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INEFFECTIVENESS OF ANTIHISTAMINES TO
INHIBIT MAST CELLS DAMAGE BY
COMPOUND 48/80 IN MAN

By

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The intravenous administration of the histamine liberator 48/80 in man causes degranulation and decrease in the number of detectable mast cells in bronchial connective tissue (*Salvato* 1961, 1962).

Degranulation and decrease in the number of recognizable mast cells are morphological effects of the release of histamine (*Mota et al.*, 1956; *Keller*, 1957; *Asboe-Hansen*, 1957; *West*, 1958; *Riley*, 1959; *Boréus & Chakravarty*, 1960; *Uvnäs*, 1961).

Recently it has been demonstrated by *Mota & Dias da Silva*, (1960) that antihistamines potentiate mast cells' damage by 48/80, when acting on guinea-pig tissues, and inhibit the same phenomenon when acting on rat tissues.

In his monograph on the mast cells *Riley* (1959) affirms that "... premedication of rats with an antihistamine effectively protects the mast cells against the disruptive action of histamine-liberator or anaphylatoxin."

We decided to investigate such problem in man.

The experiment was conducted on 2 groups of subjects:

a) a first group of 11 patients was treated with daily progressing doses of 48/80 administered intravenously, increasing from an initial minimum of 35 μ g. per kg. to a maximum of 60 μ g. per kg. of body weight (the dose has been daily increased of 5 μ g./kg.; total quantity per subject: 285 μ g./kg.).

b) a second group of 11 patients was treated with an intravenous injection of antihistamine 30 minutes before the injection of 48/80 administered by the same method described for the first group.

The compound 48/80 was used in a strength of 10 mg. to 10 ml. of physiological saline solution.

The antihistamine drug used was Ilvin Merck (1-(p-bromophenyl)-1-(2-pyridil)-3-N, N-dimethylpropylamine maleate) in daily doses of 5 mg.

The mast cells were observed in bronchobiopsy specimens taken from the orifice of the middle lobe bronchus, fixed with formalin (Merck) 10% and stained with toluidine blue 0.1% at pH 6.5 kept for 15 minutes at 50 centigrades. In all cases, a first specimen was taken before treatment with the histamine liberator 48/80 and the second one 24 hours after the last administration, taking care to excise it far from the first cicatrice.

Counting of detectable mast cells was made for each subject in 30 microscopical fields (using ocular $\times 10$ and objective $\times 100$) changing the histological section every 5 microscopical fields. This proceeding was replicated 5 times (Table 1).

The significance of data thus obtained was verified by the *variance-ratio F test*.

As shown in Table 2 the treatment with compound 48/80 produced a significant decrease of detectable mast cells ($P < 0.05$). This decrease was not significantly modified by the pre-treatment with antihistamine (1).

A conspicuous attenuation of phenomena normally following the administration of 48/80 was however observed in the subjects pre-treated with antihistamine.

About one minute after injection the patients treated only with the histamine liberator experienced a diffuse sensation of warmth, itching at the face, at the neck, at the trunk and

¹ The variances indicated with * were confronted with the residual variance having 20 degrees of freedom; the variance between blocks (**) was confronted with the variance within blocks having 176 degrees of freedom.

TABLE 1
Number of detectable mast cells before and after treatment.

Treatment with 48/80										Treatment with antihistamine & 48/80											
Subjects		Before replications				After replications				Subjects		Before replications				After replications					
a	14	26	22	24	22	35	41	31	26	27	l	94	111	97	117	79	123	98	128	108	115
b	86	81	113	115	86	64	66	87	77	78	m	63	51	42	38	49	82	71	81	64	70
c	134	96	94	117	103	36	36	39	50	44	n	75	75	74	60	74	36	51	44	49	42
d	82	95	84	99	74	51	54	52	57	52	o	70	64	70	61	61	49	46	53	58	55
e	100	132	128	154	135	60	60	111	93	91	p	63	58	86	89	82	61	65	72	60	53
f	29	30	27	25	30	63	64	51	69	69	q	49	65	82	58	43	41	60	69	52	30
g	50	49	73	44	66	26	33	43	47	26	r	65	60	79	68	49	69	79	77	88	77
h	55	53	52	58	38	55	45	43	49	54	s	92	107	110	104	101	66	49	50	53	76
i	78	87	129	98	106	40	35	53	58	48	t	63	53	76	62	53	47	65	55	45	65
j	55	61	66	74	67	34	41	41	44	51	u	66	68	93	63	73	72	73	81	69	69
k	72	58	61	64	50	26	38	43	28	26	v	79	88	85	92	98	66	54	66	53	59

TABLE 2
Analysis of variance.

Source of variation	Degrees of freedom	Deviance	Variance	F	P
Groups of treatment	1	3.199,6409	3.199,6409*	1.967	not significant
Epochs of treatment	1	12.722,4045	12.722,4045*	7.822	< 0.05
Interaction	1	3.260,9500	3.260,9500*	2.005	not significant
Experimental units	3	19.182,9954	6.394,3318*	3.931	< 0.05
Subjects	20	73.137,6364	3.656,8818*	2.248	< 0.05
Residual	20	32.528,1455	1.626,4073	—	—
Blocks	43	128.848,7773	2.903,4599**	9.06	< 0.001
Within blocks	176	56.401,0000	320,4602	—	—
Total	219	181.249,7773			

flushing of skin especially on face and neck, one third of the cases presented cutaneous urticarial eruptions sometimes followed by brief headache. All symptoms and signs disappeared in about 5 minutes.

On the other hand the subjects pre-treated with antihistamine showed: in 7 cases very light warmth sensation without any objective manifestation; in 4 cases no effect at all.

This research shows that:

a) therapeutic doses of antihistamines have no action on mast cells in man;

b) the protective action of antihistamines against effects caused by 48/80 does not influence the release of histamine by mast cells, but develops as a competitive inhibition on tissue receptors against circulating histamine.

These findings confirm the assumption that the action of antihistamines in allergic disorders is due to the same mechanism.

SUMMARY

It has been investigated whether the pre-treatment with antihistamine is able to influence the action of the histamine liberator 48/80 on the bronchial mast cells. The research has been made on two groups of subjects:

a) a first group of 11 patients has been treated with daily progressively increasing doses of 48/80 (total quantity 285 μ g. per kg. of body weight);

b) a second group of 11 patients has been treated with an intravenous injection of antihistamine (Ilvin Merck) before the injection of 48/80 given by the same method used for the first group.

The mast cells were observed in bronchobiopsy specimens taken before and after the treatment.

The findings were:

1 - The compound 48/80 caused a degranulation and a significant ($P < 0,05$) decrease in the number of the bronchial mast cells.

2 - The pre-treatment with antihistamine did not modify significantly the above detected decrease.

3 - The pre-treatment with antihistamine eliminated almost entirely the effects normally caused by the administration of the histamine liberator 48/80.

It evidences from our observations that the antihistamine drugs administered in man in therapeutic doses do not interfere with the histamine release process from the mast cells, but these drugs are active by blocking the tissue receptors against circulating histamine.

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