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Letter to the editor

Skin prick test results to artesunate in children sensitized to *Artemisia vulgaris L*

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Abstract

Artemisia vulgaris L and *Artemisia annua L* (Chinese: qinghao) are similar plants of the *Asterbaceae* family. Artesunate, a semi-synthetic derivate of artemisin which is the active principle extract of the plant qinghao, has antimalarial properties. Some cases of severe allergic reactions to artesunate have been described.

The purpose of this study was to evaluate the association between positive skin tests to *Artemisia vulgaris L* allergen and a preparation of injectable artesunate.

A total of 531 children were skin prick tested with inhalants (including *Artemisia vulgaris L*), foods, and artesunate.

Among the 59 patients positive to *Artemisia vulgaris L* only one child was also positive to artesunate. No child was positive to artesunate in those negative to *Artemisia vulgaris L*.

We conclude that *Artemisia vulgaris L* sensitization is not associated with sensitization to artesunate; consequently, skin test to artesunate should not be carried out before using the drug considering the rare allergic reactions.

Keywords

Artemisia vulgaris L, artesunate, children, skin prick tests

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Introduction

The antimalarial artemisin (Chinese: qinghaosu; belonging to the traditional Chinese medicine) is the active principle extract of the plant qinghao [*Artemisia annua Linnnaeus (L.)*]. This plant belongs to the family of *Asterbaceae* composed of more than 23,000 species. *Artemisia vulgaris L* (mugwort or common wormwood) is one of several species in the genus *Artemisia* and it is found mainly in Europe. *Artemisia vulgaris L* is very similar to *Artemisia annua L*.[1]

Antimalarial properties of this weed plant were discovered in China in 1972.

Because artemisin itself has physical properties, such as poor bioavailability, that limit its effectiveness, semi-synthetic derivates of artemisin have been developed. Two of these are artesunate (water soluble) and artemether (lipid soluble). The water soluble is used orally and by injection and the lipid soluble is used intramuscularly. In particular, artesunate is a highly efficacious and relatively safe antimalarial agent. Consequently, artesunate is the most widely used of these antimalarials worldwide.[2]

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According to a prospective study on 3500 patients, artesunate and artemether are both remarkably well tolerated.[3] Severe allergic reactions have been rarely reported with artesunate use.[4]

Severe allergic reactions to oral artesunate have been reported[4] as well as anaphylaxis to parenteral artesunate. Both events are extremely uncommon in spite of its widespread use. Literature search reveals only two case reports of anaphylaxis to intravenous artesunate.[5,6] It is poorly known whether allergic reactions to artesunate depend on cross-reactions to *Artemisia vulgaris L* and consequently whether subjects allergic to *Artemisia vulgaris L* are at higher risk of allergic reactions to artesunate. This hypothesis is biologically plausible since *Artemisia annua L* and *Artemisia vulgaris L* belong to the same genus. In the present study we evaluated in a pediatric population the association between positive skin tests to *Artemisia vulgaris L* allergens and a preparation of injectable artesunate.

Materials and methods

From September 2012 to February 2013, 530 children (mean age, 99 months; age range, 7–211 months; male to female ratio = 1.62) referred to the Allergy Unit of the Anna Meyer Children's University Hospital, were consecutively evaluated for suspected allergy to foods or inhalants.

In particular, 29% children had history of asthma, 20.7% children suffered from conjunctivitis and rhinitis, 13.6% children had rhinitis, 9.7% children had atopic dermatitis, and 10.6% children had history of reactions to foods.

Skin tests were performed and read after 10 min by the same investigator in order to avoid variability linked to the operator. We tested all children with common inhalants and foods (pollens, mites, molds, cat and dog epithelia, milk, albumen, soy, wheat, cod fish, peanut, latex; commercial extracts, at 0.1 mg/mL concentration Alk Abellò, Milan, Italy). The pollens tested were grass, olive, *Cupressus arizonica, Betula pendula* (birch), *Artemisia vulgaris* (mugworth), *Carpinus betulus*, and *Parietaria mix* (pellittory). Patients suspected to be allergic to nuts (i.e. almond, hazelnut, walnut) were tested with the culprit nut by using the prick-to-prick method. Skin prick tests were performed on the volar surface of the forearm by using a standard 1-mm tip lancet, according to the recommendations of the European Academy of Allergy and Clinical Immunology group.[7]

Positive controls for prick and prick-to-prick tests were performed with histamine (Alk-Abellò, Milan, Italy: 10 mg/mL concentration). Normal saline was used as a negative control of prick and prick-to-prick tests.

The skin prick test results were considered positive if the difference between the mean diameter of the wheal and the negative control was at least of 3 mm. Children had been off antihistamines or oral corticosteroids 10 days before skin testing.

Moreover, all children underwent skin prick test with artesunate (intravenous formulation), Guilin Pharmaceutical Co, Ltd., PR China) at 60 mg/mL concentration. Such a concentration was obtained by adding sodium bicarbonate at 5% to the vial. Given the fact that no previous studies had been published on skin prick tests to artesunate we decided to test the full strength concentration.[8]

Results

Three hundred and sixty-three (68.5%) out of 530 patients were skin test positive to one or more allergens (Table 1). Six patients were negative to inhalants but they were sensitized to food (two to milk, one to egg, one to almond, one to hazelnut, and one to walnut).

Among the 59 patients positive to *Artemisia vulgaris L* only one (1.7%) child was also positive to artesunate with a wheal diameter of 3 mm. On the other hand none was positive to artesunate in the group of children negative to *Artemisia vulgaris L*.

The child, sensitized to both *Artemisia vulgaris L* and artesunate, had a history of seasonal rhinitis and conjunctivitis, plus angioedema with almond and he was positive to almost all inhalants.

In the group of 59 patients (48 boys, 11 girls) sensitized to *Artemisia vulgaris L*, six children were monosensitized to such a pollen.

Moreover about half (27 children; 45.8%) of the 59 patients positive to *Artemisia vulgaris L* suffered from both seasonal rhinitis and conjunctivitis and 21 (35.6%) children had asthma.

Three out of 59 patients had an *Artemisia vulgaris* L wheal diameter >8 mm, in particular the only patient with a double positivity to both *Artemisia vulgaris L* and artesunate had an *Artemisia vulgaris* L wheal diameter of 8 mm.

Table 1. Inhalants and artesunate skin tests results.

Allergen	Positive children (n [%]) in the overall dataset (n = 530)	Positive children (n [%]) among allergic children (n = 363)
Dermatophagoides pteronyssinus	252 (47.5%)	252 (69.4%)
Dermatophagoides farinae	251 (47.5%)	251 (69.4%)
Grass pollen	232 (43.8%)	232 (63.9%)
Dog epithelium	157 (29.6%)	157 (43.2%)
Olive pollen	130 (24.5%)	130 (35.8%)
Cupressus arizonica pollen	127 (24%)	127 (35%)
Cat epithelium	122 (23%)	122 (33.6%)
Carpinus betulus pollen	71 (13.4%)	71 (19.6%)
Betula pendula pollen	69 (13%)	69 (19%)
Alternaria alternata	62 (11.7%)	62 (17.1%)
Artemisia vulgaris pollen	59 (11%)	59 (16.2%)
Parietaria mix	52 (9.8%)	52 (14.3%)
Horse epithelium	28 (5.3%)	28 (7.7%)
Rabbit epithelium	19 (3.6%)	19 (5.2%)
Cladosporium herbarum	8 (1.5%)	8 (2.2%)
Latex	3 (0.6%)	3 (0.8%)
Artesunate	1 (0.2%)	1 (0.3%)
Negative patients	167 (31.5%)	

Discussion

This is the first pediatric study about possible *in vivo* cross-reactivity between *Artemisia vulgaris L* and artesunate. According to our results there is no a correlation between the skin prick test to *Artemiasia vulgaris L* and the risk of being artesunate sensitized.

We studied the sensitization to artesunate in children sensitized to inhalants and in particular in the group of those sensitized to *Artemisia vulgaris L.* Fifty-nine out of 363 patients sensitized to inhalants were positive to *Artemisia vulgaris* but only one child had a double positivity to *Artemisia vulgaris* and artesunate, showing that our results were not affected by the fact that the study was carried out not in a random group of children, but in a group with an increased chance of a positive skin test.

According to the experience of Leonardi and co-workers,[9] 17,000 patients have been treated with artemisin derivatives but allergic reactions occurred in only six cases (out of them two children). The incidence of allergic reactions to artemisin derivatives was one out of 2833 treated patients. Such a low incidence of allergic reaction is in agreement with a recent paper showing the antiallergic properties of artesunate in mouse model.[10] In the publication by Leonardi and co-workers, all six patients had urticaria and in two cases, who also developed an anaphylactic reaction, epinephrine was required due to the severity of the reactions. Both patients had previously been prescribed artesunate.[9] In particular, the two children, who were treated with artemisin derivatives plus mefloquine, had urticaria, but it was not possible to prove a state of hypersensitivity because urticaria did not recur when using the drugs a second time.[3] The authors had not investigated the role of a possible Artemisia species sensitization. Anyway, artemisin derivatives should not be used to treat uncomplicated *Plasmodium falciparum* malaria if there is a previous history of allergic reactions after their use, or if an urticarial rash develops during treatment.

Dube et al.[5] and Mohapatra et al.[6] published case reports of anaphylaxis to intravenous artesunate administered to adults. Recently, adverse drug reactions to artesunate have been related to genetic polymorphisms of CYP 2A 6 as well as gender influence.[11]

The sensitization to *Artemisia vulgaris L* cannot predict the occurrence of allergy to artesunate, never mind the severity of possible reactions with the use of intravenous artesunate. Given the scarcity of reports on allergy to artesunate (fewer than 10 cases published in literature while more than 200 million treatment courses administered every year), we think that the presence of a positivity to artesunate should not be checked when intravenous administration with this drug is required, even considering that such an investigation is safe and very poorly

time-consuming. In the current literature, all patients who described having had a severe reaction to artesunate had not been previously investigated from an allergy point of view. However, since in high-endemic countries the World Health Organization[12] recommends artemisin-based combination treatments (ACTs) as the first-line therapy of uncomplicated malaria and intravenous artesunate for the treatment of severe malaria, limiting the use of a life-saving drug because of very rare possible occurrences of severe allergic reactions may be unreasonable. Therefore, careful reports of severe adverse events when administering intravenous artesunate may be more reasonably encouraged. In low-endemic countries, considering that parenteral artesunate is not currently available as manufactured under Good Manufacturing Practices and consequently is not registered by regulatory agencies, intravenous artesunate can only be administered in severe malaria with a very high parasitemia by expert physicians to reduce mortality in severe imported malaria cases.[13] In this setting, in our opinion, only in the rare subjects with a skin test positive to artesunate and a history of artemisin reaction, the intravenous use of such a drug should be carefully evaluated.

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