

Acta Medica Okayama

Volume 34, Issue 6

1980

Article 4

DECEMBER 1980

Clinical effects of HC 20-511 (ketotifen) in bronchial asthma and its inhibitory effect on antigen-induced morphological changes of basophils

Yoshiro Tanizaki*

Kiyoshi Takahashi†

Yoshinori Goda‡

Yoshihede Sasaki**

Hiroshi Harada††

Ikuro Kimura‡‡

*Okayama University,

†Okayama University,

‡Okayama University,

**Okayama University,

††Okayama University,

‡‡Okayama University,

Clinical effects of HC 20-511 (ketotifen) in bronchial asthma and its inhibitory effect on antigen-induced morphological changes of basophils*

Yoshiro Tanizaki, Kiyoshi Takahashi, Yoshinori Goda, Yoshihede Sasaki, Hiroshi Harada, and Ikuro Kimura

Abstract

Sixty-four patients with confirmed bronchial asthma were treated with HC 20-511 (Ketotifen). HC20-511 was evaluated to be very effective in 6.3%, effective in 50.0% and slightly effective in 10.9% of these patients. The appearance of reactive basophils was inhibited by HC 20-511 in 5 out of 6 cases of reaction to house dust, in all three cases with buckwheat allergy to their allergen and in 7 out of 11 cases to anti-IgE. These results confirm that HC 20-511 inhibits type I allergic reactions induced by specific allergen and IgE.

KEYWORDS: bronchial asthma, ketotifen, basophil reactivity, allergens, anti-IgE

*PMID: 6451144 [PubMed - indexed for MEDLINE]

Copyright (C) OKAYAMA UNIVERSITY MEDICAL SCHOOL

Acta Med. Okayama 34, (6), 383—388 (1980)

**CLINICAL EFFECTS OF HC 20-511 (KETOTIFEN) IN
BRONCHIAL ASTHMA AND ITS INHIBITORY
EFFECT ON ANTIGEN-INDUCED
MORPHOLOGICAL CHANGES
OF BASOPHILS**

Yoshiro TANIZAKI, Kiyoshi TAKAHASHI, Yoshinori GODA,
Yoshihide SASAKI, Hiroshi HARADA and Ikuro KIMURA

*Department of Medicine, The Second Clinic, Okayama University
Medical School, Okayama 700, Japan*

(Director: Prof. I. Kimura)

Received July 24, 1980

Abs.tract. Sixty-four patients with confirmed bronchial asthma were treated with HC 20-511 (Ketotifen). HC 20-511 was evaluated to be very effective in 6.3%, effective in 50.0% and slightly effective in 10.9% of these patients. The appearance of reactive basophils was inhibited by HC 20-511 in 5 out of 6 cases of reaction to house dust, in all three cases with buckwheat allergy to their allergen and in 7 out of 11 cases to anti-IgE. These results confirm that HC 20-511 inhibits type I allergic reactions induced by specific allergen and IgE.

Key words: bronchial asthma, Ketotifen, basophil reactivity, allergens, anti-IgE.

It is thought that drugs inhibiting IgE-mediated reactions can be used for prophylactic treatment of atopic type bronchial asthma. Martin and Römer (1) reported that HC 20-511 is a highly active antihistaminic which inhibits antigen-antibody anaphylactic reactions and anaphylactically induced increases in the airways resistance of rats. Moreover, they suggest that HC 20-511 inhibits cyclic adenosyl 3', 5'-monophosphate (cAMP) phosphodiesterase. Its anaphylactic effect, therefore, was attributed to the inhibition of cAMP phosphodiesterase activity as for DSCG (2).

In this paper, the clinical effects on HC 20-511 in patients with bronchial asthma, and its inhibitory effect on anti-IgE or antigen-induced morphological changes in basophils are described.

MATERIALS AND METHODS

Seventy-two patients with bronchial asthma were selected at random for the following investigations: The clinical effects of HC 20-511 were studied in 66 asthmatics — 37 females and 29 males aged between 16 and 64 years. Two cases

were omitted because of drowsiness. Their ages and severity of asthma are presented in Table 1.

TABLE 1. SEVERITY OF ASTHMA AND AGE OF THE 64 PATIENTS STUDIED

Age	No. of cases	Severity	No. of cases
-20	2	Slight	18
21-30	8	Moderate	36
31-40	16	Severe	10
41-50	18		
51-	20		

Inhibition tests of reactive basophils to anti-IgE or specific allergens were performed in 19 cases. Blood basophils from 11 asthmatics were examined for reactivity to anti-IgE and the cells from 6 asthmatics whose specific allergen was house dust were tested with house dust extract. Basophil reactivity to buckwheat extract was tested in 3 asthmatics with buckwheat allergy. The inhibitory effect of HC 20-511 on the morphological changes of basophils was investigated.

Sixty-six patients with bronchial asthma were treated with HC 20-511. Two cases were omitted after a few days because of excessive sedation, and finally sixty-four cases were clinically evaluated. The drug was given orally, either 1 mg or 2 mg twice a day for four weeks or longer (average duration 5.2 months). The efficacy of HC 20-511 was evaluated at the end of four weeks. The following criteria were used for clinical evaluation: Auscultatory, prolonged expiration, expectoration, the consumption of anti-asthmatic agents, and the number and duration of asthma attacks per week. The toxicity of HC 20-511 was checked by laboratory tests in long term studies. Laboratory examinations [red blood cell, hemoglobin, white blood cell, serum transaminases (GOT, GPT)] were performed before and during the treatment at intervals of 4 weeks. Serum IgE levels were measured in 64 cases by the Phadebas RIST procedure.

Inhibition tests of reactive basophils to anti-IgE (anti-human IgE goat serum, Hyland, USA) or specific allergens (Torii Co., Japan) were carried out using the method previously reported (3, 4). The morphological changes of basophils to anti-IgE or specific allergens were observed under a microscope in a Fuchs-Rosenthal chamber. In this method, reactive basophils are pear-shaped and are easily differentiated from non-reacting round-shaped basophils.

To determine the appropriate concentration for HC 20-511, the inhibitory effect of various concentrations of HC 20-511 on reactive basophils appearing after the addition of anti-IgE was investigated in comparison with the action of DSCG. As shown in Fig. 1, the inhibitory effect of HC 20-511 was most intense at a 10^{-2} M concentration of HC 20-511. Therefore, the same concentration of HC 20-511 was used in the other investigations. The inhibitory effect of HC 20-511 was judged by the finding that the frequency of reactive basophils decreased by more than 20%.

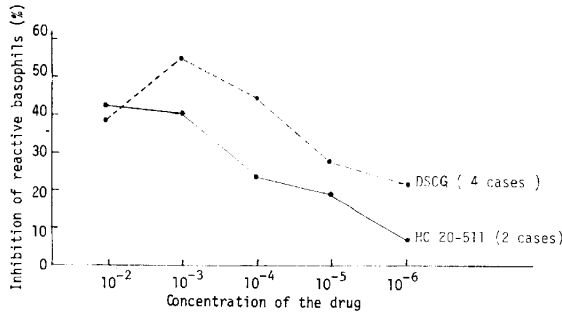


Fig. 1. Inhibitory effect of HC 20-511 on reactive basophils after the addition of anti-IgE.

RESULTS

Clinical effects of HC 20-511. HC 20-511 was very effective in 6.3%, effective in 50.0% and slightly effective in 10.9% of the cases. With respect to the severity of asthma, it was effective in 94.4% of mild patients, 61.1% of moderate patients and 40.0% of severe patients (Table 2). The efficacy of the drug did not correlate with serum IgE levels of patients with bronchial asthma (Table 3).

TABLE 2. CLINICAL EFFECTS OF HC 20-511 ADMINISTRATION IN 64 PATIENTS WITH BRONCHIAL ASTHMA

Severity of patients with asthma	Improvement				Efficacy (%)
	Very effective	Effective	Slightly effective	Not effective	
Slight	4	11	2	1	94.4
Moderate		18	4	14	61.1
Severe		3	1	6	40.0
Total	4	32	7	21	67.2

TABLE 3. THE RELATIONSHIP BETWEEN CLINICAL EFFICACIES OF HC 20-511 DOSES AND SERUM IgE LEVELS OF PATIENTS WITH BRONCHIAL ASTHMA

Serum IgE level of patients with bronchial asthma (IU/ml)	Improvement				Efficacy (%)
	Very effective	Effective	Slightly effective	Not effective	
701-	2	8	1	7	61.1
301-700		10	3	5	72.2
101-300	2	8	3	5	72.2
0-100		6		4	60.2

Laboratory tests during long-term administration showed that toxicity due to HC 20-511 was very low. Serum bilirubin concentrations were measured in

26 cases, and no abnormal increase of serum bilirubin levels was found. Serum GOT, GPT and alkaline phosphatase activities were examined in 47 cases. Three of these cases showed slightly abnormal elevations of GOT or GPT activity at 1, 1 and 5 months after the start of administration, although the abnormal elevation was transient and became normal within one month of ceasing the drug. Slight and transient abnormal elevation of alkaline phosphatase activity was observed in 2 out of 47 cases. The long-term observation of serum transaminases and alkaline phosphatase demonstrated that the mean values of GOT and GPT remained normal during the treatment, and that alkaline phosphatase activity tended to increase slightly 6 or 7 months after the beginning of treatment, although only a few cases showed slightly abnormal elevation. No adverse effect was found in the peripheral blood.

Both 1 and 2 mg of HC 20-511 administration per day were free of severe adverse effect during long term treatment. Five patients complained of drowsiness and one of nasal obstruction.

Inhibitory effect of HC 20-511 on reactive basophils. The inhibitory effect of HC 20-511 on reactive basophils to anti-IgE or specific allergens was estimated in the cases showing more than 50% of reactive basophils to each reactant. Reactive basophils had decreased by more than 20% with HC 20-511 in 7 out of 11 cases (63.6%) after the addition of anti-IgE (Fig. 2), in 5 out of 6 cases

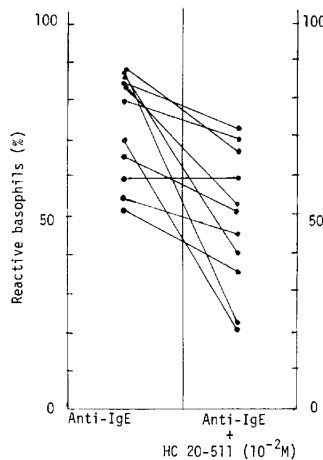


Fig. 2. Inhibitory effect of HC 20-511 on reactive basophils after the addition of anti-IgE in eleven patients.

(83.3%) to house dust extract, and in all three cases with buck-wheat allergy to their allergens (Fig. 3). These results show that HC 20-511 inhibited the immediate hypersensitivity induced by such specific allergens.

Effects of HC 20-511 in Bronchial Asthma

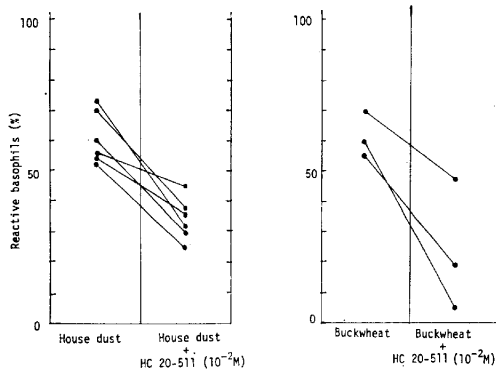


Fig. 3. Inhibitory effect of HC 20-511 on reactive basophils after the addition of specific allergens.

The clinical efficacy of HC 20-511 was compared with its inhibitory effect on reactive basophils induced by anti-IgE, and found to be effective in 5 out of 6 cases showing more than 20% decrease of reactive basophils, although the effect of HC 20-511 was observed in 2 out of 3 cases with less than 20% decrease of reactive basophils. This requires further confirmation in a larger number of cases.

DISCUSSION

Since DSCG inhibits the release of chemical mediators from tissue mast cells and blood basophils in immediate hypersensitivity, it has been used with prophylactic effect for bronchial asthma (2). A new therapeutic approach has been developed and many compounds have been synthesized recently (1). HC 20-511 is an antiallergic drug inhibiting the release of chemical mediators in the same way as DSCG. We reported previously that DSCG inhibited the morphological changes of basophils induced by anti-IgE (5). In this study, inhibition tests of basophils reactive to anti-IgE and specific allergens were carried out. The results confirm that HC 20-511 inhibits IgE- or specific allergen-induced type I allergic reactions. Comparison of clinical observations with the *in vitro* action of HC 20-511 demonstrated, however, that the efficacy of the drug did not always parallel serum IgE levels. HC 20-511 was effective in patients even with low serum IgE levels. HC 20-511 may, therefore, inhibit other types of allergic reactions besides type I allergy, possibly by inhibiting type III allergic reactions. Although Pauwels *et al.* reported that late asthmatic responses were inhibited by HC 20-511 and DSCG (6), definitive results for the effects of the drug on type III reactions are not yet available and more clinical investigation is needed. HC 20-511 seems to be an interesting, prophylactic drug for bronchial asthma.

REFERENCES

1. Martin, U. and Römer, D.: The pharmacological properties of a new, orally active anti-anaphylactic compounds: Ketotifen, a Benzocycloheptathiophene. *Arzneim. Forsch. Drug Res.* **28**, 770-782, 1978.
2. Foreman, J. C. and Garland, L. D.: Cromoglycate and other allergic drugs: A possible mechanism of action. *Br. Med. J.* **1**, 820-821, 1976.
3. Kimura, I., Tanizaki, Y., Goda, Y., Sasaki, Y., Akagi, K., Kobayashi, M. and Soda, R.: New *in vitro* method for detecting asthma allergen—Counting reactive basophils after addition of allergen. *Clin. Allergy* (in press).
4. Kimura, I., Moritani, Y. and Tanizaki, Y.: Basophils in bronchial asthma with reference to reagin-type allergy. *Clin. Allergy* **3**, 195-202, 1973.
5. Kimura, I., Tanizaki, Y., Sato, S., Takahashi, K., Saito, K. and Ueda, N.: Morphological changes of basophils in immunological reactions—Effect of sodium cromoglycate. *Clin. Allergy* **5**, 181-187, 1975.
6. Pauwels, R., Lamont, H. and Van Der Straeten, M.: Comparison between Ketotifen and DSCG in bronchial challenge. *Clin. Allergy* **8**, 289-293, 1978.