

BACITRACIN: A CUTANEOUS ALLERGEN AND HISTAMINE LIBERATOR¹

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Abstract. Patch testing of 1 000 patients who had suspected contact dermatitis disclosed only three patients allergic to bacitracin, all of whom also had positive tests to neomycin. After intracutaneous injection of bacitracin the three patients showed a delayed eczematous reaction. A strong immediate wheal and flare reaction was induced by intracutaneously injected bacitracin. This was inhibited by a simultaneous local injection of the antihistamine mepyramine which also abolished the vascular response to histamine and to the histamine liberator polymyxin B. Depletion of cutaneous histamine by pretreatment with polymyxin B diminished the wheal and flare induced by bacitracin. Apparently, the vascular effects of bacitracin in human skin are due to a release of histamine.

Allergic contact dermatitis due to topically applied drugs is frequently observed. The most common allergens, according to a recent international survey (1) are benzocain, neomycin, wool fat alcohols, hydroxyquinolines and parabens. The experience of our department supports these findings (6). In earlier reports bacitracin was also named among common offenders, primarily in cases of concomitant allergy to neomycin (3, 10). Since neomycin-bacitracin combinations are still frequently used in topical therapy the first aim of the present work was to study the frequency of eczematous contact allergy to bacitracin.

Both Hjorth (3) and Pirilä & Pirilä (9) noted a "histamine-like" reaction following intracutaneous injection of bacitracin. The basis for this vasoactive effect has not previously been studied. The wheal and flare observed might be caused by a direct effect on the vascular tissue. Alternatively, bacitracin might liberate a vasoactive substance from the skin, such as histamine. These two possibilities were investigated in the second part of the present work.

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ALLERGIC REACTIONS TO BACITRACIN

Material and methods. Eczematous contact allergy to bacitracin was sought by including the antibiotic (30% in petrolatum) in our battery series for epicutaneous testing of patients with suspected contact allergy. Hereby, 1 000 consecutive patients attending our allergy laboratory were tested with bacitracin. Patch testing was performed according to generally accepted techniques. The patches were Al-test (Astra Agency, Imeco, Sweden) + Leukoflex (Beiersdorf, West Germany). They were applied on the upper back, lateral to the vertebral column, for 48 hrs. All tests were read 72 hrs after application, i.e. 24 hrs after removal.

The patients positive to bacitracin were also tested with bacitracin 5%, and with zinc bacitracin 30% and 5%. They were further tested intracutaneously with the antibiotic, and with bacitracin/mepyramine mixtures, final concentrations of which are shown in Table I. The tests were read after 20 min for wheal and erythema, and after 72 hrs for inflammatory induration.

Results. Patch testing of 1 000 patients with suspected contact allergy disclosed 3 patients with positive reactions to bacitracin. Patch tests with the same concentrations of zinc bacitracin were weaker but clearly positive in 2 of the patients, and negative in the third (Table I). These 3 patients all belonged to the 22 cases of neomycin allergy occurring during the same period (Table II).

The intracutaneous test to bacitracin in the 3 patch test positive patients showed a positive delayed reaction in all. In no case was it of the regular tuberculin type, but clearly eczematous in 2 cases, and "dermo-epidermal" in one. It may be seen from Table I that addition of mepyramine did not result in any considerable change of the delayed allergic reaction; the values obtained in all 3 patients, and with both concentrations, were, however, slightly lower. The immediate reaction consisted of a wheal and flare response, not de-

Table I. Results of testing 3 patients allergic to bacitracin

Upper part: epicutaneous (+ = erythema, ++ = erythema and infiltration or papules/vesicles, +++ = strong reaction). Lower part: intracutaneous (diameter in mm of induration given). Readings after 72 hrs

	Patient (sex, age, diagnosis)		
	TJ (M 56) Hypostatic ulcer and dermatitis	IN (F 59) Seborrhoeic dermatitis	RS (F 69) Hypostatic dermatitis
Bacitracin 30%	+++	++	++
Zinc bacitracin 30%	++	-	++
Bacitracin 5%	++	++	++
Zinc bacitracin 5%	++	-	+
Bacitracin 0.1%	23	19	20
Bacitracin 0.1% + mepyramine 0.02%	22	17	17
Bacitracin 0.01%	15	20	16
Bacitracin 0.01% + mepyramine 0.002%	14	15	13

viating in intensity from that found in controls (see below).

THE VASCULAR EFFECT OF INTRA-CUTANEOUSLY INJECTED BACITRACIN

This study was divided into two parts, both of which were carried out in the same 9 healthy volunteers, 23-25 years of age.

Part I

In this part the wheal and erythema reaction of bacitracin was compared with that of a histamine liberator, polymyxin B, and of histamine itself. The effect of a simultaneously injected antihista-

Table II. Frequency of positive epicutaneous tests to bacitracin and neomycin

Country	Year	Bacitracin		Neomycin	
		Number pos.	% of tested	Number pos.	% of tested
Finland (7)	1955-1966	1365	7.8	1715	9.8
	1971	127	7.5	161	9.6
	1962-1967	27	0.6-0.7		
Denmark (4)	1962-1967				
Sweden (present study)	1971-1972	3	0.3	22	2.2

mine, mepyramine, on the vascular reactions was also studied.

Method. Optimal concentrations of the substances under study were titrated in preceding pilot experiments. The following eight solutions freshly prepared in saline were used (final concentrations given):

Bacitracin (H. Lundbeck & Co. A/S, Copenhagen, Denmark) 0.1%

Bacitracin 0.1% + Mepyramine maleate 0.02%

Polymyxin B sulphate (Novo Industri A/S, Copenhagen, Denmark) 0.1%

Polymyxin B sulphate 0.1% + Mepyramine maleate 0.02%

Histamine hydrochloride 0.01%

Histamine hydrochloride 0.01% + Mepyramine maleate 0.02%

Mepyramine maleate 0.02%

Saline

Intracutaneous injections of 0.1 ml were given with a 2 ml syringe, needle gauge 25, on the back, lateral to the vertebral column. The vascular reactions were read after 20 minutes. The area of the wheal was calculated by marking the edge with ink, transferring the outline to a transparent plastic sheet, and measuring it planimetrically. The area of the erythema was approximated from the mean of two right-angled diameters.

Part II

In this part the vascular effects of bacitracin and of histamine after pretreatment of the skin with a histamine liberator, polymyxin B, were studied.

Method. Bacitracin, polymyxin B, and histamine were used in the same concentrations as above. First, two intracutaneous injections with polymyxin B and one with saline were given on the back on well dispersed sites. Six hours later, bacitracin was injected exactly into the areas pretreated with polymyxin B and saline, respectively. At the same time, histamine was injected into the remaining site pretreated with polymyxin B. The reactions were read as above.

Results. Part I. Following intracutaneous injection, bacitracin, polymyxin B, and histamine all caused quite similar vascular reactions with a marked wheal and erythema; with the admixture of antihistamine both wheals and erythemas appeared much smaller (Fig. 1). The mean values for wheal and erythema induced by the three compounds, as well as by mixtures with the antihistamine, are given in Table III and Fig. 2. The difference for both wheal and erythema between the compounds and their respective mixtures was highly significant ($p < 0.001$) in all three cases.

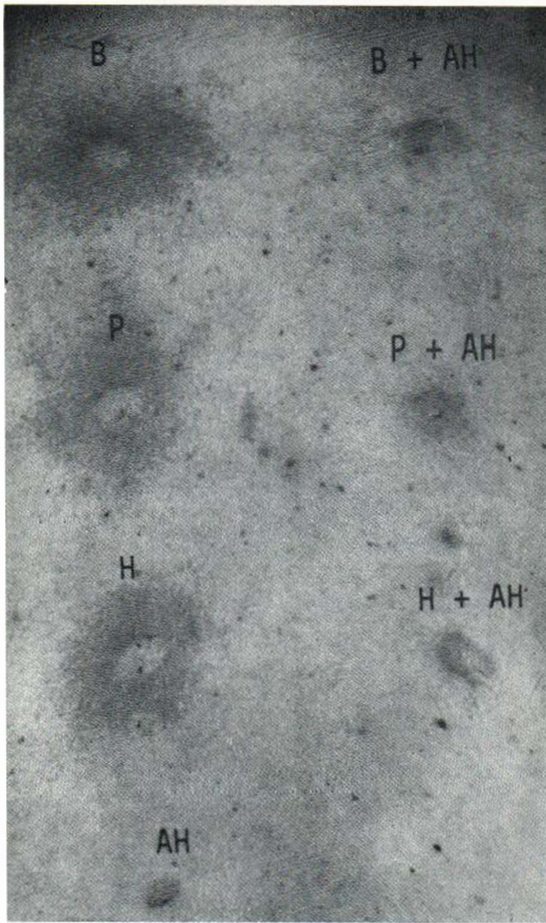


Fig. 1. Wheal and erythema response 20 min after intracutaneous injections in one subject.

Abbreviations:

B = bacitracin P = polymyxin B
H = histamine AH = antihistamine

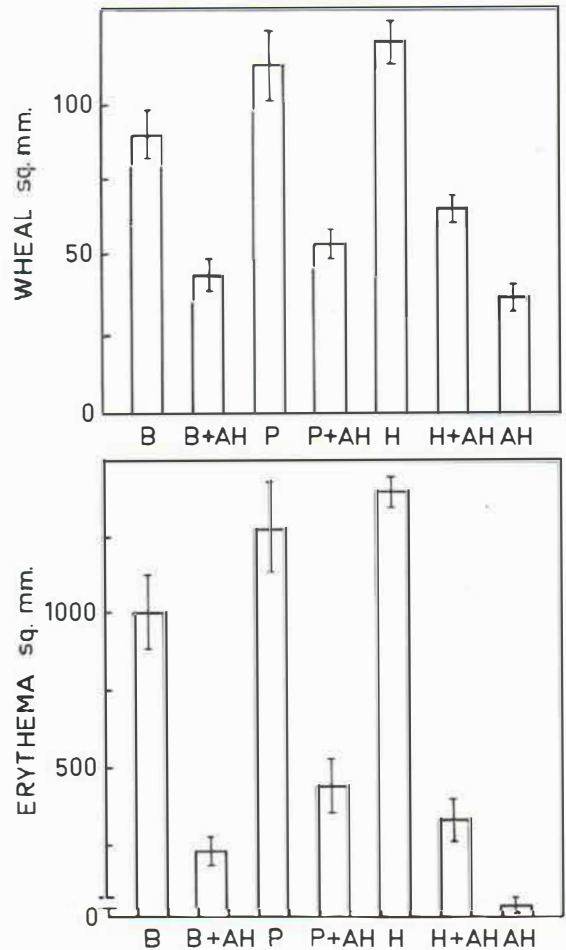


Fig. 2. Wheal and erythema response of intracutaneously injected test solutions (for abbreviations, see Fig. 1). Mean values $\pm$ S.E.M. in 9 subjects are indicated.

Part II. Bacitracin injected into skin pretreated with polymyxin B gave diminished vascular reactions than when injected into skin pretreated with saline (Fig. 3). With regard to erythema, this was not only smaller but also much paler in all subjects. The mean values for wheal and erythema are given in Table IV. For the wheals the difference was significant ($0.02 > p > 0.01$); for the erythemas it was highly significant ($p < 0.001$). Even after pretreatment with polymyxin B, histamine elicited a marked wheal and erythema (Fig. 3, Table IV).

DISCUSSION

Allergology. In our material, the frequency of positive patch test reactions to bacitracin was low

in comparison with reported reactions to other topically applied medicaments (1). In Table II it has been compared with a slightly higher frequency from Denmark (4) and a very much higher one in Finland (7). This difference may be explained by the fact that bacitracin-containing ointments are available without prescription in Finland (7).

Our 3 patients with contact allergy to bacitracin also showed positive patch tests to neomycin. Such combined sensitivity agrees with earlier experience (3, 10). On the other hand, in a large material of contact allergy to neomycin, 77% of the patients were also sensitized to bacitracin (8). The combined reactions are examples of concomitant sensi-

Table III. The mean values (mm²) and S.E.M. for wheal and erythema induced by the test compounds in 9 subjects

	Wheal	Erythema
Bacitracin	90 ± 8	999 ± 116
Bacitracin + antihistamine	43 ± 5	255 ± 48
Polymyxin B	112 ± 11	1276 ± 147
Polymyxin B + antihistamine	53 ± 5	437 ± 90
Histamine	119 ± 7	1397 ± 52
Histamine + antihistamine	65 ± 5	327 ± 68
Antihistamine	36 ± 4	40 ± 3

tivity induced by the simultaneous presence in the same preparations of the two antibiotics, rather than of cross-sensitivity. The relatively higher frequency of neomycin vs bacitracin allergy in our material (Table II) might be explained by the fact that neomycin in this country is more often prescribed without bacitracin than in a combination with that antibiotic. Difference in purity of bacitracin may also be of importance.

In topical preparations, bacitracin may occur as such or as a zinc bacitracin complex. Comparative testing in our 3 bacitracin-sensitive patients with different concentrations of bacitracin and of zinc bacitracin showed somewhat weaker reactions to zinc bacitracin.

The contact allergy to bacitracin was confirmed by intracutaneous testing showing delayed eczematous reactions in all 3 cases. This accords with earlier findings (3). It has been shown that a delayed allergic reaction may be suppressed by the addition of a wheal-producing substance, such as histamine, in the intradermal test (5). Such "addition" is actually what happens, since bacitracin has pharmacologic as well as allergic properties (see below). It may thus be assumed that the de-

Table IV. The mean values (mm²) and S.E.M. for wheal and erythema induced by bacitracin and histamine after pretreatment

	Wheal	Erythema
Bacitracin after saline (S → B)	99 ± 9	988 ± 98
Bacitracin after polymyxin B (P → B)	66 ± 7	191 ± 64
Histamine after polymyxin B (P → H)	135 ± 11	1173 ± 189

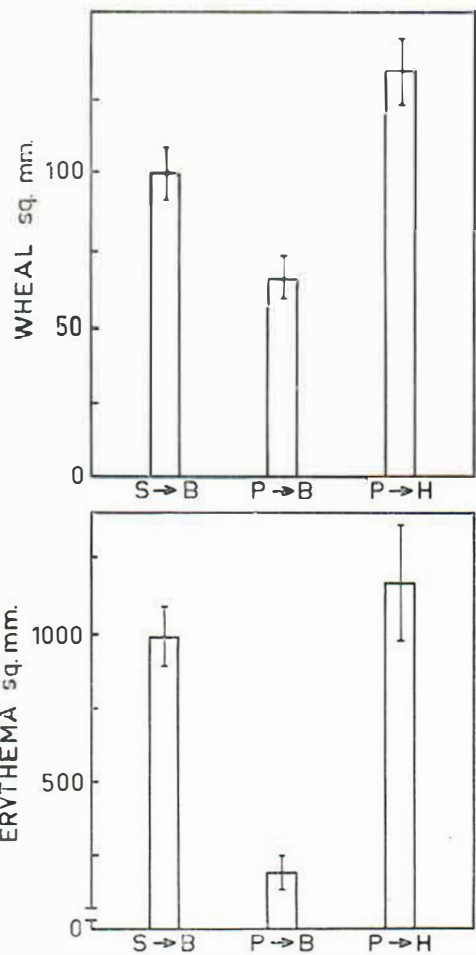


Fig. 3. Wheal and erythema response of intracutaneously injected bacitracin (B) and histamine (H) 6 hrs after pretreatment with saline (S) or polymyxine B (P). Mean values ± S.E.M. in 9 subjects are indicated.

layed allergic reactions to bacitracin might have been stronger if the intracutaneous test had not started with a "histamine-like" response. Nevertheless, when this latter was suppressed with an admixture of antihistamine, the consequent delayed response was not greater than that evoked by bacitracin alone (Table I). We have at present no explanation for this seemingly contradictory result; the material, however, was too small for conclusions to be drawn from this finding.

The immediate wheal and flare did not deviate in strength and size from those in the healthy controls taking part in our pharmacologic study (see below). Thus, this intracutaneous test did not

disclose any signs of circulating reagins as have been demonstrated in two cases of anaphylaxis after topical treatment with bacitracin (2, 11).

Pharmacology. It could be deduced that the immediate vascular reactions induced by intracutaneously injected bacitracin were mediated by histamine for the following reasons: first, the response was clinically very similar to that of histamine; secondly, it was also very similar to that of polymyxin B which is a potent releaser of histamine in human skin (12); thirdly, both wheal and erythema was effectively inhibited by the antihistamine mepyramine (Figs. 1–2, Table III). As a matter of fact, mepyramine suppressed the whealing responses of bacitracin, polymyxin B, and histamine, to the same level as those induced by the antihistamine itself (Fig. 2).

A preceding intracutaneous injection of saline did not influence the vascular activity of bacitracin (Figs. 2–3). In skin pretreated with polymyxin B, however, bacitracin caused a reduced wheal and erythema (Fig. 3, Table IV). This is the fourth piece of evidence: obviously, polymyxin B had depleted the cutaneous stores of histamine, and bacitracin was left devoid of a mediator to liberate. Bacitracin apparently has no significant vascular effect on its own. On the other hand, pretreatment with polymyxin B did not reduce the capacity of the skin to react with wheal and erythema, which was demonstrated by a normal histamine response (Fig. 3).

The histamine-releasing potency of polymyxin B is obvious 1 hour after an intradermal injection and normal levels of cutaneous histamine are reached 4 days later (12). It is not known if the duration of histamine depletion is even shorter; the present results show it to last at least for 6 hours.

It is concluded that the "histamine-like" vascular effect of bacitracin depends largely on a liberation of cutaneous histamine.

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Addendum

After submitting the manuscript for publication three cases of contact allergy to the histamine liberator polymyxin B became available for examination. The result of intracutaneous injections with polymyxin B was opposite to that with bacitracin, related above: addition of the antihistamine mepyramine to polymyxin B resulted in a larger delayed reaction than without the antihistamine. Also, the delayed reaction was clearly of the tuberculin type which may be of importance for the influence of initial histamine.