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FAILURE OF BROCRESINE (NSD 1055)—
A HISTIDINE DECARBOXYLASE
INHIBITOR—TO INFLUENCE SKIN HISTAMINE
IN MICE

By

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The evidence of assigning histamine an active role in allergy has lead to an intensive search for antagonists. Studies on structure-activity relationship produced a great many drugs. To-day, recognized competitive inhibitors have an appreciated position in medical therapy. These pharmacological agents, however, are not always potent enough, and sideeffects such as sedation, dizziness and fatigue may be troublesome. Therefore the search for anti-histaminic drugs has continued. Numerous substances have been tested for their ability to inhibit histamine formation. Recent experiments by Levine and co-workers (5, 6) suggested that the histidine decarboxylase inhibitor brocresine or NSD 1055, which is 4-bromo-3-hydroxy-benzyloxyamine-dihydrogen phosphate; inhibits histamine biosynthesis in man and experimental animals. Since then several clinical and experimental reports on this drug have appeared with conflicting results (1, 2, 3, 9, 10).

The present paper reports on skin histamine in mice after prolonged treatment with brocresine. The data are from non-tumerous mice in a study intended to investigate the influence

of brocresine on tumour formation. The study on tumour formation is not completed.

MATERIAL AND METHODS

Histamine was investigated in approximately 100 mg skin of 17 albino Strit Leo mice (weight approximately 40 g) after 18 weeks' treatment with daily intraperitoneal injections of brocresine 1 mg in 0.5 ml physiological saline, and in 21 control mice treated with daily injections of 0.5 ml physiological saline. All mice were non-tumorous mice painted with 9,10-dimethyl-1,2-benzanthracene twice weekly through the first four weeks of the study. The skin samples were from grossly normal non-painted back skin. The skin samples freed of panniculus carnosus and subcutaneous fat were minced and lyophilized for 48 hours over phospho-pentoxide at room temperature under a pressure of 2 mm Hg. Defatting was carried out by shaking twice with 15 ml ether through one hour. The dried and defatted samples were homogenized in 5 ml of 0.4 N perchloric acid using a motordriven glass homogenizer. The homogenate was centrifuged, and a 4 ml aliquot of the supernatant was analyzed for histamine by the spectrofluorometric method of assay (8).

RESULTS

The results of the histamine determinations are summarized in Tables 1 and 2. The skin histamine content of mice treated with brocresine did not differ significantly from skin histamine of control mice treated with physiological saline. Most mice displayed skin histamine within the range of normal values for mouse skin found in previous studies by one of the authors (8). A few mice of each group showed somewhat elevated skin histamine. All histamine values are given as microgram histamine base per gram dried defatted skin.

DISCUSSION

The results of the present study agree with previous investigations by our group on skin histamine in man (9, 10). Brocresine in daily oral doses from 600 to 1800 mg did not reduce skin histamine in patients with chronic urticaria or urticaria pigmentosa. Brocresine also failed to diminish histamine excretion. Although all mice in our study were painted with 9,10-dimethyl-1,2-benzanthracene during the first weeks of the investigation,

we have no reason to believe that the conclusions drawn from the fact that skin histamine of controls and brocresine treated animals are identical are not valid. Our data are also in accordance with studies by *Green & Erichsson* (2), who found no significant change in rat heart histamine after brocresine.

Although brocresine is a specific histidine decarboxylase inhibitor (4, 7) which under certain experimental conditions such as histidine loading (5) may lead to reduced histamine excretion, it seems that formation of histamine from exogenous histidine is much more strongly inhibited than is the decarboxylation of endogenous histidine (3). Consequently the tissue stores of histamine are not influenced by brocresine. The results of the present studies do not encourage further clinical trials with brocresine.

TABLE 1

Skin histamine in grossly normal back skin of mice treated through eighteen weeks with daily intraperitoneal injections of 1 mg brocresine in 0.5 ml physiological saline.

No.	µg histamine per g dried defatted skin
1	299.0
2	283.4
3	117.5
4	560.2
5	619.6
6	350.4
7	534.1
8	143.9
9	180.7
10	165.3
11	164.6
12	400.6
13	461.1
14	274.6
15	589.3
16	466.9
17	441.7
Mean ± S. E.	356.0 ± 41.7

TABLE 2

Skin histamine in grossly normal back skin of mice treated through eighteen weeks with daily intraperitoneal injections of 0.5 ml physiological saline.

No.	μg histamine per g dried defatted skin
1	293.8
2	319.4
3	507.8
4	256.7
5	365.9
6	555.9
7	262.5
8	541.0
9	312.5
10	363.7
11	163.7
12	194.6
13	282.4
14	374.2
15	273.7
16	234.0
17	681.3
18	310.8
19	382.8
20	343.3
21	266.8
Mean $\pm$ S. E.	346.9 $\pm$ 28.2

SUMMARY

Skin histamine was studied in seventeen mice treated through eighteen weeks with daily intraperitoneal doses of 1 mg of the histidine decarboxylase inhibitor brocresine (NSD 1055) in saline and in twenty-one control mice treated with injections of saline. No significant difference was found between the groups. The results are in accordance with the results of previous work by two of the authors on skin histamine in man.

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