

A Double Blind Controlled Trial of N-(3', 4'-Dimethoxycinnamoyl) Anthranilic Acid on Children with Bronchial Asthma

N-5' STUDY GROUP IN CHILDREN*

A double blind controlled trial of N-(3',4'-dimethoxycinnamoyl) anthranilic acid (N-5') was carried out for treating children with bronchial asthma to determine its efficacy and safety.

The results showed that the drug was significantly more effective in the N₁₀ and N₅ groups than in the N₀ group. Adverse reactions appeared only in one patient in the N₁₀ group who complained of slight anorexia while another patient in the N₀ group reported moderate diarrhoea. Moreover there was no indication of abnormality in further laboratory investigations. It can be therefore concluded that this drug is useful for the treatment of children with bronchial asthma.

Key words: anti allergic drug, N-5'; bronchial asthma.

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N-5' (Fig. 1) introduced by Koda et al. (3) is a new drug which is similar to disodium chromoglycate (DSCG) and can be given orally as it is well absorbed by the gastrointestinal tract. They have also reported that the drug inhibited Type 1 hypersen-

sitivity (1) and a reduction in the rate and volume of respiration and also inhibited an increase in viscosity of the bronchus tract in animals with allergic asthma (4).

In this study, a double-blind controlled trial was carried out to determine the efficacy of the drug in the treatment of children with bronchial asthma.

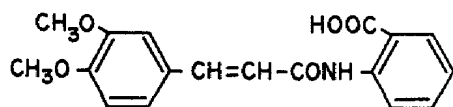


Fig. 1. Chemical structure of N-(3',4'-dimethoxycinnamoyl) anthranilic acid (N-5')

PATIENTS

The test subjects were selected from among children who were in- and outpatients suffering from bronchial asthma and who satisfied the following criteria:

1. patients have filled in the asthma diary (Fig. 2).
2. patients have had an asthma attack at the beginning of the trial.
3. patients have remained clinically stable although previously subjected to desensitization or non-specific therapy.
4. patients have not been affected by complications such as chronic bronchitis, pulmonary emphysema or bronchiectasis.

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date			day of month		
			morning	daytime	night
state of attack	severe				
	moderate				
	slight wheezing				
	no attack				
self-assessment of symptoms	cough				
	nasal symptoms	sneeze			
		nasal obstruction			
		nasal discharge			
	amount of sputa	much			
		little			
		none			
	expectoration of sputa	difficult			
		smooth			
	fever				
urticaria					
daily life	impossible				
	troubled				
	normal				
night sleep	impossible				
	troubled				
	normal				
cause of attack					
therapy	inhalation				
	injection				
	orally	habitual			
		temporary			
		adreno-corticoids			
			preventive-* medicine		
remarks					

* column of N-5*

Fig. 2. Asthma Diary

METHODS

Patients were divided at random into three groups. The first group was given N-5' 10 mg/kg/day (N_{10} group), the second, N-5' 5 mg/kg/day (N_5 group) and the third, inactive placebo, i.e. lactose (N_0 group). The drug was administered orally three times a day immediately on waking, at midday and just before going to bed.

The trial lasted 6 weeks. During the first 2 weeks, the effect of the placebo was determined by a single-blind method. Lactose powder was given to all patients. During the following 4 weeks, patients were treated with the drug as stated above by a double-blind method.

Clinical symptoms including state of attack, cough, and sputum were noted in the asthma diary. Adverse reactions were carefully observed.

Concomitant drugs such as DSCG, sustaining adrenocorticoids, adrenocorticotrophic hormones and antihistamines were not used throughout the trial. Bronchodilators including xanthine derivatives were given only during an attack. Adrenocorticoids were not administered unless it was absolutely necessary; if given the dose was kept to a minimum. Desensitization and non-specific therapy were not started during the trial. If a

patient had acute infection during the trial, he was treated accordingly.

The severity of the asthmatic attack (attack score) and the use of concomitant drugs (therapeutic score) were scored as shown in Table 1. The asthma score was defined as the summation of attack score and therapeutic score.

Laboratory investigations were performed as follows. Haematological investigations were made including erythrocyte, leukocyte, thrombocyte, haemoglobin, haematocrit count, as well as differential counting of leukocytes. Urinalysis for protein, sugar, pH, precipitation, urobilinogen. Biochemical analysis of serum-total bilirubin, GOT, GPT, LAP, alkaline phosphatase, cholesterol, protein, A/G, BUN and IgE. Pulmonary functions.

The results were statistically analyzed by Fisher's exact probability test or Wilcoxon's signed rank test and the efficacy and safety of the drug were then determined.

RESULTS

This trial comprised 284 cases, seven of which were excluded. Statistical analysis was made on 277 cases.

In Table 2, the overall evaluation in each group is indicated. It was found that more

Table 1

Scoring criteria for the severity of the asthmatic attack and the use of concomitant drugs, and asthma score

Attack score**		Therapeutic score***	
Status	Score/time	Concomitant drugs	Score/time
Severe	9	Oral	2
Moderate	6	Inhalation or suppository	3
Slight wheezing	3	Bronchodilators i.d. or i.m.	5
No attack	0	i.v.	8
		drip	15
Cough	1	Steroids	2*

*2/1 mg prednisolone

**Attacks in morning, daytime and night are recorded separately.

***Treatment in morning, daytime and night is recorded separately.

Asthma score = Attack score + Therapeutic score.

than 60% of patients improved after taking the drug; this is statistically significant ($P < 0.001$).

In Fig. 3, attack, therapeutic and asthma scores were compared within a group. As can be seen, attack and asthma scores were

Table 2
Overall efficacy

Group	No. patients	Effective	Non-effective	Unknown	Efficacy (%)
N ₀	92	30	59	3	33
N ₅	93	60	30	3	65*
N ₁₀	92	56	33	3	61**

Analyses: The drug showed more significant efficacy in N₁₀ group and N₅ group than in N₀ group according to Fisher's exact probability test.

* $P < 0.001$

** $P < 0.001$

Table 3
Assessments of efficacy in each group according to age

Factor	Group	n	Effective	Non-effective	Unknown	Efficacy* %
Under 6 years old	N ₀	37	11	23	3	30 (11/37)
	N ₅	27	18	8	1	67 (18/27)
	N ₁₀	32	21	10	1	66 (21/32)
	Total	96	50	41	5	52 (50/96)
From 6 to 10 years old	N ₀	34	14	20	0	41 (14/34)
	N ₅	37	23	12	2	62 (23/37)
	N ₁₀	32	20	11	1	63 (20/32)
	Total	103	57	43	3	55 (57/103)
10 years old or more	N ₀	21	5	16	0	24 (5/21)
	N ₅	29	19	10	0	66 (19/29)
	N ₁₀	28	15	12	1	54 (15/28)
	Total	78	39	38	1	50 (39/78)

Analyses (Fisher's exact probability test):

*Under 6 years: the drug showed more significant efficacy in N₅ and N₁₀ groups than in N₀ group ($P < 0.01$, respectively).

From 6 to 10 years: no significance among the three groups. 10 years or more: the drug showed more significant efficacy in N₅ and N₁₀ groups than in N₀ groups ($P < 0.01$, $P < 0.1$, respectively).

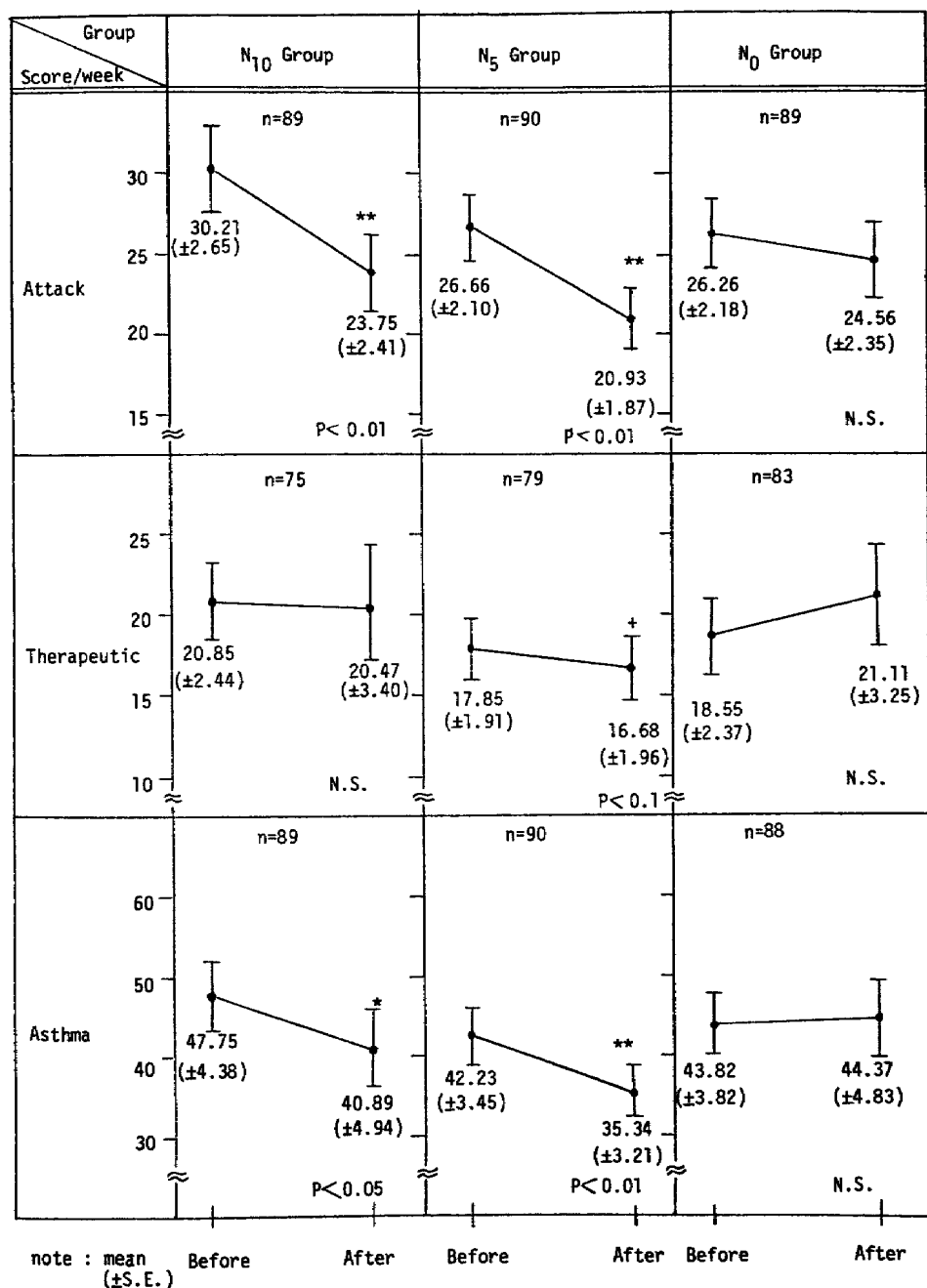


Fig. 3. Change of attack, therapeutic and asthma score between before and after treatment within a group.

significantly reduced in the drug-taking groups. For therapeutic score, although no significant change in N_{10} and N_5 groups was observed, there was an apparent increase in N_0 group.

These results suggested that the drug was useful for the treatment of patients with bronchial asthma.

Three groups were further subdivided according to age or severity of disease (Tables 3 and 4). Table 3 shows that the drug was significantly effective in children under 6 years of age and in children of more than 10 years. However, the drug was not significantly effective in children between 6

and 10 years of age. This might be because a relatively high proportion of children seemed to improve spontaneously in the N_0 group (Table 3).

Each group was subdivided according to severity of disease and a statistical analysis of the results is shown in Table 4. It seemed that the drug was clearly effective in "moderate" cases of asthma, less effective in "slight" cases, and not obviously effective in "severe" cases. However, it was stressed that a relatively high proportion of children in the N_0 group improved in "slight" cases and too few "severe" cases were analysed.

No patient had adverse reaction in the N_5

Table 4
Assessments of efficacy in each group according to the severity of bronchial asthma

Factor	Group	n	Effective	Non-effective	Unknown	Efficacy %
Slight	N_0	29	13	14	2	45 (13/29)
	N_5	27	19	7	1	70 (19/27)
	N_{10}	19	14	5	0	74 (14/19)
	Total	75	46	26	3	61 (46/75)
Moderate	N_0	45	12	33	0	27 (12/45)
	N_5	52	36	15	1	69 (36/52)
	N_{10}	51	34	17	0	67 (34/51)
	Total	148	82	65	1	55 (82/148)
Severe	N_0	18	5	12	1	28 (5/18)
	N_5	14	5	8	1	36 (5/14)
	N_{10}	22	8	11	3	36 (8/22)
	Total	54	18	31	5	33 (18/54)

Analyses (Fisher's exact probability test):

Slight: the drug showed a more significant tendency towards efficacy in N_5 and N_{10} groups than in N_0 ($P < 0.1$).

Moderate: the drug showed more significant efficacy in N_5 and N_{10} groups than in N_0 group ($P < 0.001$).

Severe: no significance among the three groups.

group, and only one had in the N_{10} group – he complained of slight anorexia, while one patient in the N_0 group had moderate diarrhoea. Moreover the other laboratory investigations were normal. Therefore it can be concluded that N-5' is a useful drug for treating children with bronchial asthma.

DISCUSSION

It was clearly demonstrated that this new drug (N-5') was effective for treating patients with bronchial asthma because: 1) more than 60% of patients improved; 2) less symptoms were noted; 3) less concomitant drugs were likely to be needed; 4) no other side effects except for slight anorexia were observed; and 5) no abnormality was found in the laboratory investigations. The reason why no statistical significance was noted in the group of 6–10-year-old patients and the group with slight bronchial asthma might be due to spontaneous recovery.

The efficacy of the drug during long-term administration (more than 6 months) has been studied by Kano et al. (2) Nishimuta et al. (5) and Torii et al. (6). They found that the drug caused no severe adverse reaction and that steroids were not needed during the trials (over 7 months). One of the advantages of this drug is that it can be administered orally, thus infantile asthma can be treated without difficulty.

A report has suggested that not only Type I but also Type III hypersensitivity could be suppressed by this drug (3). It has been established in animal experiments that the drug inhibited the release of anaphylactic mediators from activated mast cells and also inhibited the primary reaction of Type III hypersensitivity (4). This evidence makes us wonder whether it is possible to treat patients with other forms of allergic disorder, as well as patients with ulcerative colitis, Crohn's disease, urticaria pigmentosa, cold urticaria, vasomotor rhinitis or interstitial nephritis, whose symptoms may be due to increase in mast cells. If this is the

case, the drug may be useful. It was observed by one of us (H.S.) that a child with ulcerative colitis clinically improved with this drug. We felt certain that it relieved a local asthmatic attack and total bodily reaction; this encourages us to perform further trials.

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