Research article/Raziskovalni prispevek

SAFETY OF VENOMENHAL® VENOM IN MAINTENANCE HYMENOPTERA VENOM IMMUNOTHERAPY

VARNOST PRIPRAVKA VENOMENHAL® ZA VZDRŽEVALNO IMUNOTERAPIJO BOLNIKOV, ALERGIČNIH ZA STRUPE KOŽEKRILCEV

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Arrived 2001-04-23, accepted 2001-06-26; ZDRAV VESTN 2001; 70: 531–3

Key words: *allergen extracts; Hymenoptera venom allergy; immunotherapy; safety*

Abstract – Background. *Venomenhal® (V) is a new brand of Hymenoptera venom allergen for diagnosis and immunotherapy of venom allergy. We studied the safety of switching the patients treated with other brands of venom to V.*

Methods. *We performed duplicate skin prick tests with V and ALK Reless® (R) venom extract (100 µg/ml) in 68 patients (50 males, 42 ± 15 years) on maintenance immunotherapy with honey bee (26) or wasp (42) venom. On two consecutive maintenance injection days 53 patients received in random order either 100 µg of R or V venom.*

Results. *Weal diameter in skin prick tests (mean ± st.dev.) were 3.9 ± 1.1 mm (V) and 4.1 ± 1.0 mm (R) for bee venom (NS) and 3.4 ± 1.0 mm (V) and 3.9 ± 1.2 mm (R) for wasp venom ($p < 0.01$). Local reaction 30 minutes after maintenance injection were 6.1 ± 1.7 cm (V) and 5.4 ± 2.5 cm (R) for bee venom (NS) and 5.1 ± 1.8 cm (V) and 6.1 ± 1.8 cm (R) for wasp venom ($p < 0.05$).*
Late local reactions (LLR) and tiredness (T) on the day of injection and 24 hours after injection were equally distributed among both groups and were mild (LLR on the day of injection: 38% of patients [V] vs. 43% [R]. LLR after 24 hours: 28% [V] vs. 28% [R]. T on the day of injection: 21% [V] vs. 23% [R]. T after 24 hours: 0% [V] vs. 6% [R]).

Conclusions. *V was at least as safe as A. There were no adverse reactions due to switching from one brand to another. Slightly but significantly smaller weal in skin prick tests and immediate local reactions might be due to lesser potency or better purification of V wasp extract.*

Ključne besede: *pripravek alergena; alergija za strupe kožekrilcev; imunoterapija; varnost*

Izvleček – Izhodišča. *Venomenhal® (V) je nov pripravek strupa kožekrilcev. Namenjen je za kožno testiranje in za imunoterapijo bolnikov, alergičnih za strup kožekrilcev (čebel, os, sršenov). Zanimalo nas je, ali je varno bolnike, ki so bili zdravljeni z alergenskim pripravkom drugega proizvajalca, prevesti na pripravek V.*

Metode. *68 bolnikom (50 moških, starost 42 ± 15 let), ki so bili vsaj eno leto zdravljeni z imunoterapijo s pripravkom čebeljega (26 bolnikov) ali osjega (42 bolnikov) strupa ALK Reless® (R), smo v dvojniku naredili kožne vbodne teste s pripravki V in R (100 µg/ml).*
Pri dveh zaporednih vzdrževalnih odmerkih je 53 bolnikov v slučajnem vrstnem redu dobilo 100 µg pripravka R ali V.

Rezultati. *Premer urtike v kožnem testu (srednja vrednost ± st.dev.) je bila 3,9 ± 1,1 mm (V) in 4,1 ± 1,0 mm (R) s strupom čebele (NS) ter 3,4 ± 1,0 mm (V) in 3,9 ± 1,2 mm (R) s strupom ose ($p < 0,01$). Premer lokalne reakcije 30 minut po vzdrževalnem odmerku je bil 6,1 ± 1,7 cm (V) in 5,4 ± 2,5 cm (R) po strupu čebele (NS) ter 5,1 ± 1,8 cm (V) in 6,1 ± 1,8 cm (R) po strupu ose ($p < 0,05$).*
Pogostost kasne lokalne reakcije (KLR) in utrujenosti (U) na dan injekcije in 24 ur po injekciji je bila enakomerno razporejena med obema skupinama bolnikov (KLR na dan injekcije: 38% bolnikov [V] proti 43% [R]. KLR po 24 urah: 28% [V] proti 28% [R]. U na dan injekcije: 21% [V] proti 23% [R]. U 24 ur po injekciji: 0% [V] proti 6% [R]).

Zaključki. *V je vsaj toliko varen kot A. Pri prehodu iz ene vrste alergenskega pripravka na drugega ni bilo pomembnih zapletov. Nekoliko, vendar pomembno manjši premer urtike pri kožnem vbodnem testu in manjši premer takojšnje lokalne reakcije, je lahko posledica manjše moči ali boljše prečiščenosti pripravka osjega strupa V.*

Introduction

About 0.4% of the population develop systemic allergic reactions after Hymenoptera insect stings (1). Specific immunotherapy is the treatment of choice for patients who experienced a severe systemic IgE mediated reaction after Hymenoptera insect sting (2). In different immunotherapy protocols a cumulative dose of 100 µg of venom is reached in few hours or days. Thereafter most patients receive 100 µg maintenance dose in 4–12 week intervals (3). Nearly complete tolerance was confirmed in sting challenge controlled study performed by Hunt (4). Immunotherapy is potentially dangerous because allergen material is injected into a sensitised person (5, 6).
The number of producers of aqueous venom extracts is rising. Patients moving from one immunotherapy centre to other might present a problem if centres are using different brands of extracts.
We studied clinical equipotency of two brands of aqueous venom extracts used for skin testing and specific immunotherapy.

Patients, material and methods

Patients

After informed consent 68 patients (50 males, 42 ± 15 years) were included into a prospective double blind crossover study. All patients were receiving venom immunotherapy with 100 µg maintenance dose of R for at least 1 year. 26 patients were treated with honey bee and 42 with wasp venom. No patient experienced systemic side effect in previous 6 months of immunotherapy.

Allergens

Commercial bee and wasp venom aqueous extracts Reless® (ALK) (R) and Venomenhal (HAL) (V) were used for skin prick testing and immunotherapy according to the instructions of the manufacturer.

Procedure

We performed duplicate skin prick tests with V and R venom extract (100 µg/ml) in all 68 patients. Albumin diluent for venom (HAL) was used as a negative control and histamine dihydrochloride 1 mg/ml (Allergopharma) as a positive control. Results were read after 20 minutes.The largest and perpendicular diameters of weal were measured and result expressed as a mean of 4 measurements (7).
On two consecutive maintenance injection days 53 patients (42 males) received in a random order either 100 µg of R or V venom. Patients were closely monitored for an hour for a possible immediate systemic reaction. Resuscitation equipment was stand by. After an hour a mean diameter of local reaction (redness) was measured. Patients were given a questionnaire, where they indicated local tenderness at injection site, tiredness and possible systemic reaction 6 and 24 hours after injection. Patients were also asked to measure the diameter of local oedema at injection site 24 hours after injection.
Study was approved by State ethic committee of Slovenia.

Statistical analysis

Results are shown as mean ± standard deviation. Possible differences between two venom extracts were calculated using paired t-test.

Results

All patients finished the study. Mean weal diameters in skin prick tests were significantly smaller when using V wasp venom compared to R wasp venom. There was no difference between both brands in skin tests with bee venom (Tab. 1). Also immediate local reaction 1 hour after maintenance injection were significantly smaller when using V wasp venom compared to R. There was no difference in immediate local reaction with bee venom (Tab. 1).

Tab. 1. *Results of skin prick tests and diameter of local reaction 1 hour after maintenance injection of 100 µg venom. R: Reless venom, V: Venomenhal venom.*

Tab. 1. *Rezultati kožnih testov in premer lokalne reakcije eno uro po vzdrževalnem odmerku 100 µg strupa. R: Reless, V: Venomenhal.*

Skin prick test weal diameter (mm) Premer urtike kožnega testa (mm)	R	V	p
Bee / Čebela	4.1 ± 1.0	3.9 ± 1.1	NS
Wasp / Osa	3.9 ± 1.2	3.4 ± 1.0	< 0,01
Local reaction 1 hour after injection (cm) Lokalna reakcija 1 uro po injekciji (cm)			
Bee / Čebela	5.4 ± 2.5	6.1 ± 1.7	NS
Wasp / Osa	6.1 ± 1.8	5.1 ± 1.8	< 0,05

Late local reactions and tiredness 6 hours after injection and 24 hours after injection were equally distributed among both groups and were mild (Tab. 2).

Tab. 2. *Presence of local tenderness, tiredness and oedema 6 and 24 hours after maintenance injection of 100 µg venom. R: Reless venom, V: Venomenhal venom.*

Tab. 2. *Prisotnost občutljivosti na mestu injekcije, utrujenosti in otekline 6 in 24 ur po vzdrževalnem odmerku 100 µg strupa. R: Reless, V: Venomenhal.*

	Bee / Čebela			Wasp / Osa		
Symptoms after 6 hours Simptomi po 6 urah	R	V	p	R	V	p
Tenderness at the site of injection Občutljivost na mestu injekcije	45%	32%	NS	49%	42%	NS
Tiredness Utrujenost	9%	9%	NS	32%	29%	NS
Symptoms after 24 hours Simptomi po 24 urah						
Tenderness at the site of injection Občutljivost na mestu injekcije	23%	23%	NS	32%	32%	NS
Tiredness Utrujenost	9%	0%	NS	3%	0%	NS
Local oedema Oteklina	14%	27%	NS	39%	42%	NS

There were no immediate systemic reactions, and no patients reported signs of systemic allergic reaction during next 24 hours.

Discussion

Immunotherapy with standardised extracts is relatively safe procedure (6). Before standardisation was accepted as a necessary procedure in allergen extract production, patients experienced systemic and even fatal reaction when switching from one batch of allergen extract to another and a diminish of a dose was proposed when changing from one batch to another. Nowadays the concentrations of allergen epitopes are held on the same level in every batch (8).
As a concentration of purified venom allergen is the same in the products of different pharmaceutical companies, we speculated that switching from one brand to another is possible

and safe. This is important as some patients move during immunotherapy to another immunotherapy centre, where allergen extract of different pharmaceutical company is used. Even in one center problem may arise as sometimes a pharmaceutical company is temporary unable to provide adequate supply of allergen.

To show biological equipotency of two venom extracts we performed comparative skin prick tests. Bee venom extracts were shown to be of identical biologic activity as they elicited weals of the same diameter. On the other hand, V wasp venom elicited slightly but significantly smaller weal diameter than R.

After getting information, that V doesn't have greater biological activity as R, we switched patients receiving R in a double blind manner to V. Patients were injected a single 100 µg dose. Dividing of the dose would diminish the risk of side effects and hide a possible disadvantage of V over R.

Similarly as in skin prick tests we didn't notice any difference in diameter of immediate local reaction after bee venom, but slightly and significantly smaller reactions after wasp venom. No patient experienced clinically significant immediate side effect when switching from a single injection of V back to R. A good tolerance might be due to equipotency of both venoms. On the other hand, most patients tolerate maintenance injection even if a single dose is skipped (9). The design of the study allowed us only to detect unsafety of switching to V in the case that V contained much more relevant allergen epitopes or other relevant epitopes than R.

To conclude, we showed that V was at least as safe as R in maintenance venom immunotherapy. In patients on stable maintenance immunotherapy there were no adverse reactions due to switching from R to V. Slightly but significantly smaller weals in skin prick tests and immediate local reactions might be due to lesser potency or better purification of V wasp extract.

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Stanko Pšeničnik, Oddelek za biomedicinsko tehniko, Splošna bolnišnica, Maribor

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