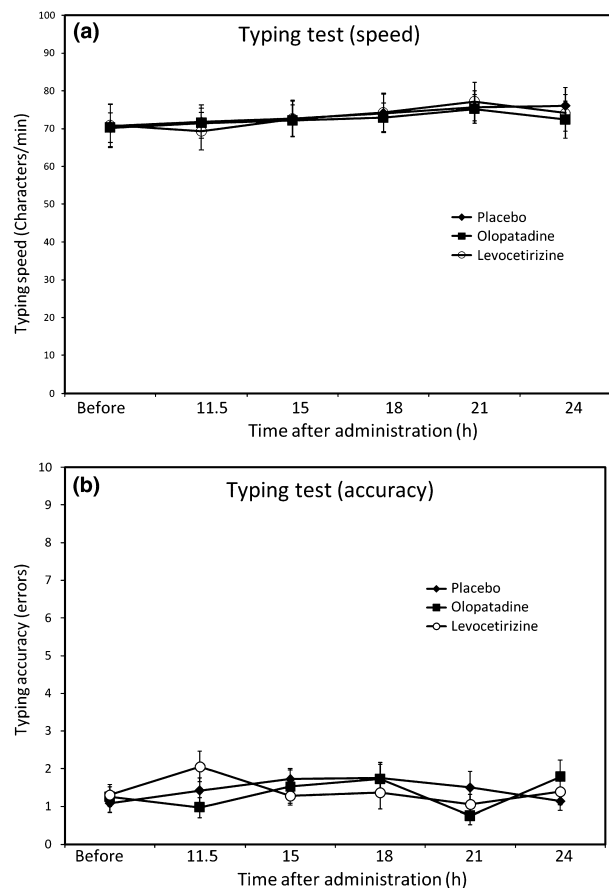


Figure 5. Effects of antihistamines on subjective cognitive function. Typing speed (a) and typing accuracy (b) were evaluated with typing training software in 12 subjects. Data are presented as mean $\pm$ standard error.

antihistamine effect, up to next dose, was determined by examining the wheals and flares at 3-h intervals from 11.5 to 24 h after the first dose. By iontophoresis, histamine challenge using a current of 0.1 mA was applied to obtain a model for moderate symptoms and a current of 0.2 mA was applied to obtain a model for severe symptoms.

Both drugs proved to be effective in suppressing the flare response even to the high histamine challenge, while suppression of the wheal response was different. Olopatadine completely suppressed the wheals induced by 0.1-mA histamine challenge throughout the study. On the other hand, suppression by levocetirizine began to decline at 18 h after drug administration, and there was a significant difference in the wheal suppression at and after 21 h between levocetirizine and olopatadine. These results may suggest that levocetirizine is likely to have reduced efficacy by the standard application.

The challenge tests with 0.2 mA histamine, providing models for severe symptoms, defined marked differences in suppression of the wheal response among these drugs. It was noteworthy that olopatadine proved to be a potent antihistamine, because it completely suppressed even 24 h after the wheal formation with 0.2-mA iontophoresis. The wheals were significantly larger with levocetirizine than with olopatadine after 18 h, and the effect of levocetirizine appears to decline at earlier phases after dosage in severe cases. These results indicate that adequate antihistamines should be prescribed for patients while considering the efficacy and duration of the antihistamine effect, especially in patients with severe symptoms. Very recently, an article¹¹ which supports our results has been published. The article, published by Kabashima's group, demonstrated that double dose of levocetirizine inhibited iontophoresis-induced skin reactions more strongly, more rapidly and more sustainably than a single administration of the drug.

The reasons for the difference between the efficacies of the two drugs is uncertain, but pharmacokinetic/pharmacodynamic information that is described in their information or in published papers may give suggestions on it. T_{1/2} of a single administration of 5 mg olopatadine and 5 mg levocetirizine in healthy subjects were 8.75 ± 4.63 h (mean $\pm$ standard deviation [SD])¹² and 7.33 ± 0.98 h (mean $\pm$ SD, described in the information for levocetirizine), respectively. This simply suggests that the efficacy of a single administration of 5 mg olopatadine should last longer than that of 5 mg levocetirizine. The antagonistic activities of olopatadine and levocetirizine were compared in receptor binding assay by Iwata's group.¹³ The authors demonstrated that K_i values of olopatadine and levocetirizine for the human H₁ receptor were 25 ± 3 and 160 ± 20 nmol/L (mean $\pm$ SEM) in phosphate buffer, respectively. Unfortunately, no other paper shows direct comparison of antihistamine activities of olopatadine and levocetirizine clearly shows biological equivalence of 5 mg levocetirizine to that of 10 mg cetirizine. Accordingly, their results, combined with pharmacokinetic data of the drugs, support stronger efficacy of olopatadine in a standard application described in their information. In addition, Sil *et al.*¹⁴ demonstrated the stronger efficacy of olopatadine than that of levocetirizine in urticaria patients by daily usage. Aside from wheals, it is well known

that itching associated with urticaria leads to substantially reduced QOL, limiting patients' daily activities and adversely affecting emotions, sleep, relaxation and performance at work.^{2,10} Thus, improvement of itching by antihistamine is very important. Compared with the placebo, both drugs significantly suppressed the itching induced by 0.1- and 0.2-mA histamine iontophoresis, but the effect of olopatadine seemed to be greater than that of levocetirizine, but not significantly. These results indicated that both drugs may improve QOL of urticarial patients by reducing itching associated with wheals.

Side-effects such as sedation and performance impairment are a major concern of antihistamine usage, especially if higher doses of drug were to be used in difficult cases of CSU.^{2,3,10} In this study, we did not observe any statistically significant effects with either drug on sedation and performance impairment. As this study was primarily designed to evaluate the efficacies of the drugs during 24 h, assessments were not made at the time point when drug concentration in the blood reached a maximum (0.9 h after dose for levocetirizine;⁸ 1.0 h for olopatadine).⁷ For olopatadine, however, their twice daily dosing schedule enabled us to assess drowsiness and cognitive function at 3 h post-dose (15 h after the first dose). It is noteworthy that the assessments at this time point showed no significant differences between olopatadine, levocetirizine and placebo, suggesting that drowsiness and performance impairment associated with medication are similar among the tested second- and the third-generation antihistamines. The minimal sedation by olopatadine would be explained by low H₁ receptor occupancy in the human brain measured by positron emission tomography with ¹¹C-doxepin in healthy subjects.¹⁵ The authors also demonstrated in another article that cetirizine, proven to be biologically equivalent to half dose of levocetirizine, occupied H₁ receptors in the human brain as much as olopatadine.¹⁶ Accordingly, the article also supports our results showing the minimal sedation of levocetirizine.

In conclusion, mild to moderate urticaria could be controlled by a standard application of olopatadine and levocetirizine as described in their information. On the other hand, severe urticaria could be managed by a standard application of olopatadine, but levocetirizine may need an additional dose to control severe urticaria. Further large clinical study will be needed to the compare clinical effectiveness of these drugs in the treatment of CSU.

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CONFLICT OF INTEREST: None declared.

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