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EFFECTS OF BP 400,
AN ANTIAMINE, ON SKIN HISTAMINE AND
POLYMYXIN B INDUCED WEALING

By

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It is recognized that common antihistamine drugs have a particular affinity for receptors activated by histamine (1, 6). This relationship between antihistamines and histamine is referred to as competitive inhibition. Lately, however, it has been proposed that, depending upon their concentration, antihistamines may act in three different ways: By competitive inhibition, by destroying mast cells and releasing histamine, and by preventing mast cell damage and histamine release (5). The present study was undertaken to investigate whether BP 400, a new antiamine drug (4, 7), might protect human mast cells against the histamine releasing effect of polymyxin B (8). The effect of intravenous BP 400 on human skin was also studied as well as the antiwealing activity of the drug on polymyxin B induced weals.

MATERIAL AND METHODS

The study included 13 patients aged 22 to 72 suffering from local skin diseases not involving the skin of the thighs. The patients received no systemic drug treatment. Samples of approximately 30 mg grossly normal thigh skin were obtained by punch biopsy. An injection of 5 mg polymyxin B dissolved in 0.25 ml physiological saline was given intradermally into the same thigh at least 6 cm from the biopsy. After 30 minutes the resultant weals were outlined in ink and traced on transparent paper. Within a further 30 minutes, biopsies were taken from the polymyxin B induced weals. The whole procedure was repeated

one hour after the intravenous injection of 4 mg BP 400.¹ A new skin biopsy was performed symmetrically on the other thigh, another injection of polymyxin B was given intradermally, the resultant weals were traced on paper after 30 minutes, and within a further 30 minutes biopsies were taken from the wealing skin.

The areas of the weals were measured planimetrically. The skin specimens were frozen down immediately at -20°C . Histamine determinations were performed on the dried and defatted skin samples according to a fluorometric procedure previously described (9) with two minor changes. Butanol was substituted by a 3:2 mixture of butanol and chloroform according to Burkhalter (3), and tissue blanks were substituted with reagent blanks, as these were found to be almost identical.

TABLE 1

Size of Polymyxin B Induced Weal before and 60 Minutes after Intravenous Injection of 4 mg BP 400.

Case no.	Before BP 400 mm ²	Size of weal	
		After BP 400 mm ²	per cent ¹
1	924	603	67
2	568	488	86
3	873	513	59
4	747	583	78
5	907	600	66
6	748	521	70
7	537	689	128
8	1107	779	70
9	633	459	73
10	1113	737	66
11	799	699	88
12	4487	1573	35
13	1073	640	60
Mean	1116	683	73
±SE	±285	±36	±5

¹ Per cent of size before BP 400.

RESULTS

The results of the study show that BP 400 significantly ($p < 0.05$) reduced the size of the polymyxin B induced weals

¹ Kindly supplied by Sandoz Ltd., Basle, Switzerland.

one hour after intravenous administration (Table 1). The histamine determinations are summarized in Table 2 and Fig. 1. The mean reduction in skin histamine after polymyxin B was significant ($p < 0.025$), while BP 400 produced no significant difference in the polymyxin B induced skin histamine reduction. Neither did the intravenous injection of BP 400 produce any significant difference in skin histamine.

TABLE 2

Skin Histamine before and after Local Injections of 5 mg Polymyxin B, with and without Pretreatment with 4 mg BP 400 Intravenously.

Case no.	μg histamine per g dried and defatted skin			
	Before treatment	After polymyxin B	After BP 400	After BP 400 & polymyxin B
1	28.1	22.4	25.2	18.5
2	26.6	9.4	31.4	10.8
3	14.1	18.9	23.5	28.0
4	26.9	19.2	24.1	14.7
5	13.8	19.4	15.0	15.9
6	20.9	10.7	18.6	17.3
7	20.0	19.4	18.4	18.9
8	17.9	15.3	13.3	14.4
9	16.8	8.7	16.1	5.0
10	27.9	14.1	26.8	20.1
11	11.0	14.3	18.6	11.2
12	41.0	15.3	60.9	36.2
13	41.9	22.9	31.8	16.7
Mean	23.6	16.5	24.9	17.5
$\pm$ SE	± 2.7	± 1.3	± 3.4	± 2.2

The side-effects of the polymyxin B injections were, besides the local wealing response, local irritation, slight itching, and a moderate pain at the site of the injection. No patients displayed generalized urticaria. A more or less pronounced drowsiness was experienced by all patients, presumably due to BP 400.

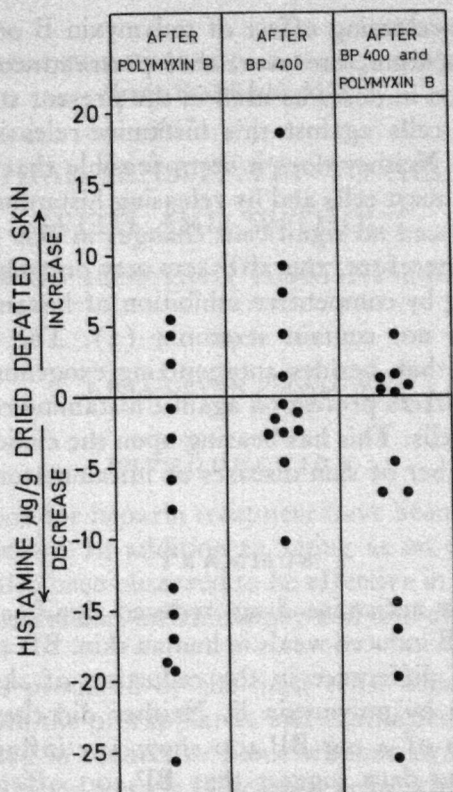


Fig. 1.

Alterations in skin histamine after 5 mg polymyxin B intradermally before and after pretreatment with intravenous injections of 4 mg BP 400, and after BP 400 alone. The zero line represents the normal histamine content of the patients thigh skin.

DISCUSSION

In previous studies by two of us the antihistaminic effect of BP 400 has been confirmed (4). It was also demonstrated that BP 400 offered protection against serotonin induced weals, hence the term, antiamine (4). The present investigation shows that mg BP 400, given intravenously, significantly reduces polymyxin B induced wealing. The study also confirms

the histamine-releasing effect of polymyxin B on human skin (8). It is apparent, however, that pretreatment with intravenous BP 400 in doses as used in the present study does not protect mast cells against this histamine-releasing effect of polymyxin B. Neither does it seem feasible that BP 400 acts by destroying mast cells and by releasing histamine, as BP 400 in itself produced no significant changes in skin histamine. It is assumed, therefore, that BP 400 acts on polymyxin B induced wealing by competitive inhibition of histamine. Human mast cells do not contain serotonin (2). The data of our study suggest that, besides antagonizing exogenous histamine, BP 400 also offers protection against histamine released from human mast cells. This has bearing upon the clinical use of the drug in a number of skin diseases of inflammatory or allergic nature.

SUMMARY

BP 400, a new antiamine drug, reduced significantly the size of polymyxin B induced weals in human skin. BP 400 produced no significant difference in the reduction of skin histamine brought about by polymyxin B. Neither did the intravenous administration of 4 mg BP 400 show any influence on skin histamine. The data suggest that BP 400 offers protection against histamine released from human mast cells by competitive inhibition of histamine.

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