A COMPARATIVE STUDY OF BUDERONIDE NASAL SPRAY IN TWO DOSE LEVELS IN CHILDREN SUFFERING FROM HAY-FEVER

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SUMMARY

50 children took part in a randomized, double-blind study with parallel groups. Budesonide nasal spray (freon-propelled) in two daily dose regimens, 100 ug b.i.d. and 200 ug b.i.d., was compared during three weeks' treatment. The treatment was effective in both groups and well accepted by the children. Small but statistically significantly lower symptom scores with 200 ug/day were seen in some of the nasal symptoms, but this may be due to lower scores already before treatment. The adverse reactions were very few and mild in both treatment groups.
PURPOSE OF THE TRIAL

The purpose of the trial was to clinically compare the efficacy and possible side-effects of budesonide nasal spray (freon-propelled) in two dose levels, 200 ug/day and 400 ug/day, in children suffering from hay-fever.

INCLUSION CRITERIA

Children, both boys and girls, 16 years or younger, with a history of typical hay-fever symptoms for at least the last two seasons. The diagnosis pollen allergy was confirmed by skin testing and/or by anamnesis.

EXCLUSION CRITERIA

Children older than 17 years of age were not allowed to enter the trial, nor were children with microbial infections, nor children with a previous history of tuberculosis.

PATIENTS

50 children, 30 boys and 20 girls, entered the study. All of them reported a history of sensitivity to trees, 27 of them were also sensitive to grass and 10 to different kinds of flowers. 48 of the children were tested with skin-prick test and 15 were reported sensitive to birch-pollen in group I (200 ug/day) and 17 were sensitive to birch-pollen in group II (400 ug/day). 14 children were RAST-tested, 7 in each group.

The age of the children in group I ranged from 5 - 16 years with a mean of 10.8 years. 7 were boys and 18 girls. In group II the mean age was 11.4 years and ranged from 5 - 15 years. In this group there were 13 girls and 12 boys.

In group I the duration of their disease ranged from 2 - 11 years with a mean of 4.9 years and in group II the mean was 5.7 and ranged from 2 - 10 years. For comparison of other vital data see Table I.
METHODS

The trial was carried out as a double-blind, comparative study with parallel groups. After an initial examination and entry of the children's history on a patient form, they were allocated to one of the two treatment groups according to a randomized scheme prepared at Draco.

Two budesonide nasal sprays were used in the study. One had a strength of 1 mg/ml given in doses of 25 ug (batch no. DHD-1-C). The other budesonide spray used had a strength of 2 mg/ml, each puff delivering 50 ug (batch no. DGM-6-C).

All children were given 2 puffs into each nostril morning and evening. Thus, the first group received 200 ug daily and the second group 400 ug daily.

The trial started with a two-day run-in period in order to make sure that the children were allergic. During these two days the children were told to start recording on a diary card the following symptoms

* nasal obstruction
* nasal secretion
* sneezing bouts
* nasal itching
* eye symptoms
* asthma symptoms

every evening during the last 24 hours with the following severity scores

0 = no symptoms = no sneezing bouts
1 = slight symptoms = 1 - 5 sneezing bouts
2 = moderate symptoms = 6 - 10 sneezing bouts
3 = severe symptoms = > 10 sneezing bouts

The patients were also told to try to estimate the duration (in hours) of the nasal symptoms every day and to note it on their diary cards.
The treatment period was 3 weeks. The patients visited the investigator twice: at the entry visit before the start of the run-in period and within one week after the treatment period. At this visit the diary cards were collected and controlled to see that they were properly filled in. The investigators also stated their opinion of the treatment and noted the result of this. They also asked the children about their opinion of the treatment by asking the following question:

Was the effect of the preparation

- very good
- good
- moderate
- slight
- none

CONCOMITANT THERAPY

During the trial (including the run-in period) the children were not allowed to use any other drug for rhinitis. If the nasal symptoms were too severe, the patients were allowed to take Lumerin R mite tablets (brompheniramine + phenylpropanol amine) and if eye-symptoms would appear Antasten R -Privin R eye-drops (Antazolin. + naphazolin. nitr.) were allowed if noted on their diary cards. Other concomitant drugs had to be recorded, as well.

ADVERSE REACTIONS

The children were told to record any adverse reaction observed on their diary card.

LABORATORY TESTS

When possible, a blood sample for plasma cortisol was taken before the start of the treatment and at the last treatment week.

INFORMED CONSENT

Before entering the study all the children and their parents were fully informed about the study both in writing and verbally, and about their
right to withdraw from the study without consequences for future treatment. All the children and/or their parents gave their written informed consent to participate.

The trial protocol was approved by both the National Finnish Medical Board and the regional ethical committee of the Tampere University Central Hospital.

STATISTICAL METHODS

When evaluating the patients' diary cards Wilcoxon's rank sum test for comparison between groups (two-sided) has been used. The patients' and the investigators' opinion of the treatment results was analysed by using chi²-test with Yates' correction. (The opinions 'good' and 'very good' were put together in one group and 'moderate', slight' and 'none' in another).

RESULTS AND STATISTICAL CONSIDERATIONS

Entry values

The results from the two-day run-in period can be seen in Table II and Fig. 1 - 8. As can be seen there are significantly lower scores in group I regarding the symptom nasal obstruction. In the other parameters evaluated, i.e. nasal secretion, nasal itching, sneezing bouts, total nasal symptom scores, hours of nasal symptoms, eye symptoms and asthma symptoms there are differences, but none of them are significant.

Treatment results

The results from the treatment periods can be seen in Table III - X and Fig. 1 - 8.

The symptom nasal obstruction (Table III and Fig. 1) showed a significant decrease in symptom scores during all three treatment weeks as well as the whole treatment period in group II. In group I the symptoms decreased but were significant during the third treatment week and the whole period.
The symptom nasal secretion (Table IV and Fig. 2) shows a decrease in the symptom scores in group I, significant during treatment week 2 and 3 and the whole period. In group II a decrease can be seen during the first treatment week and the whole period, but it is not significant. When comparing the two treatments, lower scores are found in group I during all three treatment weeks, significant during week 2 and 3.

Nasal itching (Table V and Fig. 3) displays a significant decrease in both the groups during the three treatment weeks except the last week in group I.

Between the treatments there is a difference favouring group I during all the treatment weeks. This difference is significant during week 2.

When analysing the symptom sneezing bouts (Table VI and Fig. 4) significant decreases are found during all treatment weeks in both groups. When compared no difference could be detected between them.

When putting together the nasal symptoms to 'total nasal symptoms' (Table VII and Fig. 5), a significant decrease is found in both groups during all the three treatment weeks. When the treatment groups are compared a significantly better effect is found in group I during the second treatment week.

The patients' estimation of the duration of their nasal symptoms (Table VIII and Fig. 6) revealed a shorter duration during the treatment in comparison with the run-in in both groups, significant the first week and the whole period in treatment group I. No difference is found between the groups.

The parameters eye symptoms (Table IX and Fig. 8) and asthma symptoms (Table X and Fig. 7) revealed no statistical differences neither in the treatment period, nor between the two groups.

As can be seen in Table IX there is no statistical difference between the two groups according to the evaluation of the treatment results, neither in the children's evaluation, nor in that of the investigators. (The symptoms 'very good' and 'good' are put together in one group and 'moderate', 'slight' and 'none' in another).
LABORATORY INVESTIGATIONS

The result of the plasma cortisol analysis (see Table XIII) shows a slight decrease in group I (n=13) from a mean of 475.6 nmol/l to 462.0 nmol/l. 7 children increased their values and 6 children decreased their values after treatment. In group II (n=9) the mean values increased from 395.2 nmol/l to 507.0 nmol/l. 7 children increased their values while 2 decreased. The mean values are within the normal range in both groups both before and after treatment. 1 child in group I has a value below the lower limit after treatment (a decrease from 367.08 before to 220.80 nmol/l afterwards) and 1 child in group II has a lower value before (276.00 nmol/l) which after treatment was 477.45 nmol/l.

CONCOMITANT THERAPY

In group I 14 patients used eye-drops during 74 days altogether and 5 patients used altogether 25 antihistamine tablets during 17 days.

In group II 14 patients used eye-drops for 56 days and 6 patients used 22 antihistamine tablets during 21 days.

1 patient used 2 tablets of acetylsalicylic acid in this group during the treatment period (see Table XIV).

ADVERSE REACTIONS

The adverse reactions noted in the patients' diary cards or reported by the investigators in the patient forms can be seen in Table XV. 6 patients reported adverse reactions in group I and 3 patients in group II. They were all mild and transient.

MANUFACTURER'S EVALUATION

In a study on 50 children suffering from hay-fever, budesonide 100 ug b.i.d. was compared with 200 ug b.i.d. during 3 weeks' treatment.

All the children had a history of birch-pollen induced rhinitis, which was verified by prick-test in 15 children in group I and in 17 children in group II.
Although the children had an equal history, a significant difference appeared already during the two-day run-in period in the symptom nasal obstruction. Also in some of the other symptoms evaluated (nasal itching, sneezing bouts, hours of nasal symptoms and eye symptoms) there were differences. This may be the reason for the differences in the results during the treatment period.

The treatment results were good in both dosages. However, a small but significantly better result (i.e. less symptoms) in the lower dose-regimen could be seen.

The treatment was well accepted by the children and the side-effects were mild and few.

The manufacturer concludes that budesonide nasal spray in the given dosages is an effective drug and that 200 ug/day seems to be enough to treat hay-fever in children.

SEPTMBER 6, 1983
ASN/AEK
**Pediatric Studies Rhinocort**

**Terho** (April - May, 1982)

### 2 mg/mL/400 ug/day

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<th>SEX</th>
<th>AGE</th>
<th>DURATION OF TREATMENT</th>
<th>ADVERSE REACTIONS</th>
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<tr>
<td>M</td>
<td>5</td>
<td>3 weeks</td>
<td>2 children reported nasal bleeding 3 times altogether</td>
<td>14 children used eye-drops for 56 days</td>
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<tr>
<td></td>
<td>6</td>
<td>3 weeks</td>
<td>1 x headache (3 days)</td>
<td>22 antihistamine tablets for 21 days</td>
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<td></td>
<td>7</td>
<td>3 weeks</td>
<td>1 x cough (2 days)</td>
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**PLASMA CORTISOL**

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### 1 mg/mL/200 ug/day

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<tbody>
<tr>
<td>M</td>
<td>5</td>
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<td>3 children reported nasal bleeding 7 times altogether</td>
<td>14 children used eye-drops for 74 days</td>
<td>-</td>
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<tr>
<td></td>
<td>6</td>
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<td>4 children reported sneezing or itching after spray 5 times altogether</td>
<td>25 antihistamine tablets for 17 days</td>
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<td>7</td>
<td>3 weeks</td>
<td>1 x cough (1 day)</td>
<td>-</td>
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**PLASMA CORTISOL**

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