

University of Copenhagen, Department of Skin and Venereal Diseases,
Rigshospital, Copenhagen, Denmark.

COMPARISON OF THE ANTIWEALING EFFECT
OF THE ANTIAMINES BP 400 AND
CYPROHEPTADINE AND AN ANTIHISTAMINE
HS 592

By

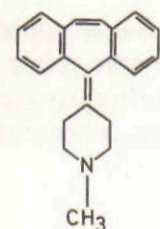
STEN JUEL HENNINGSSEN & HUGH ZACHARIAE

Observations on skin histamine suggest that histamine plays a part in a number of skin diseases of inflammatory or allergic nature (5). Histamine, however, is no longer considered the only chemical mediator in these conditions. Serotonin, although probably of greater importance in the rat than in man, and kinin peptides may also contribute (2, 6). Antiamine is a new term characterising drugs which possess not only antihistaminic properties but also antagonize other biogenic amines and possibly also kinin peptides such as bradykinin. The present study offers a comparison of the effect of two antiamines, BP 400 and cyproheptadine, as well as the effect of a new antihistamine drug HS 592, on histamine, serotonin and bradykinin induced weals.

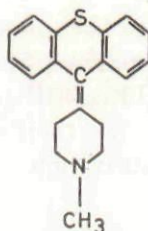
The tricyclic structure of BP 400 and cyproheptadine is shown below (Fig. 1). HS 592 belongs chemically to the benzhydryl ether group. It is the hydrogen fumarate of (+)-1-methyl-2-(2-(α -methyl-p-chlorbenzhydryloxy)ethyl)pyrrolidine (Fig. 2).

MATERIAL AND METHODS

The study included 13 patients aged 22 to 76 suffering from local skin diseases not involving the skin of the forearms. The patients received no systemic drug



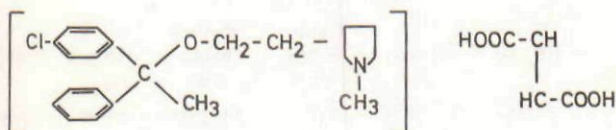
Cyproheptadine



BP 400

Fig. 1.

The chemical structure of the antiamines cyproheptadine and BP 400.

*Fig. 2.*

The chemical structure of HS 592.

treatment. Intradermal tests were performed on the flexor surfaces of the forearms with 0.1 ml doses containing 100 μ g histamine, 100 μ g serotonin and 10 μ g synthetic bradykinin in aqueous solution¹. The tests were done before and 5 and 120 minutes after the intravenous injection of 2 mg BP 400¹, cyproheptadine, or HS 592¹. The distance between each intradermal test was at least 6 cm. After 15 minutes the resultant weals were outlined in ink and traced on transparent paper. In initial studies it had been demonstrated that the intradermal injections gave a wealing response in a suitable position on the log-dose response curve. The procedure was repeated with each of the other two drugs after an interval of at least 48 hours. The order in which the effect of the drugs were studied was arbitrary. The areas of the weals were measured planimetrically and expressed in per cent of corresponding areas prior to the intravenous injection.

RESULTS

The results are summarized in Table 1, 2 and 3. All three drugs reduced histamine weals significantly 120 minutes after their intravenous administration ($p < 0.05$). The antihistamine, HS 592, also gave a significant reduction in the weal-

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

ing response to histamine 5 minutes after administration ($p < 0.05$). A comparison of the antihistaminic effect of the three drugs showed that BP 400 had a significantly higher wealing reducing potency than cyproheptadine when measured two hours after intravenous injection ($p < 0.01$).

TABLE 1

Size of Histamine Induced Weals 5 and 120 Minutes after Intravenous Injections of 2 mg BP 400, Cyproheptadine, and HS 592 Expressed in per Cent of Corresponding Histamine Weals Prior to Injection.

Case no.	Size of weal (per cent).					
	BP 400	BP 400	Cyproheptadine	Cyproheptadine	HS 592	HS 592
	5 min.	120 min.	5 min.	120 min.	5 min.	120 min.
1	107	49	92	61	53	32
2	59	19	41	57	90	81
3	64	32	146	57	29	21
4	66	48	34	28	100	34
5	104	33	120	74	63	50
6	99	46	61	55	43	19
7	56	27	105	33	27	21
8	77	28	83	51	82	48
9	91	44	85	60	66	63
10	99	12	105	77	91	47
11	80	44	117	23	77	60
12	71	60	121	60	108	72
13	159	51	86	79	78	54
Mean $\pm$ SE	87 $\pm$ 8	38 $\pm$ 4	92 $\pm$ 9	55 $\pm$ 5	70 $\pm$ 7	46 $\pm$ 6

The antiamines cyproheptadine and BP 400 both furnished protection against serotonin induced weals. The reduction in the size of the serotonin weals was significant ($p < 0.05$) for BP 400 both 5 minutes and 120 minutes after injection, while cyproheptadine only gave a significant reduction after 120 minutes.

Cyproheptadine and HS 592 both gave a moderate, but statistically significant ($p < 0.05$), reduction in the size of the

bradykinin weals 120 minutes after their administration. This effect of HS 592 was found already 5 minutes after the injection. When comparing the effect of the drugs on bradykinin induced weals, cyproheptadine was found significantly ($p < 0.05$) more potent than BP 400.

TABLE 2

Size of Serotonin Induced Weals 5 and 120 Minutes after Intravenous Injections of 2 mg BP 400, Cyproheptadine, and HS 592 Expressed in per Cent of Corresponding Serotonin Weals Prior to Injection.

Case no.	Size of weal (per cent).					
	BP 400	BP 400	Cypro-hepta-dine	Cypro-hepta-dine	HS 592	HS 592
	5 min.	120 min.	5 min.	120 min.	5 min.	120 min.
1	51	57	70	53	88	62
2	80	66	59	41	100	104
3	50	65	160	44	78	56
4	94	77	73	64	110	59
5	91	87	90	65	79	152
6	69	62	77	100	118	77
7	72	46	109	115	44	26
8	84	95	96	151	84	96
9	126	107	132	91	121	82
10	73	27	80	64	58	35
11	116	82	89	44	87	85
12	84	73	63	60	140	231
13	79	61	104	72	83	90
Mean $\pm$ SE	82 $\pm$ 6	70 $\pm$ 6	93 $\pm$ 8	74 $\pm$ 9	92 $\pm$ 7	89 $\pm$ 15

A more or less pronounced drowsiness was experienced by all patients following the injections of all three drugs. No other undesirable side-effects were noted.

DISCUSSION

Our findings confirm the antihistaminic effect of all three drugs. The study also confirms the antiserotonin action of

cyproheptadine and its analogue BP 400, while the antihistamine HS 592 seemed to give no protection against the wealing response to serotonin. Most antihistamines have been known to possess only slight or no antikinin properties (3). BP 400, however, in relatively high concentrations, inhibits the bradykinin induced contractions of the isolated rat uterus (4). In our study no antikinin effect could be demonstrated following the intravenous injection of 2 mg BP 400. A moderate protection against bradykinin was found after cyproheptadine and HS 592. Whether this effect is a true antikinin effect or an indirect effect due to the antihistaminic property of the agents has not been shown. Edema formation may lead to mast-cell degranulation (1) and histamine release. Kinin weals, therefore, may partially be due to histamine.

TABLE 3

Size of Bradykinin Induced Weals 5 and 120 Minutes after Intravenous Injections of 2 mg BP 400, Cyproheptadine, and HS 592 Expressed in per Cent of Corresponding Bradykinin Weals Prior to Injection.

Case no.	Size of weal (per cent).					
	BP 400	BP 400	Cyproheptadine	Cyproheptadine	HS 592	HS 592
	5 min.	120 min.	5 min.	120 min.	5 min.	120 min.
1	91	126	90	90	118	65
2	92	90	47	43	89	89
3	87	119	129	57	88	65
4	73	81	79	82	89	72
5	41	101	154	99	89	109
6	90	118	164	57	95	83
7	67	53	67	76	92	60
8	95	89	93	83	89	102
9	85	96	106	84	77	99
10	82	101	82	89	88	72
11	101	100	103	72	114	113
12	95	100	60	90	96	99
13	150	88	177	102	86	106
Mean $\pm$ SE	88 $\pm$ 7	97 $\pm$ 5	104 $\pm$ 11	79 $\pm$ 5	93 $\pm$ 3	87 $\pm$ 5

A comparison of the antihistaminic effect of the three drugs showed a moderate superiority of BP 400 over cyproheptadine, when the two drugs were given intravenously in the same weight doses. On the other hand, cyproheptadine seemed more effective than BP 400 as far as their "anti-kinin" action was concerned. All three drugs produced drowsiness. An evaluation of possible quantitative differences in side-effects was not attempted.

SUMMARY

An objective method for comparing the antiwealing effect of two antiamines, BP 400 and cyproheptadine, and an antihistamine, HS 592, was used. The antihistaminic effect of all three drugs was confirmed. BP 400 and cyproheptadine also showed antiserotonin activity. Cyproheptadine and HS 592 gave a moderate reduction of bradykinin induced weals. The antihistaminic effect of BP 400 was found significantly higher than that of cyproheptadine, while cyproheptadine showed a significantly higher protection against bradykinin wealing.

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