

The Butterbur Extract Petasin Has No Effect on Skin Test Reactivity Induced by Different Stimuli: a Randomized, Double-Blind Crossover Study Using Histamine, Codeine, Methacholine, and Aeroallergen Solutions

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Abstract. *Background:* Petasin (Ze 339) was recently introduced on the market as a potent herbal antiallergic drug for treatment of respiratory allergies such as hay fever. Few clinical studies have been performed so far addressing the clinical effectiveness of Ze 339.

Objective: To evaluate the antiallergic properties of Ze 339 using skin prick tests with different stimuli, such as codeine, histamine, methacholine, and a relevant inhalant allergen.

Methods: A randomized, double-blind, placebo-controlled study was performed in which Ze 339 was compared to acrivastine, a short-acting antihistamine, in 8 patients with respiratory allergy and in 10 nonatopic, healthy volunteers. Antiallergic activity of Ze 339 was determined by analyzing inhibitory potency in skin prick tests with codeine, histamine, methacholine, and an inhalant allergen. Wheal-and-flare reactions were assessed 90 minutes after a double dose of Ze 339, acrivastine, or placebo. An interval of at least 3 days was left between the skin tests.

Results: Acrivastine was identified as the only substance that significantly inhibited skin test reactivity to all solutions analyzed in all study subjects. In contrast, no significant inhibition could be demonstrated for Ze 339 with any test solution. Moreover, the results of Ze 339 did not differ significantly from placebo.

Conclusions: In this study we found no antiallergic, particularly antihistaminic, effect of Ze 339 in skin tests using a variety of stimuli often used to evaluate immediate skin test reactivity. The mechanism by which Ze 339 is effective in the treatment of seasonal allergic rhinitis still needs to be elucidated.

Key words: Petasin. Ze 339. Herbal drug. Acrivastine. Antiallergic drugs. Skin prick test. Wheal-and-flare reaction

Resumen. *Antecedentes:* Recientemente se ha empezado a comercializar Petasin (Ze 339) como potente fitofármaco antialérgico para el tratamiento de la alergia respiratoria, como la fiebre del heno. Pero hasta el momento se han realizado pocos estudios clínicos para demostrar la eficacia clínica de Ze 339.

Objetivo: Evaluar las propiedades antialérgicas de Ze 339 mediante pruebas de punción cutánea (prick) con diferentes estímulos como la codeína, la histamina, la metacolina y un aeroalérgeno pertinente.

Métodos: En este estudio controlado con placebo y con doble ciego, se comparó de forma adicional Ze 339 con acrivastina, un antihistamínico de acción corta, en 8 pacientes con alergia respiratoria y en 10 voluntarios sanos no atópicos. La capacidad antialérgica de Ze 339 se determinó mediante el análisis de la actividad inhibidora en prick respecto a codeína, histamina, metacolina y un aeroalérgeno. La reacción se determinó al cabo de 90 minutos de haber ingerido una dosis doble de Ze 339, acrivastina o placebo. Entre cada prueba cutánea, se dejó un intervalo de al menos 3 días.

Resultados: La acrivastina fue la única sustancia que inhibió de forma significativa la reactividad a las pruebas cutáneas realizadas con todas las soluciones analizadas en todos los participantes incluidos en el estudio. En cambio, no se pudo demostrar una inhibición significativa causada por Ze 339 en ninguno de los extractos ni soluciones usados en las pruebas. Asimismo, los resultados obtenidos con Ze 339 no difirieron de forma significativa de los resultados obtenidos con placebo.

Conclusiones: En este estudio no se pudo demostrar ningún efecto antialérgico, especialmente antihistamínico, de Ze 339 mediante pruebas cutáneas con diferentes estímulos usados habitualmente para evaluar la reactividad inmediata a las pruebas cutáneas. La eficacia de los mecanismos de Ze 339 en el tratamiento de la rinitis alérgica estacional todavía está por demostrar.

Palabras clave: Petasin, Ze 339. Fitofármaco. Acrivastina. Fármaco antialérgico. Prueba cutánea

Introduction

Petasin (Ze 339), an extract of the butterbur plant *Petasites hybridus*, has been approved by the Swiss government agency Swissmedic as an antiallergic drug (Tesalin; Zeller AG, Romanshorn, Switzerland) to treat seasonal allergic rhinitis. To control allergic symptoms, the intake of 2 tablets of Tesalin (8 mg) per day is recommended. So far, 2 studies have suggested a clinical efficacy of Ze 339 in subjects with pollen allergic rhinitis. In a study by Schapowal [1], the clinical effect of Ze 339 was compared with that of cetirizine and improvement was similar in the 2 treatment groups of 125 patients. However, clinical outcome over a 2-week study period was based on a questionnaire (SF-36), and Ze 339 was given 4 times a day (a total of 32 mg). In a more recent study, the same author evaluated Ze 339 against fexofenadine [2]. That study also used subjective criteria as efficacy indicators and no difference was found between the 2 drugs studied. Lee et al [3] recently measured peak nasal inspiratory flow after adenosine monophosphate challenges and did not find significant flow differences between subjects receiving petasin at a dose of 50 mg twice daily and those receiving 180 mg fexofenadine once daily. To date, most studies published suggest an antiallergic effect of butterbur or butterbur products [2, 3, 18]. However, the mechanisms of action of Ze 339 have not been clarified.

The aim of this study was to assess the effectiveness of Ze 339 in reducing wheal skin reactivity induced by substances known to trigger mast-cell activation leading to degranulation, and to determine whether or not Ze 339 has antihistaminic activity. In order to obtain the most potent effect of Ze 339, the dose chosen for testing corresponded to 16 mg of petasin.

Material and Methods

Study Subjects

The study included 10 healthy volunteers (7 women and 3 men) with a mean age of 43 years (range, 20-63 years) and 8 otherwise healthy patients (2 women and 6 men) with a mean age of 39 years (range, 28-59 years) with seasonal allergic rhinoconjunctivitis for several

years. Seven of those patients were allergic to grass pollen and 1 to ash tree pollen. At the time of testing, no patient experienced hay fever symptoms. The study protocol was approved by the local ethics committee of the University of Bern. The study participants were thoroughly informed by the study investigators by written text as well as verbally, and all gave signed informed consent.

Study Design

A randomized, double-blind, cross-over study was performed in which each participant received 2 tablets of either Ze 339 (8 mg), acrivastine (8 mg), or placebo according to the randomization code. The washout interval between each test period was at least 3 days. Randomization and blinding of the test drug substances prepared in capsules were done in the laboratories of Zeller AG, Romanshorn, Switzerland. The participants and investigating doctors were not able to distinguish between the drugs tested either by shape or flavor. Participants were not allowed to drink or eat for 90 minutes before and after the intake of the drugs. All skin tests were performed 15 minutes before and 90 minutes after each test drug intake. In every participant, skin prick tests were performed with codeine phosphate, histamine HCl, and methacholine chloride. In the allergic patients, we also tested an inhaled allergen (grass or ash pollen). Side effects were recorded if mentioned; in addition, participants were specifically asked about side effects before a new test was started.

Skin Test Substances and Test Dilutions

The following test substances were used: 9% codeine phosphate (Stallergènes SA, Antony, France), 0.2% histamine HCl (Allergopharma, Reinbek, Germany), 9% methacholine chloride (Pharmacy, Inselspital, Bern, Switzerland) and for pollen allergic subjects the appropriate pollen allergen (grass or ash; Allergopharma). The following test concentrations diluted with 0.9% sodium chloride were used for testing: codeine, 9%, 3%, and 1%; histamine, 0.2% and 0.02%; methacholine, 9% and 3%; grass or ash pollen allergens, 50 000 therapeutic units (TU) per mL and 5000 TU/mL.

Skin Testing

Test solutions were applied on the volar side of both forearms of each study participant according to the guidelines of the European Academy of Allergology and Clinical Immunology [4] using a standardized prick needle (Stallerpoint, Stallèrgenes, Antony, France). Before the intake of any test drug, skin tests were done on the right arm, with test concentrations running from high to low in a proximal to distal arrangement. After administration of the test drug, tests were performed in the same sequence

and alignment on the left forearm. Tests were not performed during the pollen season and participants were not allowed to use concomitant drugs such as corticosteroids, antihistamines, cromoglycates, or leukotriene antagonists.

Assessment and Documentation of Skin Test Reactivity

Wheal-and-flare reactions were documented 15 minutes after test application. A transparent adhesive tape

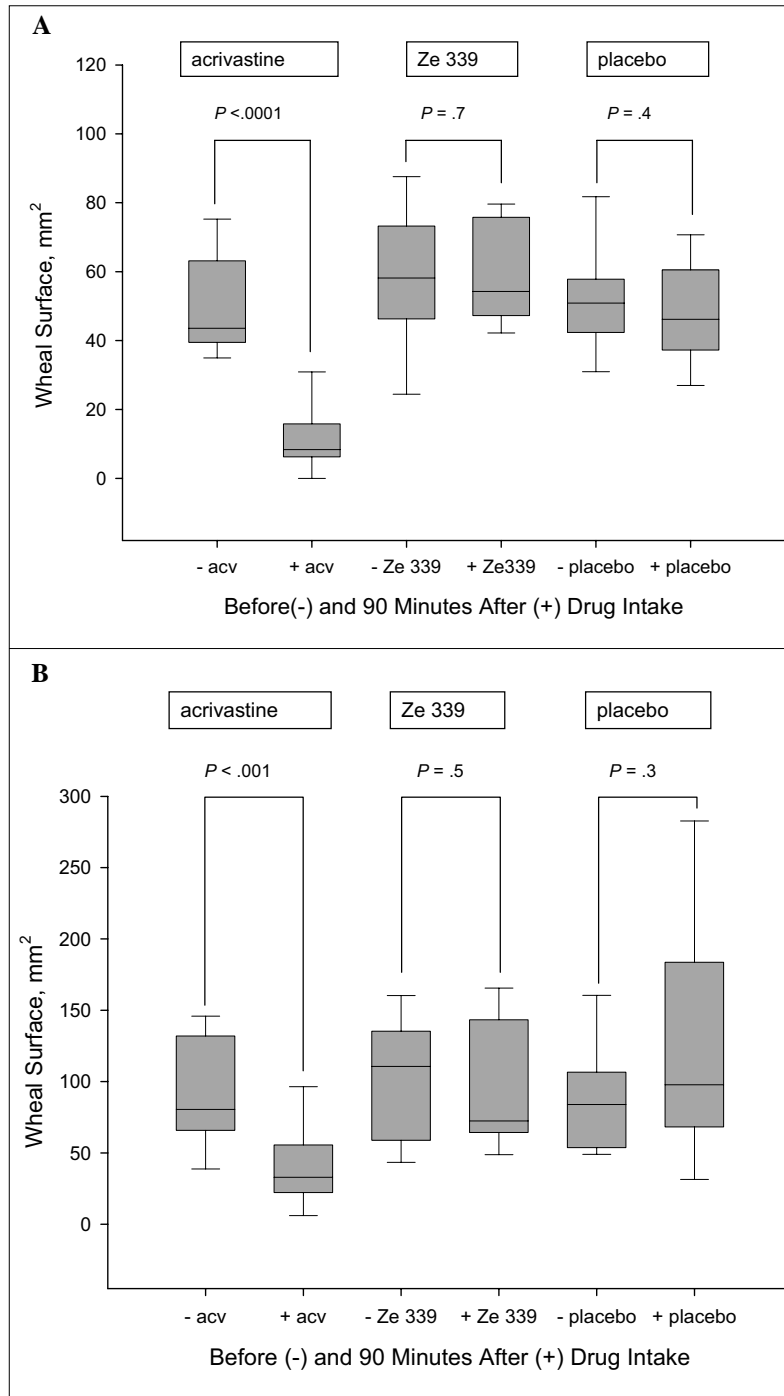


Figure 1. Inhibition of wheal reaction induced by A) 9% codeine and B) pollen allergen—both mast-cell dependent mediators—90 minutes after intake of Ze 339, acrivastine (acv), and placebo in 18 subjects.

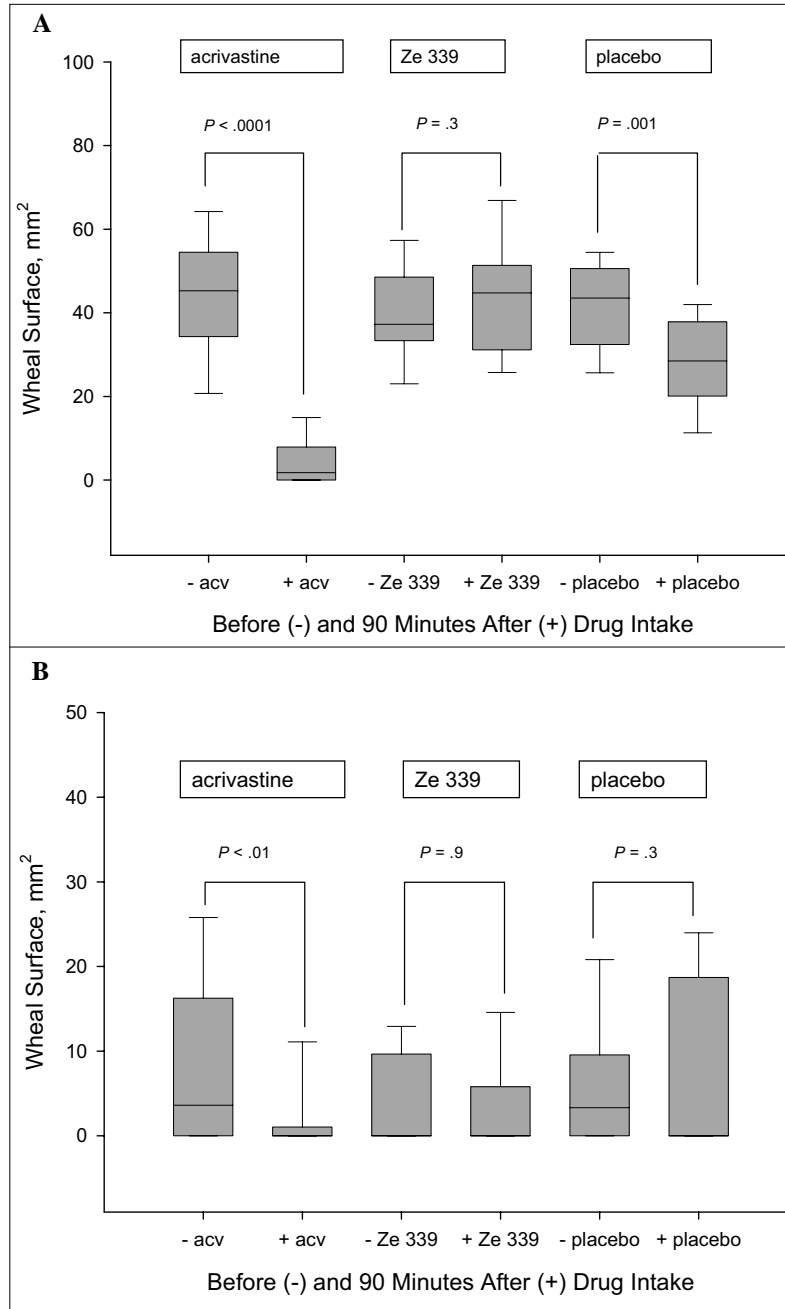


Figure 2. Inhibition of wheal reaction induced by A) 0.2% histamine and B) 9% methacholine—both mast-cell independent mediators—90 minutes after intake of Ze 339, acrivastine (acv), and placebo in 18 subjects.

was put on the pen-marked skin wheal-and-flare reaction 15 minutes after prick testing and then removed gently. The surface area of the skin reactions were measured using a computer-aided design program (AutoCAD LT2005, Autodesk GmbH, Munich, Germany).

Statistical Analysis

Statistical analysis was performed by paired *t* test using the SigmaPlot 8.0 program (Statistical Solutions Ltd, Cork, Ireland). A *P* value of less than .05 was considered statistically significant.

Results

All 18 study subjects completed the study. No adverse drug reaction after any study medication was reported. After breaking the code, 8 participants (4 healthy and 4 allergic) received Ze 339, 5 (4 healthy and 1 allergic) received acrivastine, and 5 (2 healthy and 3 allergic) received placebo as the first test drug.

Skin Test Results

Baseline skin test reactivity—15 minutes before any

test drug intake— did not differ significantly during the test phase days ($P > .37$ for wheals and $P > .25$ for flares). Differences in wheal size induced by 9% codeine and pollen allergens according to the test drugs used are shown in Figure 1. Figure 2 shows skin reactivity to 0.2% histamine and 9% methacholine. Compared with baseline skin test reactivity, wheal-and-flare reactions did not differ significantly following Ze 339 intake, irrespective of the test solution and concentration used (codeine [9%, $P = .7$; 3%, $P = .7$; 1%, $P = .2$]; pollen allergen [50 000 TU/mL, $P = .5$; 5000 TU/mL, $P = .5$]; histamine [0.2%, $P = .3$; 0.02%, $P = .3$]; methacholine [9%, $P = .9$; 3%, $P = .2$]).

In 4 subjects, placebo intake resulted in a significant inhibition of the wheal reaction induced by 0.2% histamine (40 mm² vs 28 mm², $P = .001$) and the flare reaction induced by 3% codeine (542 mm² vs 352 mm², $P = .004$). Since similar but not significant skin test variability in response to other substances was noticed in these subjects before and after placebo, this effect is probably due to artifacts of the test procedure.

Wheal-and-flare reactivity to each test substance at each test dilution was significantly reduced with acrivastine (1%-9% codeine, $P < .0001$; pollen allergen [50 000 TU/mL, $P < .0001$; 5000 TU/mL, $P < .05$; 0.2%-0.02% histamine, $P < .001$; methacholine [9%, $P < .01$; 3%, $P < .05$]).

Discussion

Pollen allergic rhinitis is primarily an IgE-mediated disease. Allergic symptoms commonly arise within minutes of mast cell degranulation, which causes instant release of histamine, leukotrienes, and other mediators. Most drugs that effectively suppress acute allergic rhinitis or rhinoconjunctivitis counteract the active substances released by cells that are responsible for symptoms. This mast cell activation process can be simulated by skin tests with allergen solutions, a method that is considered the main tool for diagnosing IgE-mediated allergies [4-6]. Skin tests with allergens and nonspecific, mast cell-derived substances have been used to demonstrate the effectiveness of antiallergic drugs, especially antihistamines [7-12].

Ze 339 has been compared exclusively to potent, highly effective antihistamines such as cetirizine and fexofenadine, and similar effectiveness of Ze 339 has been observed [1, 2]. However, the mechanism of action of Ze 339 has yet to be elucidated. Both an antihistaminic action and an inhibitory effect on leukotriene synthesis have been suggested [13, 14]. Our results, based on skin test reactivity to allergens and specific mast-cell activating substances, show that Ze 339 has no antihistaminic effect.

To date, there has been no definitive consensus regarding the recommended dose of Ze 339 for the treatment pollen allergic rhinitis. In most studies, the dose of Ze 339 for comparing clinical effectiveness with an antihistamine exceeded the officially recommended dose of 16 mg per day [1, 2, 15]. In order to obtain an optimal

effect on skin test reactivity, we performed the study with 2 tablets of Ze 339 (8 mg) provided at the same time. Acrivastine, a short-acting antihistamine that is also effective in allergic rhinitis [16, 17], was also administered at a double dose, since this is recommended for treatment in the case of an allergic emergency situation [11, 16, 17]. While acrivastine had a clear inhibitory effect on all test substances, irrespective of the concentration applied, no effect was seen with Ze 339. Although it could be argued that the time period of 90 minutes between intake and testing was too short, the pharmacokinetics of petasin uptake and the reported relief of symptoms within 90 minutes suggest that the time period was appropriate [18].

Skin test reactivity to methacholine and histamine, both substances that affect tissue cells and nerves rather than acting directly on mast cells, was not inhibited by Ze 339. Methacholine, a cholinergic agonist, usually induces a wheal-and-flare reaction if injected intradermally [19]. Although the exact mechanism is not clear, that study showed that histamine is not directly released from the tissue mast cells. In contrast, skin reactivity to both substances was significantly inhibited by acrivastine.

A possible explanation for the activity of Ze 339 is through an inhibitory effect on leukotrienes. Even though the release of leukotrienes through mast-cell activation has been experimentally and clinically demonstrated [20, 21], inhibition of immediate skin tests using histamine and allergen solutions with zafirlukast and montelukast failed [22-25]. In contrast, an effect of leukotriene antagonists on pollen allergic rhinitis has been shown in several clinical studies [26-31]. Montelukast and loratadine display a comparable clinical efficacy in reducing pollen allergic symptoms and improve quality of life parameters [28]. These findings led to the approval of montelukast for treatment of seasonal rhinitis in several countries. Thus, Ze 339 may act similarly to montelukast in allergic rhinitis symptoms but, to date, no study has compared Ze 339 with an antileukotriene compound, despite the hypothesis that Ze 339 mainly targets similar mediators.

In our study group, no adverse reactions were reported, irrespective of the test drug taken. This may be explained by the small study population. On the other hand, since each individual had to take 2 tablets of a test drug on 3 separate occasions in a double-blind study, it might be expected that at least some subjects would have complained of side effects such as sedation, dizziness, fatigue, or headache. Nevertheless, this result confirms that both Ze 339 and acrivastine are well tolerated and may exert only a minimal, if any, sedative effect [1, 10, 15, 17, 32].

In conclusion, Ze 339 does not appear to have an antihistaminic effect, and therefore, should not be compared with antihistamines. The mechanism underlying Ze 339 activity remains to be identified. Further studies are needed to locate this compound within the range of antiallergic treatments.

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