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## IMMUNOGLOBULINS IN SERUM AND NASAL SECRETION. A COMPARISON BETWEEN PATIENTS WITH ASPIRIN HYPERSENSITIVITY AND ALLERGIC RHINITIS

By

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Aspirin hypersensitivity is particularly common and well recognised among patients with asthma (16) and patients with chronic urticaria and/or angio-oedema (10). Chronic vasomotor rhinitis, sometimes with recurrent nasal polyps, is also frequently found among aspirin intolerant patients (13).

The nature of aspirin hypersensitivity is still obscure. Immunological reactions do not seem to be involved in the asthma group (6, 14, 18). However, in patients with urticaria/angio-oedema there is evidence that at least a few cases are caused by reaginic antibodies. de Weck (5) has shown the existence of antibodies to aspirin anhydride, which is a frequent contaminant of aspirin preparations. Phills & Perelmutter (11) have confirmed this observation.

In patients with allergic rhinitis the IgE-level in the serum as well as in the nasal secretion is usually increased (8, 19). In this study we have measured immunoglobulin concentrations in serum and nasal secretion from patients with allergic rhinitis and patients with chronic rhinitis and known aspirin intolerance.

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## MATERIAL AND METHODS

Sixteen patients (8 men, 8 women, mean age 43 years, range 22-66 years) known to be sensitive to aspirin participated in the study. Fifteen had both asthma and rhinitis. The sixteenth, a woman, suffered from severe chronic rhinitis and chronic urticaria. In all but three a radioallergosorbent test (RAST) (20) was performed and was negative to a panel of the eight most common allergens. An intracutaneous skin test against an extended panel of common allergens was carried out in all but two patients and no significant reactions were found. A weak, non-specific skin reaction, probably due to impurities and irritants in the allergen extract, occurred in seven patients. In these cases provocation tests were performed and were negative. A careful examination of the family history revealed possible atopic manifestations in eight of the 16 patients.

Fifteen patients (8 men, 7 women, mean age 27 years, range 18-39 years) with allergic rhinitis were studied as an allergic group. In 10 patients the rhinitis was perennial, caused by daily contact with the allergen (house dust, animal dander or flour). The other five had rhinitis during the pollen season or on sporadic contact with animals, and were symptom-free at examination.

No patient in either group was receiving corticosteroid treatment and in the 48 h preceding the study no anti-allergic treatment was administered. No evidence of upper respiratory tract or other infection was found in any of the subjects.

A control group of 10 healthy persons (5 men, 5 women, mean age 30 years, range 23-59 years) was selected from the hospital staff. They had no history of allergy or aspirin hypersensitivity.

Samples of 3-5 ml of nasal washout fluid were collected from all subjects by the technique described by Johansson & Deuschl (8). A venous blood sample was taken simultaneously and the serum was separated and stored at  $-20^{\circ}\text{C}$  pending analysis. The secretion samples were thawed and thoroughly mixed by centrifugation before analysis.

IgE concentrations were measured by the paper disc radioimmunosorbent technique (PRIST) (2) and the results are expressed in kU/l, using WHO reference 68/341 as a standard.

IgA, IgG and albumin concentrations were determined by single radial immunodiffusion (9) and the results are expressed in g/l.

The technique for collection of secretion samples involved dilution of an unknown magnitude, and to allow relevant mathematical comparisons the immunoglobulin concentrations in the secretion were expressed in relation to albumin as described earlier (8).

The local production of the immunoglobulin in question was calculated from the formula  $\frac{\text{Ig N/S}}{\text{Alb N/S}}$ , where N is the numerical value for the concentration of the immunoglobulin (Ig) and of albumin (Alb) in the nasal secretion

sample and S the corresponding value in serum. A ratio greater than 1 indicated local production or selective transport of the immunoglobulin concerned (4).

TABLE 1  
*Concentrations of Immunoglobulins and Albumin in Serum.*

| Clinical group | No. of subjects | IgE (kU/l)         | IgA (g/l)        | IgG (g/l)          | Alb (g/l)           |
|----------------|-----------------|--------------------|------------------|--------------------|---------------------|
| Control        | 10              | 27.3<br>(6.5-80)   | 2.0<br>(0.7-3.4) | 9.9<br>(7.7-12.1)  | 36.6<br>(22.7-51.8) |
| Allergic       | 15              | 330<br>(40-700)    | 2.1<br>(0.7-2.7) | 11.6<br>(6.7-15.2) | 42.3<br>(29.4-52.6) |
| Aspirin        | 16              | 50.6<br>(10.5-140) | 2.2<br>(0.9-3.9) | 9.8<br>(6.6-14.4)  | 35.5<br>(19.6-51.8) |

Arithmetic means and ranges (in parentheses) are given for each group.

TABLE 2  
*Concentration Ratios for Immunoglobulins and Albumin in Nasal Secretion.*

| Clinical group | No. of subjects | IgE nasal<br>Alb nasal | IgA nasal<br>Alb nasal | IgG nasal<br>Alb nasal |
|----------------|-----------------|------------------------|------------------------|------------------------|
| Control        | 10              | 0.6<br>(0.1-1.9)       | 0.3<br>(0.04-0.5)      | 0.4<br>(0.04-0.6)      |
| Allergic       | 15              | 25.3<br>(11.2-40)      | 0.2<br>(0.03-0.4)      | 0.2<br>(0.02-0.6)      |
| Aspirin        | 16              | 3.0<br>(0.05-17.2)     | 0.2<br>(0.03-0.5)      | 0.4<br>(0.02-0.8)      |

Arithmetic means and ranges (in parentheses) are given for each group.

## STATISTICAL METHODS

The random component of the error of the method was estimated by means of

duplicate determination and calculated by the formula  $s = \sqrt{\frac{\sum d^2}{2n}}$ , where  $s =$

standard deviation,  $d^2 =$  the square of the difference between the two readings of a sample,  $n =$  the number of samples. Its relation to the mean of the duplicate determinations was calculated, giving the coefficient of variation in per cent. The coefficients of variation for the determinations of albumin, IgA,

IgG and IgE in serum, and of albumin, IgA and IgG in secretion all lay around 12 per cent. For IgE in secretion it was 40 per cent, which should be considered in the light of occasional very low values for this immunoglobulin.

Arithmetic and geometric means and standard deviations for IgA, IgG and IgE in serum and secretion were calculated, and the differences between the different groups were tested with Student's *t*-test.

TABLE 3  
*Nasal Secretion (N)/Serum (S) Ratio for Each Immunoglobulin, Divided by the Ratio for Albumin:  $\frac{Ig\ N/S}{Alb\ N/S}$*

| Clinical group | No. of subjects | <u>IgE N/S</u>    | <u>IgA N/S</u>   | <u>IgG N/S</u>    |
|----------------|-----------------|-------------------|------------------|-------------------|
|                |                 | <u>Alb N/S</u>    | <u>Alb N/S</u>   | <u>Alb N/S</u>    |
| Control        | 10              | 1.1<br>(0.02-6.6) | 5.2<br>(0.08-10) | 0.8<br>(0.05-1.6) |
| Allergic       | 15              | 6.2<br>(1.0-20)   | 5.4<br>(0.5-10)  | 0.8<br>(0.2-1.4)  |
| Aspirin        | 16              | 2.4<br>(0.03-13)  | 3.7<br>(0.3-11)  | 1.2<br>(0.1-3.0)  |

Arithmetic means and ranges (in parentheses) are given for each group.

## RESULTS

IgE, IgA, IgG and albumin were found in all serum samples and the arithmetic means and ranges are given in Table 1. No appreciable differences were found between the groups regarding IgA, IgG and albumin. The concentration of IgE was significantly higher in the allergic group than in the aspirin and control groups ( $P < 0.05$ ). The IgE values in the aspirin group were somewhat higher than in the controls but the difference was not significant.

All samples of nasal secretion contained albumin. IgA was found in all secretion samples except one in the aspirin group, IgG in all except two in the aspirin group and IgE in all except two in the control group and three in the aspirin group. When no immunoglobulin was found, further calculation was performed, using the lowest measurable value.

In Table 2 the immunoglobulins in nasal secretion are expressed by the single ratio Ig N/Alb N. The IgE ratio was significantly higher in the allergic group than in the other two groups ( $P < 0.05$ ). No significant difference was found between the control and aspirin groups. The single ratios for IgA and IgG did not differ markedly between the groups.

The local production of immunoglobulins, expressed by the double ratio  $\frac{\text{Ig N/S}}{\text{Alb N/S}}$  is shown in Table 3. The double ratio for IgE was significantly higher in the allergic group than in the other two groups ( $P < 0.05$ ). The control group did not differ significantly from the aspirin group, which, however, had a value well above 1.0.

The double ratio for IgA did not differ significantly between the three groups and was clearly higher than 1.0 in all of them. The corresponding mean double ratio for IgG was about 1.0 for all three groups.

#### DISCUSSION

The serum concentrations of albumin, IgA and IgG lay within the normal range in all the three groups investigated.

It was not possible to calculate the absolute physiological concentration of the immunoglobulins in secretion samples, because of the dilution. To overcome this problem the values are expressed as a ratio between the concentration of immunoglobulin and of albumin. The only source of albumin in the nasal secretion appears to be plasma exudation (15). The immunoglobulins, on the other hand, may be derived both from exudation and from local production. The local production of the immunoglobulins is expressed by the double ratio  $\frac{\text{Ig N/S}}{\text{Alb N/S}}$  (8).

Immunoglobulins A and G were found in the nasal secretion in all three groups, with no difference between the groups.

It was calculated that IgA was produced locally, but not IgG, which agrees with earlier reports (4, 8).

Immunoglobulin E was found in a significantly higher concentration in the allergic group, both in the serum and in the nasal secretion. High serum concentrations of IgE in allergic subjects are well documented (1, 7), and high concentrations in nasal secretion have also been reported (19, 8). In this investigation, as in an earlier study (3), an indication of considerable local production was found in the allergic patients.

No significant difference was found between the patients with aspirin hypersensitivity and the normal controls. Serum IgE values within the normal range in patients hypersensitive to aspirin have been reported by Schlumberger (14). To our knowledge, IgE in nasal secretion has not been studied in this category of patients.

The concentrations of IgE in the aspirin group, both in the serum and in the nasal secretion, were somewhat higher than in the controls. This difference is not statistically significant, but the groups were rather small, and extension of the material might reveal a real difference. It is also striking that there was some indication of a local production of IgE in the aspirin group as the double ratio was well above 1.0. A possible explanation for this is that the group included patients with hidden allergy—as indicated by the high incidence of atopic diseases among relatives. We found no reaginic antibodies in this group, however. The weakly positive intracutaneous skin tests with the use of high concentrations are probably due to irritants in the allergen extracts (17) as the provocation tests were negative in these cases. To completely exclude all possible allergic mechanisms in patients with asthma or rhinitis is always difficult. This probably explains the difference between the normal subjects and the patients with aspirin hypersensitivity regarding the IgE values.

The IgE concentrations were significantly different between the allergic and the aspirin groups, both in the serum and nasal secretion. The severity and chronicity of the rhinitis in the aspirin group were more pronounced than in the allergic

group, where some patients only had seasonal symptoms. These facts suggest that the rhinitis in patients with aspirin hypersensitivity is not mediated by IgE. This agrees well with the conclusion of other authors that aspirin hypersensitivity in patients with asthma or rhinitis is of nonimmunological origin (12, 6, 18, 14).

#### SUMMARY

Immunoglobulins A, E and G were studied in serum and nasal secretion from patients with allergic rhinitis, chronic rhinitis and aspirin hypersensitivity, and normal controls. The allergic patients differed from the other groups in having higher IgE values, both in serum and in nasal secretion. The patients with aspirin hypersensitivity did not differ from the control group regarding the IgE values. No difference between the groups was found with respect to IgA and IgG. The results indicate that reaginic antibodies are not involved in causing aspirin hypersensitivity.

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