Potassium Iodide Inhibits Neutrophil Chemotaxis

KOICHI HONMA, KENJI SAGA, HIDEO ONODERA and MAKOTO TAKAHASHI

Department of Dermatology, Sapporo Medical College, Sapporo, Japan

We studied the effect of potassium iodide on the chemotaxis of neutrophil in 15 healthy subjects with a modified Boyden chamber method. Orally administered potassium iodide (15 mg/kg/day for 3 days) significantly inhibited the neutrophil chemotaxis in peripheral blood. It is postulated that the therapeutic effect of potassium iodide on erythema nodosum, nodular vasculitis, and Sweet's syndrome might be mediated through the inhibition of neutrophil chemotaxis by this agent. ***Key words: Modified Boyden chamber method; Leukocyte chemotaxis; Healthy subjects.***

(Accepted December 4, 1989.)

Acta Derm Venereol (Stockh) 1990; 70: 247–249.

K. Saga, Department of Dermatology, Sapporo Medical College, Minami 1 Nishi 16, Chyuou-ku, 060 Sapporo, Japan.

Potassium iodide (KI) has been successfully used for the treatment of subacute migratory panniculitis, erythema nodosum, nodular vasculitis, Sweet's syndrome and Behçet's disease (1,2,3). Although the clinical courses and dermatological signs differ in these diseases, their cutaneous lesions histologically show infiltration of neutrophils in the early stage of the diseases (4). Therefore we speculated that KI might be effective through the modulation of the function of neutrophils, chemotaxis in particular. The purpose of this investigation was to test if systemically administered KI would inhibit neutrophil chemotaxis of peripheral blood in healthy subjects. Our study has shown that KI significantly suppressed the chemotaxis of neutrophils.

MATERIALS AND METHODS

Subjects

This study was carried out according to the principles of the Declaration of Helsinki. Healthy male volunteers were recruited for the study and informed consent was obtained from each subject. The ages of 15 subjects were between 22 and 32 years, while one subject was 58 years old.

Preparation of chemotactic factor

The chemotactic factor was prepared according to the description by Wahba et al. (5). Normal human serum pooled from 5 healthy donors was incubated with 1.5 mg/ml *Escherichia coli* lipopolysaccharide for 90 min at 37°C. The endotoxin-activated serum was then heated at 56°C for 30 min. It was then centrifuged at 3000 *g* for 30 min at 40°C. Aliquots of the serum were stored at −20°C.

Preparation of neutrophil suspension

Ten ml of heparinized (100 units/ml) venous blood was mixed with 10 ml of 2% dextran 250 in phosphate-buffered saline (PBS) in a 15×150 mm glass test tube. The tubes were allowed to stand for 30–40 min at 37°C. The supernatant was transferred to a siliconized, conical 50-ml centrifuge tube. After centrifugation at 900 rpm for 8 min, the supernatant was discarded with a Pasteur pipette, leaving 3–5 ml of the dextran–plasma mixture. The cells were gently mixed with 35 ml of 0.87% ammonium chloride to hemolyze the erythrocytes. The leukocytes were then washed twice with PBS, resuspended in RPMI 1640 medium, and brought to a concentration of 2.5×10^6 cells/ml for use.

Chemotactic assay

Chemotaxis was measured by a modified Boyden chamber method (6). A two-section chamber separated by a membrane was used for the study. The chemotactic factor was diluted 1:4 in RPMI 1640 medium before being added to the lower section (0.2 ml/well) of a Blind-Well chamber. Polycarbonate membrane filters (Uni-Pore, 3 μm pore size)

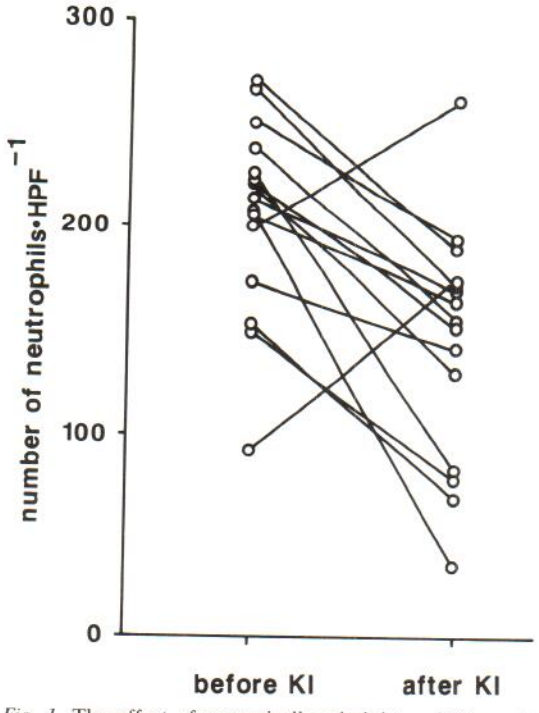

Fig. 1. The effect of systemically administered KI on the neutrophil chemotaxis in the peripheral blood. Each symbol represents the mean of a triplicate assay.

were placed between the upper and lower sections. The upper well parts were screwed into place and filled with 0.2 ml of neutrophil suspension in RPMI 1640 culture medium. the chemotactic chambers were incubated at 37°C for 90 min. After incubation, the cells in the upper well were aspirated and the upper well was washed twice with cold PBS. Then the Uni-Pore membrane was removed and air dried followed by methanol fixation. The membrane was stained with Giemsa, dehydrated, cleared with xylene, and mounted. The number of neutrophils per high-power view (×400) was counted using a microgrid. Five areas on the bottom surface of the filter were counted in each membrane and the numerical mean of the neutrophil number which migrated through the filter (cells reaching the down side of the membrane) was determined. Each assay was run in triplicate. The random migration of neutrophils, when the chemotactic factor was omitted from the lower well, was about 4% of the migration when the chemotactic factor was present in the lower well (data not shown).

Blood cell counts and serum biochemical analysis

Routine blood cell counts and serum biochemical analysis were carried out by the automatic analyzer system at the Department of Laboratory Diagnosis of the Sapporo Medical College Hospital together with patient's samples.

Materials

The *Escherichia coli* lipopolysaccharide and dextran 250 were purchased from Sigma (St. Louis, Mo.) and Pharmacia (Sweden), respectively. The Blind-Well chambers and Uni-Pore membranes (catalog no. 341–1011) were bought from Bio-Rad (Richmond, Calif.). Other chemicals were of reagent grade.

RESULTS

The subjects were given 15 mg of KI per 1 kg of body weight per day for 3 days. The chemotaxis of neutrophil was measured before and after the administration of KI. Thirteen volunteers showed a decrease in chemotaxis after KI administration, whereas 2 showed an increase (Fig. 1). Of these 2 subjects, one showed folliculitis in the course of KI administration and the other subject complained of a sore throat. However, whether or not there was a causal relation to KI is unknown. The average chemotactic activities, before and after KI administration, were 206 ± 48 and 144 ± 58, respectively. This result shows that systemically administered KI significantly ($p < 0.005$) suppresses the chemotactic activity of neutrophils in peripheral blood (Student's *t*-test, paired samples).

Total and differential blood cell counts and the following serum biochemical analyses were within normal limits before and after KI administration: total protein, albumin, total bilirubin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, creatinine, Na, K, Cl, IgG, IgA, and IgM (data not shown).

DISCUSSION

The therapeutic effects of KI on various skin diseases including subacute migratory panniculitis, erythema nodosum, nodular vasculitis, and Sweet's syndrome have been reported by various investigators, although little is known about the mechanism of the action of KI. Schulz & Whiting reported that 24 of 28 patients with erythema nodosum and 16 of 17 patients with nodular vasculitis responded to treatment with KI (3). They speculated that KI concentrates in granulomas and causes heparin to be released from mast cells. Heparin, in turn suppresses cellular immunity. Horio et al. reported that improvements were seen following KI treatment 11 of 15 patients with erythema nodosum, in 7 of 10 with nodular vasculitis, and in one of 4 with leg lesions of Behçet's syndrome (2). Since a common pathological change of the early lesions of these diseases is

the infiltration of neutrophils (4), we hypothesized that KI might exert its effect by modulating the function of the neutrophils.

There are few published studies on the effect of iodide on the function of neutrophils. Miyachi & Niwa studied the effect of potassium iodide, colchicine, and dapsone on the generation of polymorphonuclear leukocyte-derived oxygen intermediates in vitro (7). They found that potassium iodide and dapsone significantly suppressed the generation of hydrogen peroxide and hydroxy radical, and chemiluminescence. Tvedten & Till studied the effect of potassium iodide in vitro on the chemotaxis of neutrophils (8). They reported that potassium iodide had a rather dose-dependent inhibitory effect on rabbit peritoneal neutrophils, although it was not statistically significant.

This study demonstrated that systemically administered KI significantly inhibited the chemotaxis of neutrophil in healthy subjects. It is not clear, however, whether KI directly inhibited the chemotaxis or whether it indirectly modulated the function of neutrophil through an unknown mechanism, since chemotaxis is a complex process which includes the detection of the concentration gradient of a chemoattractant and the movement of the cells toward the chemoattractant. Although further studies are needed in order to understand the mechanism of the action of KI on the inhibition of the complex process of neutrophil chemotaxis, it is suggested that the therapeutic effect of KI on the above-mentioned diseases might work, at least in part, through the suppression of neutrophil chemotaxis.

ACKNOWLEDGEMENT

This study was supported in part by a grant from the Ministry of Culture and Education of Japan (59770747).

REFERENCES

1. Horio T, Imamura S, Danno K, Furukawa F, Ofuji S. Treatment of acute febrile neutrophilic dermatosis (Sweet's syndrome) with potassium iodide. Dermatologica 1980; 160: 341–347.
2. Horio T, Imamura S, Danno K, Ofuji S. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. Arch Dermatol 1981; 117: 29–31.
3. Schulz EJ, Whiting DA. Treatment of erythema nodosum and nodular vasculitis with potassium iodide. Br J Dermatol 1976; 94: 75–78.
4. Jorizzo JL, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. J Am Acad Dermatol 1988; 19: 983–1005.
5. Wahba A, Cohen H, Bar-Eli M, Callily R. Neutrophil chemotaxis in psoriasis. Acta Derm Venereol (Stockh) 1979; 59: 441–445.
6. Boyden S. The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leukocytes. J Exp Med 1962; 115: 454–466.
7. Miyachi Y, Niwa Y. Effects of potassium iodide, colchicine and dapsone on the generation of polymorphonuclear leukocyte-derived oxygen intermediates. Br J Dermatol 1982; 209–214.
8. Tvedten HW, Till GO. Effect of povidone, povidone-iodine, and iodide on locomotion (in vitro) of neutrophils from people, rats, dogs, and rabbits. Am J Vet Res 1985; 1797–1800.