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EFFECTS OF BEE VENOM IN TREATMENT OF PATIENTS WITH RHEUMATIC DISEASES

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ABSTRACT

Amongst the toxic substances of nature, Honey Bee Venom (HBV) is an ancient remedy for many disorders, particularly arthritis, Recently this Kind of remedy is named* Apitherapy*. The encouraging therapeutic results obtained by healers who had practiced bee sting apparently revealed the same effects as the modern pharmaceutical therapy. Therefore HBV preparation such as Forapin and Apicosan Introduced to clinical medicine Prior to our original research for making a new model of electrical shock device (Bee

Venom Collector) and producing a topical preparation from HBV, as a pilot study we have examined straight honey bee sting on two volunteers who had suffered from arthritis.

At First all their medications were stopped for one week, and then the clinical features and Para clinical tests such as CRP, CBC, ESR, Rheumatoid factor (RF), Serum Cortisol and HLA B_{27} were carried out before and during the Apitherapy. It was commenced with one sting on the painful joint and continued up to 40 stings to the other inflamed joints during a period of 75 days. Pain relief, improvement of joint movement and Para clinical tests such as ESR and CRP were observed, the patients were able to leave the hospital without any difficulties. They were followed up to now. One of the patients who had Reiter's syndrome improved almost completely and has no other medication so far. The other patient because of the medical ethics and no availability of HBV preparations was then given Chloroquine phosphate. The original research is going on and the results will be given during the congress.

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KEY WORDS : HONEY BEE VENOM (HBV), RHEUMATIC DISEASES

APITHERAPY, IgG_4, PHOSPHOLIPASE A_2.

INTRODUCTION

Treatment with Honey Bee (Apis mellifica) Venom, has been claimed to be beneficial in Certain human arthritic diseases including rheumatoid arthritis (Komer, J. 1938 & Steigerwaldt, F.1966). Infarct, beekeepers during their occupation continuously exposed to Bee stings, gradually become accustomed to their effects and likewise never suffer from Rheumatism, arthritis or gout (Beck, 1938).

Devera, (1978) also demonstrated the effectiveness of bee venom in the prevention of inflammatory changes associated with the adjuvant induced rat arthritis

model. The result of a study by Steigerwaldt, et. al. (1966) in 50 patients suffering from either rheumatoid or degenerative forms of arthritis elicited 84% benefit rate in those injected with the bee venom. The mode of action of HBV in preventing and or / ameliorating the symptomatology associated with the degenerative and rheumatoid arthritis is unknown. However, many of it's pharmacological effects have been described. Rekka, et. Al., (1990) demonstrated that HBV inhibits non enzymatic lipid peroxidation and possesses a considerable hydroxyl radical (HO) scavenging activity, evaluated by its competition with dimethyl sulfoxide for HO. These results, relation to the in vitro suppression mainly for interleukin-1 (IL-1) production offered by HBV, may further support that antioxidant activity is involved in the anti-inflammatory activity of HBV. Although HBV has potent anti-inflammatory properties (Banks, et.al. 1976, Devera, 1978, & Lorenzetti, et.al. 1978) it's mode of action in rheumatic diseases is unknown.

Banks,et.al. (1976), has demonstrated that protein 401 (MCD-peptide) from HBV, has three important effects:

1. It is effective in adernalectomized animals, providing evidence that an elevation in Plasma cortisol level is not necessary for this material to be effective invivo.
2. It binds to leucocytes.
3. It blocks the synthesis of prostaglandin E_2.

Hugh, et. al. (1986) pointed out that MCD-peptide prevents the release of inflammatory mediators from leucocyte infiltrating an arthritic lesion. Shkendrov, et.al. (1982) demonstrated that on a molar basis Adolapin (a constituent of HBV) is about 70 times more potent inhibitor of brain cycloxygenase than the well known anti- rheumatic preparation

Indomethacin. This protein is also pharmacologic antagonists of prostaglandins with a therapeutic index (LD50 / ED50) about 5000.

As a pilot study the effects of straight honey bee stings were performed in two patients with rheumatic diseases.

MATERIALS AND METHODS

Two young patients who had suffered from arthritis were volunteers for Apitherapy. At first all of their medications were stopped for one week and then the clinical features and Para clinical tests were carried out before and during the Apitherapy. One of them was a 18 year old male that had suffered from Reiter's syndrome. He was received Indomethacin, for the last two years. Although Prednisolon and Sulfasalazine were added during the last six months, his right knee joint movement hindrance (4+), with a large inflammation about 2cm around his affected joint, in compare with his healthy knee. The second patient was a 24 year old male who had suffered from rheumatoid arthritis and has used Indomethacin without significant effect. Both patients were treated by direct honey bee (Apis mellifica) sting on the most painful joints and the time Intervals and were continued until 40 stings. The patients were followed up to now and were seen in the Rheumatic clinic at least once every two months.

RESULTS

Some haematological, biochemical and immunological findings before, during and after treatment are summarized in next pages tables.

	NORMAL RANGE	**BEFORE Apitherapy**	**DURING* Apitherapy**	**After Apitherapy**

HLA B_{27}	**±**	**+**	**+**	**+**
RF (LATEX)	**-**	**-**	**-**	**-**
CRP	**-**	**+**	**-**	**-**
ESR(mm/h)		**35**	**17**	**4**
Serum cortisol X 10^2 mg/L	**5 - 25**	**18**	**15**	**11**
RBC x 10^9	**0 – 15**	**5.6**	**5.67**	**7.5**
WBC x 10^6	**4.8 – 10.8**	**10.28**	**9.88**	**8.08**
PLT x 10^6	**130 – 400**	**368**	**277**	**270**
Baso %	**0.0 – 1.5**	**1.2**	**1.2**	**0.8**
EOS %	**0.0 – 7.5**	**2.4**	**0.4**	**7.5**
Neut %	**40.0 – 74.0**	**65**	**65**	**47.6**
Lymp %	**19.0 – 48.0**	**22**	**18.7**	**34.2**

Table 1. *The first patients biodata.*

** The middle point of Apitherapy period.*

	NORMAL RANGE	BEFORE Apitherapy	DURING* Apitherapy	AFTER Apitherapy
HLA B27	**±**	**-**	**-**	**-**
RF (LATEX)	**-**	**+**	**+**	**+**
CRP	**-**	**+**	**-**	**-**
ESR (mm / h)	**0 -15**	**26**	**13**	**3**
Serum cortisol x 10^2 mg / L	**5 - 25**	**14**	**10**	**10**
RBC x 10^9	**4.7 – 6.1**	**6.13**	**5.9**	**6.72**
WBC x 10^6	**4.8 – 10.8**	**7.84**	**8.89**	**7.04**

PLT x 10^6	**130 - 400**	**258**	**235**	**281**
Baso %	**0.0 – 1.5**	**0.6**	**0.6**	**0.8**
Eos %	**0.0 – 7.5**	**1.2**	**3.5**	**3.9**
Neut %	**40.0 – 74.0**	**64.3**	**63.3**	**62.8**
Lymp %	**19.0 – 48.0**	**25.9**	**26.0**	**25.7**

Table 2. *The second patients biodata.*

**The middle point of Apitherapy period.*

The Para clinical data's during treatment revealed some fluctuations thus, we have Choose the middle point of them. However, CRP, ESR, and serum cortisol level reduced during and after treatment in both patients.

In clinical point of view, pain relief, improvement of joint movement was resulted during treatment in both patients. The first patients who had Reiter's syndrome, improved almost completely and has received no other medication so far. For example

his movement hindrance decreased from 4 to 0, and the large inflammation in his knee joint, reduced from 2 cm to 1 cm. In the other patient a relapse was .. given chloroquine phosphate. In this patient the number joint involvement and inflammation did not increase during Apitherapy but after starting medication, these features were increased, and some of the healthy joints became inflamed.

DISCUSSION

Tertsch, F. (1885) was the first person who pointed out that rheumatic patients tolerated Bee sting better than normal subjects (Yourish, N. 1978). Nordvall, et. al. (1984) demonstrated that phospholipase A_2 (PLA_2) is the major antigenic component of HBV, and the bee keepers may develop antibodies to PLA_2 mainly of the IgG_4 class.

Since many beekeepers and rheumatic patients (who don't received NSAIDs), are insensitive to HBV, and both two groups have high level serum IgG_4 it could postulated that there might be an antigenic similarity between PLA_2 from HBV and human endogenous PLA_2. One possible explanation for the mode of action of HBV and some other natural toxins in their anti-inflammatory effects may be this antigenic mimetic between their PLA_2 and human endogenous PLA_2. When PLA_2 is free from serum calmodulin binding, it could effects on tissue Phospholipid and produces Arachidonic acid, which in turn could make Prostaglandins and causes inflammation. Although Habermann, E. (1972) and Salari, H. et. al. (1985), have pointed out that Melittin stimulstes PLA_2 enzyme activity and increases the synthesis of Eicosanoids. Somerfield, S.D.et.al. (1986), has demonstrated that Melittin inhibited …… (O_2^-) production by human peripheral blood leucocytes and this inhibition is due to a direct effect on cells, and not indicator medium, dismutation, toxic or scavenging effects. Therefore, Melittin as a main constituent of HBV (50 – 70%) that shows high affinity for Calmodulin binding (Somerfield, S.D. et.al. 1986), has a dual effect on the body. One of it's effects is in the PLA_2-releasing from serum Calmodulin, and the other effect which has been reported by Fehlner, et.al.(1991), is Melittin antigenic characteristic. Fehlner, demonstrated that melittin specific T cell clones are found to be CD_4 + and secrete IL – 4, which induce B cell iso type switching to IgG_4 and IgG_3 in humans, invitro. The results obtained from this study are somewhat difficult to interpret, since the number of our patients were little. Our original study on the effects of IgG_4 in rheumatic patients is going on and the results will be given in future.

REFERENCES

Banks, B.E.C., Rumjanek,F.D.,Sinclar,N.M. and Vernon, C.A. (1976). Positive therapeutic use of a peptide from bee venom. Bull. Inst. Pasteur, Paris 74, 137.

Beck, B.F. (1935). Bee venom therapy. New York, D. Appleton – Century

Devera,H. (1978). Effectiveness of bee venom on adjuvant induced arthritis in the rat. Proc. N. Am. Apiother .Soc. 1, 147.

Fehlner,P.F., berg, R.H., Tam.J.P., king, T.P.(1991) Murine T cell responses to melittin And it's analogs. J. Immune. 146 (1); 799 – 806.

Habermann,E. (1972). Bee and wasp venoms. Science 117: 314.

Hugh,M., Hyre and Randall A. smith (1986). Immunological effects of honey bee (Apis mellifera) venom using Balb/c mice. Toxicon 24 (5); 435 – 440

Kroner, J., lintz, M.R., Tyndall, M., Anderson, L., Nicholls,E.E. (1938). The treatment of rheumatoid arthritis with an injectable from bee venom. Ann. Intern. Med. 11(7); 1077 – 1083.

Lorenzetti, O.J., fortenberry, B. and Busby, E. (1972). Influence of bee venom in the adjuvant – induced arthritic rat model. Res. Commun. Chem. Path. Pharmac, 4, 339.

Nordvall, S.L., Uhlin. T., Einarsson, R., Johannson, S.G.O and Ohmann, S. (1984) beekeeper's IgG and IgE antibody responses to bee venom studied by means of crossed radioimmunoelectrophosis. Clin. All. 14, 341.

Rekka, E., Kourounakis, L.,and kourounakis, P. (1990). Antioxidant activity of and Interleukin production affected by bee venom. Arzneim – Forsch. / Drug res, 40 (II), Nr.8.

Salari, H., Braquet, P., and Borgeat, P. (1985). Stimulation of lipoxygenase product synthesis in human leucocytes and platelets by melittin. Mol. Pharma 28, 546.

Shkendrov, S., Koburova, K. (1982). Adolapin a newly isolates analgetic and anti –Inflammatory polypeptide from bee venom. Toxicon, 20 (1);317.

Somerfield, S.D., Stach, J. L., Mraz, C., Beruais, F., and skamene, E. (1986). Bee venom Melittin blocks neutrophil O_2^- production. Inflammation, 10(2); 175.

Steigerwaldt, F., Mathies, H., Damrau, F.(1966). Standardized bee venom (SBV) therapy of arthritis. A controlled study of 50 cases with 84% benefit. Ind. Med. Surg, 35 – 1045.

Yourish, N. (1974). Bees and people. Chapter 7.P. 140 – 164.