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AEROSOLIZED
DEXAMETHASONE ISONICOTINATE
IN THE TREATMENT OF
BRONCHIAL ASTHMA

*A Double Blind Study**

By

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Aerosolized corticosteroids have been used in the treatment of bronchial asthma with excellent results; in some instances they have proved superior to corticosteroids taken orally (1, 2, 5, 7).

Dexamethasone isonicotinate is different from free dexamethasone in enhanced anti-inflammatory, anti-exudative and glucocorticoid effects. Its suppressive action on adrenocortical function is not greater than the free form. The increased effectiveness is observed only when administered topically or parentally, not orally (4). This has led European in-

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investigators to use it as an inhalant in the treatment of bronchial asthma (3, 6, 10). The present study was aimed at evaluating aerosolized dexamethasone isonicotinate in double blind test in patients with asthma and investigating its adrenocortical suppression.

MATERIAL AND METHODS

Double Blind Study:

Forty-three patients with bronchial asthma (27 males and 16 females) who had attended four different allergy clinics in Japan were chosen for the study. Their age ranged from 15 to 71 years with the mean of 38.1. Selection was restricted to those who required continuous or intermittent administration of oral corticosteroids in addition to sympathomimetic drugs and theophylline derivatives.

Dexamethasone isonicotinate was propelled from a portable aerosol nebulizer (Nippon C. H. Boehringer Sohn, Osaka, Japan). The size of the aerosol was less than 5 μ m in diameter.

Dexamethasone isonicotinate inhalation and placebo were each administered by two inhalations four times daily for a two week period in a double blind cross-over manner. By random selection the active inhalation was administered first in 23 patients followed by placebo, whereas the order was reversed in 20 patients. During the entire trial period patients were instructed to reduce the amount of oral corticosteroids by $\frac{1}{2}$ to 1 tablet every two to three days, as long as their symptoms showed improvement or remained improved. Corti-

TABLE 2
Effects of Dexamethasone Isonicotinate Inhalation in Comparison with Placebo Inhalation

Type of asthma	Number of subjects	Better than placebo	Worse than placebo	No difference
Atopic	6*	5	None	1
Infectious	10	5	4	1
Mixed	26	25	1	None
Psychogenic	1	1	None	None
Total	43	36(83.7§)	5(11.6)	2(4.7)

* Number of subjects.

§ Percent of the total number.

TABLE 2
Asthmatic Symptoms and Amount of Oral Steroids during the First and Last 3 Days of the First Half of Trial

Group	Number of subjects	Day of trial	Total number of steroid tablets used (per day)	Total number of episodes recorded per day*		
				Severe to moderate dyspnea	Mild dyspnea	Wheezing only
Dexamethasone		1st	24.5 (Tabs)	9	12	17
Isonicotinate		2nd	26.5	7	6	13
inhalation	20	3rd	25.5	6	3	15
		12th	10.5	1	2	8
		13th	9.0	2	2	9
		14th	8.5	1	5	7
Placebo		1st	23.0	3	14	24
inhalation		2nd	25.5	8	18	22
	23	3rd	21.5	5	13	26
		12th	35.5	3	12	21
		13th	30.0	3	14	21
		14th	25.5	2	14	19

* The episodes of asthma as listed in the table were recorded in asthma diary, in which subjects were requested to fill up 3 times a day, in the morning, in the daytime and in the evening.

costeroid tablets used were prednisolone (5 mg), dexamethasone (0.5 mg), betamethasone (0.5 mg) and methylprednisolone (4 mg). If their symptoms worsened during the graded reduction, oral corticosteroid was increased to the starting dose. Usual therapeutic regimen was continued. Patients kept daily records of frequency of dyspnea and wheezing and medications by using a scoring system (Table 2).

Participating physicians chose which of the treatments was more effective, without knowing the assignment of the treatments. They also gave global rating of improvement from 100 per cent improvement to 100 per cent worsening on the first treatment only. The basis of the judgement were 1) improvement of asthmatic symptoms, 2) reduction of oral corticosteroids and other drugs and 3) findings checked on regular visits.

Adrenocortical Suppression Study:

Five healthy subjects, all male, 30 to 40 years of age, took two inhalations of dexamethasone isonicotinate aerosol four times daily for a two weeks' period. Plasma level of 17-hydroxycorticosteroids was measured seven days, five days and immediately before, and seven days, 14 days and 21 days after the start of the inhalation schedule. Blood was drawn into heparinized tubes between 9 and 10 in the morning. The blood was centrifuged immediately and Porter-Silber chromogens were extracted from the plasma by the procedure of Peterson *et al.* (8, 9).

RESULTS

Double-Blind Study:

Forty-three subjects completed the trial. Table 1 summarizes the results. Thirty-six out of them (84 per cent) obtained better results with the inhalation of dexamethasone isonicotinate than with the placebo, while five obtained the reversed results. Among remaining two subjects there was no difference in the effect. The response to the inhalation of dexamethasone isonicotinate was highly significantly superior to that of placebo (binomial test, $P < 0.001$).

Eighteen subjects obtained better results with the inhalation of the first two weeks than with that of the second two weeks, 23 obtained the reversed results and two subjects did not show any difference between two periods. Thus there was no tendency of the order to get better results.

Some of the subjects experienced mild irritation of the throat on the inhalation. Two females, 30 and 31 years, reported irregularity of menstruation. None of the subjects discontinued the inhalation schedule because of such side-effects.

Table 2 shows the changes of the asthmatic symptoms and the amount of oral corticosteroids used during the first and the last three days of the first half of the trial in the two groups: 20 subjects placed on dexamethasone isonicotinate inhalation and 23 on placebo. In the dexamethasone isonicotinate group, the amount of oral corticosteroids and the frequency of asthmatic symptoms decreased after the inhalation, while in the placebo group they did not change essentially.

The efficacy of dexamethasone isonicotinate inhalation was evaluated in terms of the amount of oral corticosteroids. With the aid of multiple regression analysis, the extent of global rating of improvement was expressed as a linear combination of changes in oral corticosteroid consumption, in the number of dyspnea and in the number of wheezing episodes. According to this approximate expression, the difference between the averages of global improvement for active and placebo groups is equivalent to about 5 tablets/3 days (95 per cent confidence limits 1.8–8.2 tablets/3 days) of oral corticosteroids.

Adrenal Suppression:

Table 3 summarizes the results on five healthy subjects. The plasma level of 17-hydroxycorticosteroids diminished after one week's inhalation by approximately 50 per cent of the control value and remained decreased during 2 weeks' inhalation. The level returned to the control value one week after the end of the inhalation.

TABLE 3
Influence of Dexamethasone Isonicotinate Inhalation on the Plasma Level of 17-Hydroxycorticosteroids in 5 Healthy Subjects

Subjects	Sex	Age	Day-7	Day-5	Day 0	Day 7	Day 14	Day 21
1	♂	30	8.4*	4.8	8.1	6.8	0.8	7.2
2	♂	34	12.0	9.8	10.0	4.0	4.0	12.0
3	♂	34	4.8	8.15	8.65	0	0	7.2
4	♂	40	9.6	13.0	14.8	5.75	9.1	12.0
5	♂	32	8.0	8.35	12.0	7.3	7.3	12.0
Mean			8.56	8.82	10.71	4.77	4.24	10.0

Five healthy subjects took 8 inhalations of dexamethasone isonicotinate, total of 1.0 mg a day for two weeks from day 0 to day 13. The plasma level of 17-hydroxycorticosteroids on day 7 and day 14 diminished significantly, as compared with that of day 0 ($P < 0.05$, two-way classification rank test).

* Plasma level of 17-hydroxycorticosteroids, $\mu\text{g}/100$ ml of plasma.

COMMENTS

Our double-blind study showed that aerosolized dexamethasone isonicotinate was significantly effective to control asthmatic symptoms. In 84 per cent of the patients, the response to the steroid inhalation was better than that to the placebo.

The inhalation of dexamethasone isonicotinate, 1.0 mg (0.8 mg as dexamethasone) per day per person, was estimated to be as effective as oral administration of 1.7 (95 per cent interval, 0.6~2.7) tablets of steroids per day per person. Since about 50 per cent of the inhaled corticosteroid mist is estimated to reach the airway, and the retention in the mouth is minimal (1, 2) about 0.5 mg of dexamethasone isonicotinate can be assumed to reach the lower airways by the daily inhalation of 1.0 mg dexamethasone isonicotinate. Approximately 0.5 mg dexamethasone isonicotinate (0.4 mg as dexamethasone) deposited in the airway is comparable with 1.7 tablets (95 per cent interval, 0.6~2.7 tablets) of oral corticosteroids, estimated equivalent to approximately 0.85 mg (95 per cent interval, 0.3~1.36 mg) orally administered dexamethasone. Our impression is that the inhaled dexamethasone isonicotinate might be more efficient to control asthmatic symptoms than oral corticoids, confirming the previous reports (1, 2, 3, 5, 6, 7).

No significant side-effects were observed with two weeks inhalation of dexamethasone isonicotinate, confirming other clinical reports on long term use (3, 6, 10).

Adrenocortical suppression is one of the most hazardous side-effects of corticosteroid therapy. *Engelhardt* (4) administered dexamethasone isonicotinate and its free form of the same molarity to rats parenterally and measured the weight of the adrenals. The decrease of the adrenal weight due to dexamethasone isonicotinate was equal to or less than that due to free dexamethasone, suggesting that adrenocortical suppression by dexamethasone isonicotinate did not exceed that of its free form. *Bottker et al.* (3) found no eosinopenia after one week's inhalation of the dexamethasone

isonicotinate and some after 2 weeks' inhalation, suggesting that the absorption of the steroid was slow and minimal. However, our measurement of the plasma level of the 17-hydroxycorticosteroid showed that inhalation of 1.0 mg dexamethasone isonicotinate suppressed the plasma level by about 50 per cent, although the plasma level returned to the control value one week after the inhalation. We feel that one should cautiously consider adrenal suppression on using aerosolized dexamethasone isonicotinate.

Five out of 10 patients of infectious type did not show improvement, while this was the case in only 2 out of 32 patients of atopic or mixed type (Table 1), suggesting that aerosolized dexamethasone isonicotinate is more effective to atopic than infectious asthma. The subjects were selected among those with asthma of moderate severity requiring prolonged oral corticosteroid therapy. Previous reports on aerosolized steroid therapy and our preliminary study of this preparation suggested that aerosolized steroid is not effective to patients with severe bronchial constriction or with status asthmatics. Aerosolized dexamethasone isonicotinate is indicated for patients with asthma of moderate severity who require continuous or intermittent steroid therapy.

SUMMARY

Double blind evaluation of aerosolized dexamethasone isonicotinate showed that it was significantly effective to control asthmatic symptoms in the patients who required continuous or intermittent administration of oral corticosteroids and, also, suggested that it might be more efficient than oral corticosteroids. Moderate suppression of the plasma level of 17-hydroxycorticosteroids was observed with the daily inhalation of 1 mg dexamethasone isonicotinate for one to two weeks in normal subjects.

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