Rhinology, 24, 113-123, 1986

# Clinical study on beclomethasone dipropionate powder preparation (TL-102) in perennial nasal allergy

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SUMMARY

*The efficacy, safety and optimal dose of TL-102, a powder mixture of beclomethasone dipropionate (BDP) and hydroxypropylcellulose (HCP) were studied in 250 patients with perennial nasal allergy in an intergroup comparative double-blind manner. Four different capsules containing respectively 30 μg of HCP and 1,5 μg, 12,5 μg, 25 μg and 50 μg of BDP, were prepared and the drug was applied intranasally evenly between both nostrils at a dose of 2 cap./day b.i.d. for one week. The degrees of overall improvement, usefulness, improvement of nasal symptoms (sneezing, nasal discharge, nasal blockage) and improvement of rhinoscopical findings (mucosal swelling and nasal secretion) were found to be dose-dependent. Antigen provocation reaction and nasal eosinophil count were both inhibited as compared with the TL 1,5 g group . The incidence of side effects was 4.5%, but all side effects observed were mild. Using TL-102 resulted in a therapeutic effect comparable to the conventional BDP preparations using a dose 1/4th of the normal dose of these BDP preparations. The incidence of side effects was 1/3th in comparison with conventional BDP. It was suitable to administer BDP 50 μg capsule containing 30 mg of HCP twice a day.*

## INTRODUCTION

Beclomethasone dipropionate nasal spray (abbreviation: BDP) has been widely known to have an excellent therapeutic efficacy and to cause very few systemic side effects. However, the development of a BDP preparation which permits further reduction of the BDP dose, as well as an increase in efficacy and a decrease of side effects as to severity and incidence, will be valuable in clinical treatment of nasal allergy.

For this purpose, TL-102, a powder mixture preparation of hydroxypropylcellulose (abbreviation: HPC, see Figure 1), as adhesive base, plus BDP, was developed (Teijin, Japan).

From the results obtained in various basic studies using HPC the following information became apparent: determination of the optimal dosis of the spray in human (Kuroishi et al., 1984), irritant effect of TL-102 on rabbit nasal mucosa

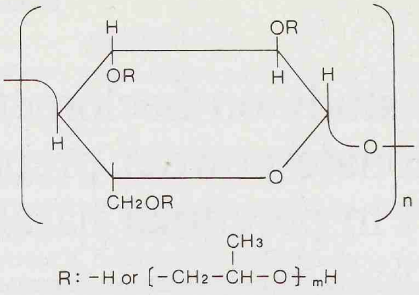


Figure 1. Chemical structure of HPC.

(Koyama et al., 1984), inhibitory effect on ciliary movement of cultured mouse nasal mucosa (Saito et al., 1982), effect on mucociliary transport of human nasal mucosa (Murai et al., 1984), antigenicity in guinea pigs (Komoriya et al., 1984), inhibitory effect on nasal provocation reaction in patients with nasal allergy (Usui et al., 1984), distribution (Yamamoto et al., 1984), and presence of the drug (Yamamoto et al., 1984) in rabbit nasal cavity after nasal application of a powder mixture of $^{3}$H-labeled BDP plus HPC, and distribution in a model of the human nasal cavity after pulverization of TL-102 (Unno et al., 1982). From the above presented results could be concluded that TL-102 can be regarded as applicable in clinical practise as a highly safe, long-acting, effective drug for treatment of nasal allergy. Furthermore TL-102 was confirmed to be safe and effective when applied intranasally to normal healthy subjects (Kuroishi et al., 1984) and patients with nasal allergy (Okamoto et al., 1984). A multicentral intergroup comparative double-blind trial was performed in a total of 250 patients with perennial nasal allergy in order to confirm the safety, efficacy and optimal dosis of TL-102.

## METHODS

### 1. *Patients*

The present study was carried out in 250 cases (aged 12 years or more) who had typical symptoms of perennial nasal allergy and were diagnosed as having perennial nasal allergy after a positive reaction in two of the following tests: intradermal test using an antigen, nasal provocation and nasal eosinophils. These patients had moderate or severe symptoms, but no nasal diseases other than nasal allergy, which would influence the efficacy evaluation. The methods used for nasal allergy tests and the criteria for classification of the severity are not mentioned in this paper, as they have already been reported on before (Okuda et al., 1983; Okuda and Semba, 1980).

### 2. *Test drug and administration*

Four types of TL-102 were prepared, changing the dose of BDP so that the follow-

ing four diferent capsules containing respectively 1,5, 12,5, 25 and 50 μg BDP, and 30 mg of HPC were made. In the present study we used a capsule containing 1,5 μg BDP as control instead of an inactive placebo. The capsules containing four different preparations could not be distinguished from each other. TL-102 was applied intranasally twice a day with a newly developed pulverizer, namely in the morning (at awakening) and at night (before sleeping). One capsule per time was sprayed in both nostrils after the nose was blown. The daily dose of BDP varied from 3 μg, 25 μg, 50 μg and 100 μg in the four groups, coded respectively as TL 3 μg group, TL 25 μg group, TL 50 μg group and TL 100 μg group.
The period of investigation consisted of a one-week wash-out (off-drug) period, a one-week TL-102 medication period and a one-week follow-up period. The combination with any other drug was not permitted during this period.

3. *Evaluation of efficacy*
Doctors in charge judged the overall improvement, side effects, usefulness, improvement of each symptom, changes in rhinoscopical findings, nasal provocation reaction by causative antigen and changes in nasal eosinophil count. Patients were instructed to record the changes in their subjective symptoms in the "Allergy Diary" and their records were taken as data indicating the changes in subjective symptoms.

4. *Statistical analysis*
For statistical analysis, $x^2$-test, Fisher's direct probability estimate test, Mann-Whitney's U-test, Student's test, Welch's test and Scheffe's test were employed.

RESULTS
Among the 250 patients to the present clinical trial, there were 3 complete drop-out cases and 25 partial drop-out cases. Therefore, there were finally 222 cases who were subjected completely to the data analysis. The TL 3 μg group consisted of 49 cases, the TL 25μg group of 55 cases, the TL 50 μg group of 61 cases and the TL 100 μg group of 57 cases.
There were no significant differences among these 4 groups subjected to the analysis in terms of distribution of sex, age, age of onset of the disease, duration of disease, severity, seasonability onset of the disease, complications, types of antigens, history of allergy of patients and their family, history of treatment, rhinoscopical findings, skin reactions, nasal provocation reaction and nasal eosinophil count.
Evaluating the overall improvement, the percentage of improvement (proportion (%) of the number of patients with remarkable or moderate improvement to the total of patients subjected to the data analysis) was 38.8% in the TL 3 μg group, 61.8% in the TL 25 μg group, 65.6% in the TL 50 μg group and 82.5% in the TL 100

Table 1:
Overall Improvement

| Groups | No. of cases | Remarkable | Moderate | Slight | Unchange | Aggravation | % improvement (remarkable + moderate) | Scheffé's test |
|---|---|---|---|---|---|---|---|---|
| 3 μg/day | 49 | 4 ( 8.2) | 15 (30.6) | 15 (30.6) | 13 (26.5) | 2 (4.1) | 38.8 (19/49) | 25 μg/day > 3 μg/day $p < 0.10$ |
| 25 μg/day | 55 | 15 (27.3) | 19 (34.5) | 11 (20.0) | 10 (18.2) | 0 (0.0) | 61.8 (34/55) | 50 μg/day > 3 μg/day $p < 0.01$ |
| 50 μg/day | 61 | 19 (31.1) | 21 (34.4) | 14 (23.0) | 4 ( 6.6) | 3 (4.9) | 65.6 (40/61) | 100 μg/day > 3 μg/day $p < 0.01$ |
| 100 μg/day | 57 | 22 (38.6) | 25 (43.9) | 8 (14.0) | 2 ( 3.5) | 0 (0.0) | 82.5 (47/57) | |

Table 2:
Incidence of Side Effect

( ) : %

| Groups | No. of cases | No side effect | Mild | Moderate | Severe | Incidence of side effect (%) | $x^2$-test |
|---|---|---|---|---|---|---|---|
| 3 μg/day | 49 | 48 (98.0) | 0 (0.0) | 1 (2.0) | 0 (0.0) | 2.0 (1/49) | N.S. |
| 25 μg/day | 55 | 52 (94.5) | 3 (5.5) | 0 (0.0) | 0 (0.0) | 5.5 (3/55) | |
| 50 μg/day | 61 | 57 (93.4) | 2 (3.3) | 2 (3.3) | 0 (0.0) | 6.6 (4/61) | |
| 100 μg/day | 57 | 55 (96.5) | 2 (3.5) | 0 (0.0) | 0 (0.0) | 3.5 (2/57) | |
| Total | 222 | 212 (95.5) | 7 (3.2) | 3 (1.4) | 0 (0.0) | 4.5 (10/222) | |

Table 3:
Usefulness

| Groups | No. of cases | Very useful | Useful | Fairly useful | Un-decidable | Not useful | % usefulness (very useful + useful) | Scheffé's test |
|---|---|---|---|---|---|---|---|---|
| 3 μg/day | 49 | 3 ( 6.1) | 19 (38.8) | 11 (22.4) | 8 (16.3) | 8 (16.3) | 44.9 (22/49) | 50 μg/day > 3 μg/day $p < 0.05$ |
| 25 μg/day | 55 | 14 (25.5) | 19 (34.5) | 12 (21.8) | 6 (10.9) | 4 ( 7.3) | 60.0 (33/55) | 100 μg/day > 3 μg/day $p < 0.01$ |
| 50 μg/day | 61 | 19 (31.1) | 20 (32.8) | 12 (19.7) | 3 ( 4.9) | 7 (11.5) | 63.9 (39/61) | 100 μg/day > 25 μg/day $p < 0.10$ |
| 100 μg/day | 57 | 23 (40.4) | 23 (40.4) | 9 (15.8) | 2 ( 3.5) | 0 (0.0) | 80.8 (46/57) | |

*Table 4:*
*Effect on*
Nasal Symptoms

| Items | | Groups | No. of cases | Evaluation at the end of treatment | | | | | | % improvement | | Scheffé's test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Disappeared | Remarkable | Improved | Unchange | Aggravation | Unknown[note)] | ≧ Remarkable | ≧"Improved" | |
| Effects | Sneeze | 3 μg/day | 49 | 3 | 1 | 24 | 20 | 1 | 0 | 8.2 (4/49) | 57.1 (28/43) | 50 μg/day > 3 μg/day p < 0.01 |
| | | 25 μg/day | 55 | 7 | 6 | 26 | 12 | 2 | 2 | 24.5 (13/53) | 73.6 (39/53) | 100 μg/day < 3 μg/day p < 0.01 |
| | | 50 μg/day | 61 | 13 | 8 | 29 | 8 | 1 | 2 | 35.6 (21/59) | 84.7 (50/59) | 100 μg/day > 25 μg/day p < 0.05 |
| | | 100 μg/day | 57 | 20 | 8 | 22 | 5 | 1 | 1 | 50.0 (28/56) | 89.3 (50/56) | |
| | Nasal discharge | 3 μg/day | 49 | 2 | 2 | 21 | 22 | 2 | 0 | 8.2 (4/43) | 51.0 (25/43) | 25 μg/day > 3 μg/day p < 0.05 |
| | | 25 μg/day | 55 | 7 | 11 | 22 | 14 | 0 | 1 | 33.3 (16/54) | 74.1 (40/54) | 50 μg/day > 3 μg/day p < 0.05 |
| | | 50 μg/day | 61 | 7 | 13 | 26 | 14 | 1 | 0 | 32.8 (20/61) | 75.4 (46/61) | 100 μg/day > 3 μg/day p < 0.01 |
| | | 100 μg/day | 57 | 15 | 13 | 15 | 13 | 0 | 1 | 50.0 (28/56) | 76.8 (43/56) | |
| | Nasal blockage | 3 μg/day | 49 | 7 | 2 | 12 | 23 | 1 | 4 | 20.0 (9/45) | 46.7 (21/45) | |
| | | 25 μg/day | 55 | 13 | 8 | 13 | 18 | 0 | 3 | 40.4 (21/52) | 65.4 (34/52) | 100 μg/day > 3 μg/day p < 0.05 |
| | | 50 μg/day | 61 | 10 | 6 | 21 | 16 | 3 | 5 | 28.6 (16/56) | 66.1 (37/56) | |
| | | 100 μg/day | 57 | 15 | 8 | 19 | 9 | 1 | 5 | 44.2 (23/52) | 80.8 (42/52) | |

*Table 5:*
Effects on
Rhinoscopical Findings

| Items | | Groups | No. of cases | Evaluation at the end of treatment | | | | | | % improvement | | Scheffé's test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Disappeared | Remarkable | Improved | Unchange | Aggravation | Unknown[note)] | ≧ Remarkable | ≧"Improved" | |
| Effects | Swelling | 3 μg/day | 49 | 3 | 0 | 19 | 24 | 1 | 2 | 6.4 (3/47) | 46.8 (22/47) | |
| | | 25 μg/day | 55 | 7 | 2 | 20 | 21 | 1 | 4 | 17.6 (9/51) | 56.9 (29/51) | 100 μg/day > 3 μg/day p < 0.05 |
| | | 50 μg/day | 61 | 10 | 7 | 18 | 21 | 0 | 5 | 30.4 (17/56) | 62.5 (35/56) | |
| | | 100 μg/day | 57 | 11 | 6 | 19 | 16 | 1 | 4 | 32.1 (17/53) | 67.9 (36/53) | |
| | Watery secretion | 3 μg/day | 49 | 3 | 2 | 14 | 24 | 2 | 4 | 11.1 (5/45) | 42.2 (19/45) | 25 μg/day > 3 μg/day p < 0.05 |
| | | 25 μg/day | 55 | 15 | 2 | 21 | 14 | 0 | 3 | 32.7 (17/52) | 73.1 (38/52) | 50 μg/day > 3 μg/day p < 0.01 |
| | | 50 μg/day | 61 | 24 | 4 | 14 | 12 | 4 | 3 | 48.3 (28/58) | 72.4 (42/58) | 100 μg/day > 3 μg/day p < 0.01 |
| | | 100 μg/day | 57 | 16 | 10 | 12 | 12 | 1 | 6 | 51.0 (26/51) | 74.5 (38/51) | |
| | Nasal provocation reaction | 3 μg/day | 49 | 4 | 1 | 9 | 15 | 2 | 18 | 16.1 (5/31) | 45.2 (14/31) | |
| | | 25 μg/day | 55 | 17 | 0 | 10 | 14 | 0 | 14 | 41.5 (17/41) | 65.9 (27/41) | 25 μg/day > 3 μg/day p < 0.10 |
| | | 50 μg/day | 61 | 14 | 1 | 8 | 14 | 0 | 24 | 40.5 (15/37) | 62.2 (23/37) | |
| | | 100 μg/day | 57 | 12 | 4 | 8 | 12 | 0 | 21 | 44.4 (16/36) | 66.7 (24/36) | |
| | Nasal eosinophilia | 3 μg/day | 49 | 6 | 0 | 12 | 18 | 3 | 10 | 15.4 (6/33) | 46.2 (18/33) | |
| | | 25 μg/day | 55 | 11 | 2 | 14 | 16 | 2 | 10 | 28.9 (13/45) | 60.0 (27/45) | N.S. |
| | | 50 μg/day | 61 | 13 | 3 | 13 | 16 | 3 | 13 | 33.3 (16/48) | 60.4 (29/48) | |
| | | 100 μg/day | 57 | 12 | 1 | 12 | 12 | 3 | 17 | 32.5 (13/40) | 62.5 (25/40) | |

Note)
"Unknown" includes cases impossible to judge, and the "unknown" cases are excluded from data analysis.

$\mu$g group (Table 1). The response was dose dependent. However, Scheffe's test demonstrated a significant difference only between the TL 3 $\mu$g group and the TL 100 $\mu$g group ($p < 0.01$). The incidence of side effects was 20% in the TL 3 $\mu$g group, 5.5% in the TL 25 $\mu$g group, 6.6% in the TL 50 $\mu$g and 3.5% in the TL 100 group and there was no significant difference in incidence of side effects among the four groups (Table 2). Three of the ten patients having side effects complained of a feeling of irritation in the nasal cavity and the remaining patients had the following complaints: nasal blockage, throat pain, feeling of pruritus at the throat, headache and tinnitus. These side effects were all mild and the continuation of medication was possible.

The percentage of cases in which the treatment can be considered useful (the proportion (%) of the number of cases in which the drug was evaluated as "very useful" or "useful" to the total number of cases subjected to the usefulness evaluation) was 44.9% in the TL 3 $\mu$g group, 60.0% in the TL 25 $\mu$g group, 63.9% in the TL 50 $\mu$g group and 80.8% in the TL 100 $\mu$g group, and there was a positive dose-response (Table 3). However, Scheffe's test demonstrated a significant difference only between the TL 3 $\mu$g group and the TL 50 $\mu$g group and between the TL 3$\mu$g group and the TL 100 $\mu$g group ($p < 0.05$ and $p < 0.01$, respectively).

The percentages found for the improvement of nasal symptoms are the following: sneezing 57.1% for the TL 3 $\mu$g group, 73.6% for the TL 25 $\mu$g group, 84.7% for the TL 50 $\mu$g group and 89.3% for the TL 100 $\mu$g group. Improvement of nasal discharge mentioned in the same group order as above, was respectively 51.0%, 74.1%, 75.4% and 76.8% and finally the improvement for nasal blockage was respectively 46.7%, 65.4%, 66.1% and 80.8%. Again a positive dose dependance was found (Table 4).

The percentages found for the improvement of rhinoscopical findings are the following: mucosal swelling 46.8% for the TL 3 $\mu$g group, 56.9 for the TL 25 $\mu$g group, 62.5% for the TL 50 $\mu$g group and 67.9% for the TL 100 $\mu$g group. A significant difference was found between the TL 3 $\mu$g group and the TL 100 $\mu$g group ($p < 0.05$). Improvement of watery nasal discharge was respectively 52.2%, 73.1%, 72.4% and 74.5% and the percentage of improvement was significantly lower in the TL 3 $\mu$g group than in the other groups ($p < 0.05$ vs TL 25 $\mu$g group, $p < 0.01$ vs TL 100 $\mu$g group).

The improvement of nasal provocation reaction was noted in 42.5% of the cases in the TL 3 $\mu$g group, 65.9% in the TL 25 $\mu$g group, 62.2% in the TL 50 $\mu$g group and 66.7% in the TL 100 $\mu$g group, and in the same group order the improvement of nasal eosinophil count was obtained respectively 46.2%, 60.0%, 60.4% and 62.5%. No dose response was found for the percentages of improvement of the nasal provocation reaction, nor for that of nasal eosinophil count (Table 5).

In an intragroup comparative analysis of the records in the so-called "allergy-diary", excluding the TL 3 $\mu$g group, sneezing, nasal discharge and nasal blockage

were significantly improved in both the medication period and the follow-up period as compared with the wash-out period (Figure 2). In an intergroup comparison, sneezing and nasal discharge were improved significantly in the TL 25 μg, 50 μg and 100 μg groups as compared with TL 3 μg group. However, there was no significant improvement for nasal blockage.

## DISCUSSION

The intranasal application of TL-102 resulted in high percentages of overall improvement and usefulness and in reduction of mucosal swelling and nasal dis-

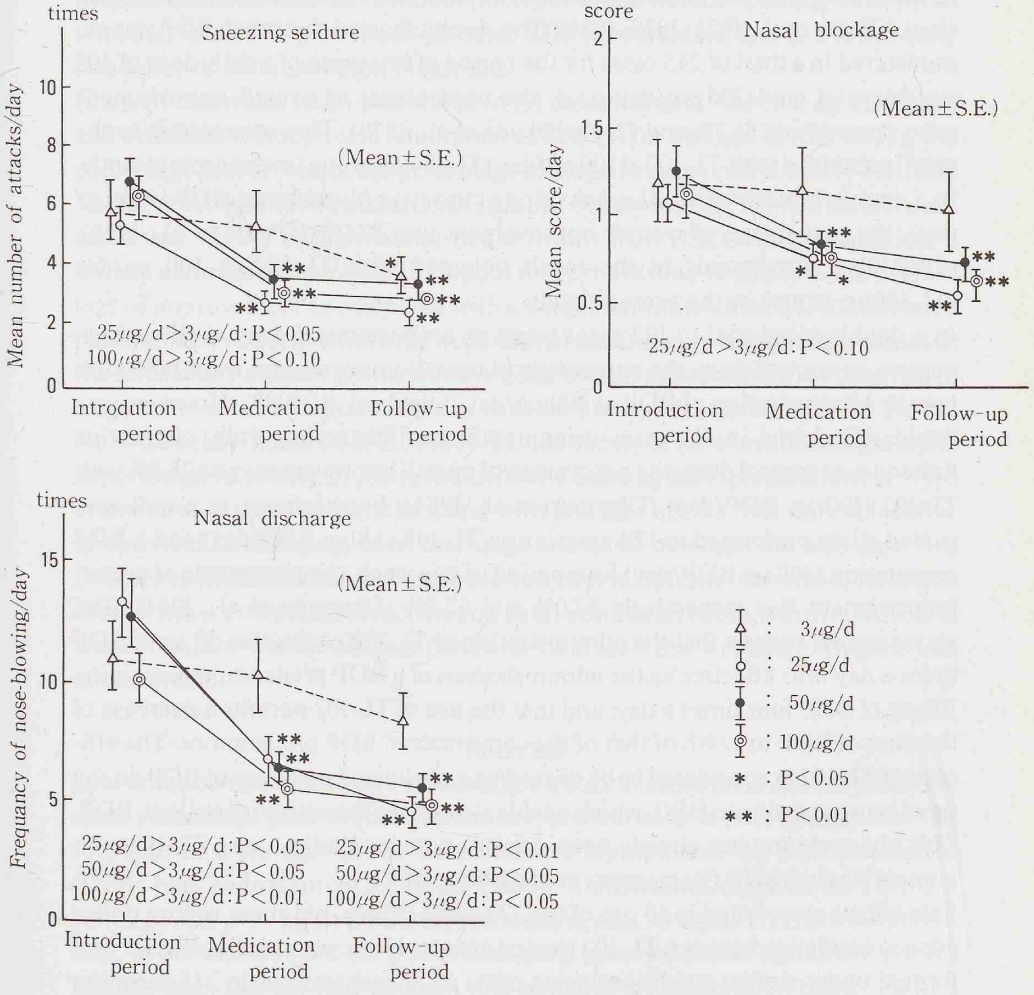


Figure 2. Changes in scores given according to symptoms (as judged from the records in "Allergy Diary").

charge. The amount of HPC was the same in the four types of TL-102 capsules and only the amount of BDP differed. Therefore, these results were considered to be related to the varying amounts of BDP. In the present study the administration of two 50 μg BDP capsules daily b.i.d. (morning and night) was suitable to treat nasal allergy.

In Europe and the U.S.A. there have been many clinical trials on BDP preparations. However, these foreign studies cannot be used as a valid comparison for our present study, because they have been carried out under conditions different from ours. So, we compared the present results with Japanese data obtained in clinical trials on BDP preparations which we have performed under similar conditions (Okuda et al., 1978; 1979; 1980). The results showed that when BDP was administered in a total of 245 cases for the period of one week of a daily dose of 400 mg/day q.i.d. and 200 μg/day q.i.d. the percentages of overall improvement were respectively 81.2% and 76.4% (Okuda et al., 1979). This corresponds to the results obtained with TL-102 at 100 μg/day (TL 100 μg group) in the present study. In a double-blind trial in 183 cases using an inactive placebo and BDP (400 μg/day), the percentage of overall improvement was 87.0% (Okuda et al., 1978), which also corresponds to the result obtained with TL-102 at 100 μg/day (TL 100μg group) in the present study.

In a double-blind trial in 192 cases using an antihistaminic drug, d-chlorpheriramine, as control drug, the percentage of overall improvement was 61.0% after 1-week administration of BDP at 400 μg/day (Okuda et al., 1980). However, in a double-blind trial in 118 cases using another antihistaminic drug, clemastine fumerate, as control drug, the percentage of overall improvement was 76.5% with TL-102 (100 μg BDP/day) (Okamoto et al., 1984). Furthermore, in a well-controlled study performed in 120 cases using TL-102 (100μg BPD/day) and a BDP preparation (400 μg BDP/day) for a period of one week, the percentage of overall improvement was respectively 83.0% and 67.3% (Okamoto et al., 1984). The above results suggest that the administration of TL-102 containing 50 μg of BDP twice a day is as effective as the administration of a BDP preparation containing 100 μg of BDP four times a day, and that the use of TL-102 permits a decrease of the dose of BDP to 1/4th of that of the conventional BDP preparations. The efficacy of TL-102 is considered to be caused by a prolonged presence of BDP on the nasal mucosa owing to HPC, which enables to release the active ingredient, BDP. This phenomenon has already been proved in tracer studies using TL-102 containing labeled BDP (Yamamoto et al., 1984a, b).

Side effects were noted in 10 out of the 222 cases (4.5%), but there was no difference in incidence between TL-102 treated groups. However, in other studies performed under similar conditions using other BDP preparations in 245 cases the incidence of side effects was respectively 14.8% and 12.6% (Okuda et al., 1978,

1979). In a well-controlled study performed in 120 cases for a period of one week using TL-102 (100 μg BDP/day) and a BDP preparation (400 μg/day), the incidence of side effect was 0% in the TL-102 group and 12.0% in the BDP group (Okamoto et al., 1984). In addition, in 22 cases treated with TL-102 (100 μg BDP/day successive for 1–7 months), no side effect was noted and no special changes in serum cortisol, hematological parameters and urinary findings were observed (Okamoto et al., 1984). The agglomeration of TL-102 on the surface of the nasal mucosa, which was expected to occur, was not found.

The fact that TL-102 causes less side effects than the existing BDP preparations is probably caused by the following reasons: 1. the use of HPC as adhesive base irritates the nasal mucosa less than freon gas which induces a strong local irritation, and is used as propellant for other BDP preparations, and 2. a lower daily frequency of administration is needed.

In a well-controlled study performed in 151 cases using TL-102 (100 μg BDP/day) and disodium cromoglycate (shortened as DSCG) for a period of four weeks, the percentage of four weeks, the percentage of overall improvement was 91.1% in the TL-102 group and 43.4% in the DSCG group (Okamoto et al., 1984). This fact indicated that TL-102 brought about better results than DSCG and, in addition, a 4-week administration of TL-102 would make it possible to increase the percentage of improvement as compared with a 1-week administration. TL-102 has been reported to be effective not only in perennial nasal allergy but also in pollinosis: the satisfactory efficacy (remarkable or good overall improvement) as obtained in 83.8% of 84 cases with pollinosis due to cedar pollen after treatment with TL-102 for two weeks (Okamoto et al., 1984). TL-102 seems to have an antiallergic effect in perennial nasal allergy, comparable to the existing BDP preparations at 1/4th of the dose of these preparations and with few side effects. Not only subjective symptoms like sneezing, nasal discharge and nasal blockage but also objective findings such as mucosal swelling observed rhinoscopically, volume of nasal discharge, nasal provocation reaction and nasal eosinophil count, were improved. It was noticeable that the efficacy persisted for at least one week following the end of treatment.

RÉSUMÉ

Une étude comparative en double aveugle a été effectuée chez 250 cas d'allergie nasal pérennante pour évaluer l'effecacité, la sécurité et la dose optimale de TL-102, une mixture sous forme de poudre de dipropionate de beclomethasone (DPB) plus hydroxypropylcellulose (HPC). 4 differentes capsules de TL-102 à 1,5, 12,5, 25,0 et 50 μg de DPB, respectivement, plus 30 mg de HPC ont été préparées, et les capsules ont été pulvérisées dans la cavité nasale également par les narines deux fois par jour pendant une semaine. L'amélioration totale, l'utilité clinique, l'amélioration symptomatique (éternuement, écoulement nasal et

obstruction nasale) et l'amélioration rhinoscopique (oedème de la membrane muqeuse et secretion nasale) dépendaient de la dose de DPB. La reaction de provocation par l'antigène et le niveau éosiniphile nasal ont été diminués par rapport au groupe traité à 3.0 $\mu$g de DPB p. jour. Le taux d'incidence d'effet secondaire était de 4.5%, et tous les effets secondaires observés étaient légers. TL-102 a permis d'obtenir l'efficacité thérapeutique comparable aux preparations de DPB de type courant à la dose équivalente à 1/4 de celle de ces préparations courantes et aussi de diminuer le taux d'incidence d'effet secondaire à 1/3 de celui dû à elles. La posologie journalière raisonnable était de deux capsules à 50$\mu$g de DPB plus 30 mg de HPC, soit 100 $\mu$g de DPB/jour b.i.d.

## REFERENCES


1. Komoriya K, Yamazaki N, Tsuchimoto M, Takeshita T, Naruchi T. Study on antigenecity of TL-102. Clin Report 1984; 18:4335-58.
2. Koyama T, Makita T, Ichikawa N. Irritating effect of TL-102 on rabbit nasal mucosa. Clin Report 1984; 18:4349-52.
3. Kuroishi T, Asaka H, Okamoto M. A basic study on beclomethasone dipropionate powder preparation (TL-102) - Determination of optimal dose of hydroxypropylcellulose. Jpn Pharmacol Ther 1984; 12:4049-53.
4. Kuroishi T, Asaka H, Okamoto M. Phase I study on beclomethasone dipropionate powder preparation (TL-102) - Single and repeat administrations. Jpn Pharmacol Ther 1984; 12:4055-71.
5. Murai S, Ohi M, Sakakura Y, Miyoshi Y. Effects of various drugs containing hydroxypropylcellulose as base on transfer function of nasal mucosal cilia. ORL Tokyo 1984; 27:97-102.
6. Okamoto M et al. Clinical study on beclomethasone dipropionate powder preparation (TL-102) in perennial nasal allergy (Report 1). ORL Tokyo 1984; 27:58-74.
7. Okamoto M et al. Clinical study on beclomethasone dipropionate powder preparation (TL-102) in perennial nasal allergy (Report 3) - Comparative study with beclomethasone propionate nasal spray. ORL Tokyo 1984; 27:171-80.
8. Okamoto M et al. Clinical study on beclomethasone dipropionate powder preparation (TL-102) in perennial nasal allergy (Report 4) - Double-blind trial with clemastine fumurate. ORL Tokyo 1984; 27:181-92.
9. Okamoto M et al. Clinical study on beclomethasone dipropionate powder preparation (TL-102) in perennial nasal allergy (Report 6) - Comparative study with disodium cromoglycate. ORL Tokyo 1984; 27:671-96.
10. Okamoto M et al. Long-term use of beclomethasone dipropionate powder preparation (TL-102) in nasal hypersensitivity. ORL Tokyo 1984; 27:652-69.
11. Okamoto M et al. Clinical study on beclomethasone dipropionate powder preparation (TL-102) in nasal allergy - Pollinosis due to cedar pollen. ORL Tokyo 1984; 27:613-32.
12. Okuda M et al. Double-blind clinical study on beclomethasone dipropionate nasal aerosol in nasal allergy. Pract Otol Kyoto 1978; 7:977-1004.
13. Okuda M et al. Clinical study on beclomethasone nasal spray in nasal allergy - Optimal dose, efficacy and safety. ORL Tokyo 1979; 25:1283-1309.
14. Okuda M, Semba O. Effects of beclomethasone dipropionate nasal spray on subjective and objective findings in perennial allergic rhinitis. Clin Otolaryngol 1980; 5:315-21.
15. Okuda M et al. Clinical study on intranasal beclomethasone dipropionate (Aldecin Nasal) and oral d-chlorpheniramine maleate (Polaramine long-acting tablet). Otologia 1980; 477-98.

16. Okuda M, Sakaguchi K, Ohtsuka H. Intranasal beclomethasone. Mode of action in nasal allergy. Ann Allergy 1983; 50:116–20.
17. Saito H, Uede K, Terazono T, Miyoshi S, Hoshino A, Takenaka H. Examination of inhibitory effect on ciliary movement of nasal mucosa by tissue culture – Mainly for HPC. ORL Tokyo 1982; 25:319–29.
18. Unno T, Okude Y, Yanai O, Onodera S. Distribution of beclomethasone dipropionate aerosol particles in the nasal cavity. Jpn J Otol Tokyo 1982; 85:277–82.
19. Usui N, Iwata A, Uchiyama M, Tsukasa M, Ogoshi T. Effect of TL-102 on perennial nasal allergy in nasal provocation test by metered-dosing. ORL Tokyo 1984; 27:486–98.
20. Yamamoto M, Okabe K, Kubo J, Naruchi T, Ikura H, Suzuki Y. Behavior of TL-102 in nasal cavity – Study on distribution of active ingredient, BDP, in nasal cavity by microautoradiography. Clin Report 1984; 18:4364–70.
21. Yamamoto M, Okabe K, Kubo J, Naruchi T, Ikura H, Suzuki Y. Behavior of TL-102 in nasal cavity – Study on adhesion and stay of active ingredient following intranasal application. Clin Report 1984; 18:4359–63.

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