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SEROTONIN AND A SEROTONIN ANTAGONIST IN ALLERGY

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BIOLOGICALLY active substances which have been implicated as mediators of allergic reactions[1,2] include histamine, acetylcholine, serotonin, bradykinin, heparin, leucotaxin, slow reacting substance (SRS) and complement. Histamine,[3] first synthesized in 1907, is derived from the amino acid histidine by decarboxylation and is found in virtually all body tissues,[4] especially those comprising the lungs, skin, and gastrointestinal tract, central and peripheral nervous systems and skeletal musculature. In 1929, Dale[5] pointed out that anaphylaxis is an intracellular reaction between antigen and antibody resulting from cell injury or sensitivity and producing symptoms not unlike those evoked by histamine. Feldberg[6] stated that histamine was formed in the tissues and released by the antigen-antibody reaction. Ricci et al[7] were able to induce bronchial asthma in guinea pigs by means of both inhalation of a histamine aerosol and the administration of a histamine-releasing agent. The latter produced a more delayed asthmatic attack which was characterized by dyspnea of seven to ten hours' duration and had a distinct resemblance to human bronchial asthma.

The usefulness of antihistaminic agents for the symptomatic control of hay fever, urticaria, perennial allergic rhinitis and other severe allergic manifestations (with the exception of chronic eczema and severe asthma) has been well documented. These agents apparently act by denying histamine access to a receptor in the (intact) cell, blocking thereby a given response to histamine.

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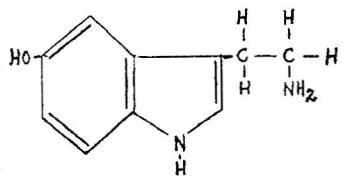
Recently, serotonin (5-hydroxytryptamine),[8] a naturally occurring, biologically active indole-amine has been implicated in the anaphylactic or hypersensitive reaction. In addition,[9] serotonin may also be involved in abnormal mental behavior, microcirculation of the skin, renal function, muscular activity, bronchoconstriction, vasodilation of the pulmonary circulation and in carcinoid tumors.

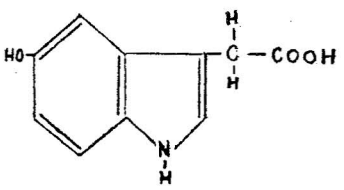
Although more than 600 papers have been published concerning the physiology and pharmacology of serotonin, there appears to be confusion as to its exact physiological role. Its role in mental health and emotional phenomena is more advanced and better understood than that dealing with purely physiological processes. This paper will briefly elucidate the possible role of serotonin (5 HT) in allergy and the effects of a serotonin antagonist (BP-400) in clinically inhibiting various allergic reactions.

In 1933, Erspamer[10] isolated the active substance enteramine from intestinal mucosal extracts, and in 1947, Page[11] isolated from the serum a substance identical with enteramine. This substance was named serotonin because of its occurrence in serum[12,13] and its tensing action on smooth muscle. Twarog and Page[14] later found serotonin in the brain. Serotonin (5-HT),[15,16] found in many species in the same tissue as histamine and sharing with it structural, chemical and pharmacological properties in common, is produced in the human body by decarboxylation of the amino acid, tryptophan.

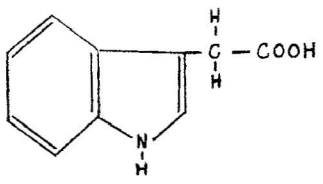
The chemical relationship of serotonin with other important indoles is as follows:[17]



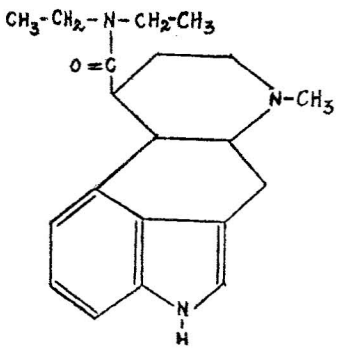
Serotonin



5-Hydroxy-Indole Acetic Acid



Auxin



Lysergic Acid Diethylamide

Page[15,16] stated that 90-95 per cent of the total serotonin is present in the gastrointestinal mucosa (2-15 μg.) in man, with smaller amounts demonstrable in blood platelets, mast cells, spleen and brain. Normal blood has been estimated to contain 0.1 to 0.2 μg./ml.[18]

The major metabolic pathway of serotonin[19] in man is that of oxidative deamination (by monoamine oxidase),[20] resulting in 5-hydroxyindoleacetic acid. Normal individuals excrete 2 to 9 mg. of this substance per day via the urine.

Crout and Sjoerdsma[21] stated that ingestion of bananas (3.7 mg. serotonin per average banana pulp) caused an increased urinary excretion of 5-HIAA to suggest falsely a diagnosis of malignant carcinoid. Analysis of other fruits by West[22] showed the presence of small amounts of serotonin in tomatoes, red plums, avocado and egg plant (3-14 μg/Gm.).

Lewis[23] has reported a high concentration in certain pain-producing venoms and stings, for example, in nettles, poisonous amphibians, certain cephalopods and in the octopus.

Serotonin captured the allergist's attention because of the wheezing seen in the carcinoid syndrome[24] and there is sound evidence that serotonin is released during antigen-antibody reactions in laboratory animals.[16,25,26] Clinically the blood levels of 5-HT in allergic patients were found to be higher than normal by MacHaffie and his co-workers.[27] Specific hyposensitization therapy did not seem to influence these blood levels.

Weissbach et al[28] correlated the pulmonary aspects of anaphylaxis in different species with the relative amounts of serotonin and histamine in lung tissue. Mouse lung contains predominately serotonin and guinea pig lung mainly histamine. This may be a partial explanation of the fact that antihistamines block the pulmonary responses of anaphylaxis in guinea pigs and the antiserotonin compound D-lysergic acid diethylamide blocks certain sensitivity reactions in mice whereas pretreatment with reserpine affords complete protection.[3] Human lung resembles that of guinea pigs in its amine content. Evidence of release of serotonin from animal platelets but not from tissue during anaphylaxis has been obtained.[25,29] Serotonin could gain access to organs such as the lung by entrapment of platelets. Disappearance of circulating platelets has been shown during hypersensitivity reactions in laboratory animals and man[30] and a rise in pulmonary serotonin accompanies a fall in circulating platelets in rabbits.

Studies in animals have indicated that reactions of a anaphylactoid nature are brought about by serotonin in the skin.[31] These studies carried out on rats have shown that serotonin release is even more important than histamine in this reaction. Skins of species other than rodents contain little or no serotonin. In these two rodents, serotonin is found in the mast cells,[32] some

of which are located in the skin. In man, mast cells are essentially devoid of serotonin.[33]

Selye[34] demonstrated that serotonin acts as a challenger in the phenomenon of calciphylaxis in sensitized rats when administered during the "critical period" after sensitization, in the presence of a sensitizing system factor (parathyroid hormone, dihydrotachysterol, and vitamin D).

TABLE I. ANTISEROTONIN POTENCY OF DERIVATIVES OF D-LYSERGIC ACID

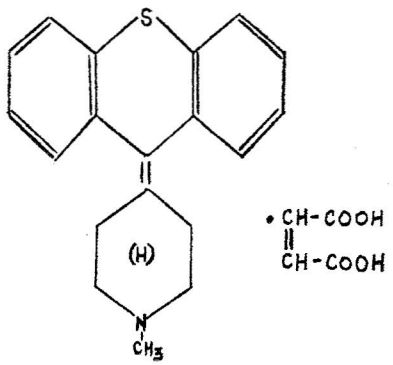
Group	Name	ED (Base) in 50 mcg/kg	Inhibition of Serotonin Edema of Rat's Paw % Relative Activity (LSD=100)	Isolated Rat Uterus % Relative Activity (LSD=100)
LSD-derivatives	D-lysergic acid diethylamide (LSD 25)	56.8	100.0	100
	dihydro-LSD	470.0	12.1	
	1-methyl-LSD (MLD 41)	62.2	91.3	370
	2-brom-LSD (BOL 148)	196.5	28.9	103
	1-methyl-2-brom-LSD (MBL 61)	218.0	26.1	533
Other amide derivatives of D-lysergic acid	D-lysergic acid dimethylamide (DAM 57)	455.0	12.5	
	D-lysergic acid ethylamide (LAE 32)	275.0	22.1	12
	1-methyl-D-lysergic acid ethylamide (MLA 74)	96.8	58.7	835
Ergotamine group	ergotamine	844.0	6.7	
	dihydroergotamine (DHE 45)	833.0	6.8	
	1-methylergotamine	430.0	13.2	
Ergonovine group	D-lysergic acid propanolamide	122.0	46.8	17
	dihydro-D-lysergic acid propanolamide	895.0	6.4	
	1-methyl-D-lysergic acid propanolamide (PML 946)	21.9	259.4	398
Methylergonovine group	D-lysergic acid butanolamide (Methergine)	37.4	151.9	61
	dihydro-D-lysergic acid butanolamide	271.0	21.0	
	1-methyl-D-lysergic acid butanolamide (UML-491)	12.9	440.3	400

Woolley[35] first attempted to study the effectiveness of various antiserotonin agents in laboratory animals. Since then a number of serotonin antagonists of varying chemical structure, namely yohimbine and ergot alkaloids,[36,37] chlorpromazine,[38] promethazine,[39] nicotinamide,[40] and the benzyl analogues of bufotenine (dimethyl serotonin) and serotonin (BAS, 1-benzyl-2, 5-dimethyl serotonin)[41] have been studied. In more recent work diethylamide d-lysergic acid (LSD 25),[42] 2-brom-lysergic acid diethylamide (BOL 148)[43] and 1-methyl-D-lysergic acid butanolamide (UML 491)[44] have been demonstrated to be powerful antagonists of serotonin (Table I).

The compound designated as BP-400, or 9-(N-methyl-piperidyliden-4')-thioxane maleate* has been shown in animal studies to possess antiserotonin,

*Sandoz Pharmaceuticals, Hanover, New Jersey.

antihistamine and antiacetylcholine properties. The structural formula may be depicted as follows:



The following will summarize the pharmacology of BP-400:[45]

1. BP-400 is capable of antagonizing the following serotonin-induced effects:

(a) Contraction of rat uterine smooth muscle *in vitro*.

(b) The inhibition of serotonin-induced edema of the rat's paw *in vivo*.

2. The inhibition by BP-400 of the histamine-induced contraction of smooth muscle (guinea pig ileum) has been observed at a concentration of 1:3000000000. This effect is long-lasting and more pronounced than those elicited by other antihistamines such as antazoline, diphenhydramine, thenalidine and mepyramine.

In the inhibition of histamine asthma in the guinea pig, BP-400 is four times more potent than isothipendyl. BP-400 is fifty times more potent than thenalidine in the inhibition of the histamine vasopressor effects in cats. It is nine times more potent than isothipendyl in its ability to protect the guinea pig from lethal doses of histamine dihydrochloride (20 mg./Kg.) by subcutaneous injection.

3. In contrast to the strong anticholinergic effect exhibited by BP-400 on smooth muscle *in vitro*, its activity *in vivo* is about 100 times weaker than that of atropine.

Acute and chronic toxicity tests in mice, rats and rabbits (Table II) have demonstrated no untoward effects of a type that would preclude the use of BP-400 in man. Accordingly, the study reported in this communication was undertaken to determine the safety and efficacy of BP-400 in the management of various allergic disorders.

TABLE II. RESULTS OF ACUTE AND CHRONIC TOXICITY STUDIES IN ANIMALS

Acute toxicity in mice, rats and rabbits

Compound	LD_{50} (mgm. of base/kgm.)				
	Mice		Rats		Rabbits
	I.V.	P.O.	I.V.	P.O.	I.V.
BP-400	22.5	310	13	850	18
Thenalidine	42	165	42	1060	20

Chronic toxicity in rats

Daily Dose (mgm/kgm) of BP-400 for 3 Months	Animal Mortality per Group of 30
0	0/30
5	0/30
50	0/30
100	1/30*

Comments:
*1. The single death occurred 10 weeks after start of the study.
2. The principal untoward effect was sedation.
3. Hematological examination was negative.
4. Autopsies of test animals revealed no signs of toxicity.

MATERIALS AND METHODS

Two hundred and seventy-five patients from both the private practice of the author and a local allergy clinic were selected for this study. These individuals manifested a variety of allergic disorders. Two hundred and forty-seven patients completed the study which extended from April 1, 1961 to March 31, 1962. This number included 91 children and 156 adults ranging in age from 3 months to 14 years and from 15 years to 72 years, respectively, and 64 females, 7 of whom were in the first trimester of pregnancy.

Information pertinent to each patient was obtained from history, physical examination and allergy skin tests. In addition, those with respiratory allergies received pulmonary function tests and an x-ray examination of the chest and paranasal sinuses. Environmental controls (in an attempt to minimize exposure to allergens such as house dust, feathers, animal danders) and dietary restrictions were prescribed as required. Hyposensitization therapy was carried out in 183 patients. All subjects were encouraged not to resort, unless directed, to the use of medications other than those under study.

The efficacy of BP-400 was evaluated by comparison, using the double blind method, with chlorprophenpyridamine and placebo. Medications were enclosed in capsules of identical appearance and designated by a code which was not "broken" until completion of the study. Patients were provided with supplies of each (marked 1, 2, and 3) sufficient for three 14-day periods, at the end of which nothing was prescribed for at least two weeks. Upon recurrence of symptoms, the individual was given a supply of the coded preparation which had proven most effective during any given 14-day period.

TABLE III. THERAPEUTIC RESPONSE TO BP-400, CHLORPROPHEN-PYRIDAMINE, AND PLACEBO IN 247 PATIENTS

Allergic Condition	Patients Age Group	Results											
		BP-400				Chlorprophen-pyridamine				Placebo			
		+++	++	+	0	+++	++	+	0	+++	++	+	0
Urticaria	7 children	6	1	0	0	1	3	2	1	0	0	0	7
	16 adults	12	1	0	0	4	5	7	0	0	0	2	14
Angio-neurotic edema	2 children	2	0	0	0	0	1	1	0	0	0	0	2
	6 adults	5	1	0	0	1	1	3	1	0	0	1	5
Atopic dermatitis	16 children	6	9	1	0	2	5	7	2	0	0	1	15
	11 adults	5	5	1	0	1	3	5	2	0	0	2	9
Contact dermatitis	4 children	2	2	0	0	1	0	2	1	0	0	0	4
	7 adults	5	2	0	0	0	2	4	1	0	0	1	6
Allergic conjunctivitis	5 children	2	3	0	0	4	1	0	0	0	0	0	5
	9 adults	4	2	3	0	7	1	1	0	0	0	2	7
Allergic rhinitis	28 children	2	11	12	3	12	9	7	0	0	0	3	25
	43 adults	7	19	15	2	15	21	7	0	0	2	10	31
Bronchial asthma	19 children	0	2	13	4	0	3	9	7	0	0	1	18
	31 adults	0	3	19	9	0	5	22	4	0	2	8	21
Drug reactions	3 children	1	2	0	0	0	1	2	0	0	0	0	3
	8 adults	3	4	1	0	0	4	4	0	0	0	2	6
Headaches (all types)	3 children	1	2	0	0	0	0	2	1	0	0	0	3
	14 adults	9	5	0	0	0	4	7	3	0	0	3	11
Gastro-intestinal allergy	4 children	1	3	0	0	0	0	1	3	0	0	0	4
	11 adults	3	8	0	0	0	1	8	2	0	1	3	7
Total	247	76	88	65	18	48	70	101	28	0	5	39	203

This medication, then, was continued for periods ranging from 14 to a maximum of 210 days.

The initial adult dosage consisted of one capsule* every 6 hours; that for children, 1 capsule every 12 hours. This regimen was subsequently modified in such a manner as to meet individual requirements. Patients were seen at intervals approximating one week, at which times the following information was obtained: (1) dates on which each medication was taken, (2) time required to obtain relief, (3) duration and degree of relief and (4) side effects. Additional procedures included examination of lungs, nose, paranasal sinuses, eyes, pharynx, skin, standard blood parameters and offspring of the pregnant subjects participating in the study (no untoward effects of any kind were observed).

Results were classified as specified herewith: Excellent (relief within 40 minutes, persisting 4 or more hours), good (50-75 per cent relief for two or more hours), fair (25-50 per cent relief for one to two hours) and poor (less than 25 per cent relief).

RESULTS

The clinical responses to BP-400 are summarized in Table III and below as follows:

Urticaria (23 patients)—188 excellent, 5 good. Itching was generally relieved within 30 to 40 minutes, followed by the subsidence of (urticarial) wheals.

*Containing either 2 mgm BP-400 or 4 mgm chlorprophenpyridamine.

Angioneurotic Edema (eight patients)—7 excellent, 1 good.

Atopic Dermatitis (27 patients)—11 excellent, 14 good, 2 fair.

Contact Dermatitis (11 patients)—7 excellent, 4 good.

Perennial and Seasonal Allergic Rhinitis (71 patients)—9 excellent, 30 good, 27 fair, 5 poor. Relief of itching (nose, soft palate) was marked. Shrinkage of the nasal mucosal was observed to a lesser degree.

Bronchial Asthma, Intrinsic and Extrinsic (50 patients)—5 good, 32 fair, with 13 obtaining no symptomatic relief.

Allergic Conjunctivitis (14 patients)—6 excellent, 5 good, 3 fair relief of symptoms.

Drug Reactions (11 patients)—4 excellent, 6 good, 1 fair.

Recurrent Headache (17 patients)—Of 12 with so-called "common migraine," the response in 9 was classified as excellent; 3 as good. One of three patients with headache of the "cluster" type reported excellent results, two others, "good," while two with classical "sino-nasal" headaches obtained no relief.

Gastrointestinal Allergies (15 patients)—4 excellent, 11 good.

TABLE IV. LONG TERM THERAPY DOSAGE OF BP-400 IN 44 ALLERGIC PATIENTS

Age (At Start of Study)	Diagnosis	Number of Patients	Duration Therapy (in Days)	Daily Dose Range (in mgs.)	Total Dose Range (in mgs.)	Side Effects (Number of Patients)
3 months to	Atopic derm.	2	30- 90	4-6	120- 540	0
8 months	Atopic derm.	1	91-150	4-6	364- 900	0
(5 patients)	Atopic derm.	2	151-210	4-6	604-1260	0
9 months to	Atopic derm.	1	30- 90	4-6	120- 540	0
24 months	Atopic derm.	3	91-150	4-6	364- 900	0
(5 patients)	Atopic derm.	1	151-210	4-6	604-1260	0
2 years to	Urticaria	1	30- 90	4-6	120- 540	0
4 years	Atopic derm.	2	91-150	4-6	364- 900	0
(4 patients)	Atopic derm.	1	151-210	4-6	604-1260	0
5 years to	Cont. derm.	2	30- 90	6-8	180- 720	0
9 years	Cont. derm.	1	91-150	6-8	546-1200	0
(7 patients)	P.A.R.	3	91-150	6-8	546-1200	0
	P.A.R.	1	151-210	6-8	906-1680	0
10 years to	Headache	2	30- 90	8-16	240-1440	0
14 years	P.A.R.	2	30- 90	8-16	240-1440	0
(9 patients)	P.A.R.	3	91-150	8-16	728-2400	0
	Urticaria	2	151-210	8-16	1208-3360	0
15 years to	Cont. derm.	4	30- 90	8-20	240-1800	0
72 years	P.A.R.	3	30- 90	8-20	240-1800	0
(14 patients)	P.A.R.	1	91-150	8-20	728-3000	0
	Headache	2	91-150	8-20	728-3000	2
	Urticaria	2	91-150	8-20	728-3000	1
	Headache	2	151-210	8-20	1208-4200	0
	Total	44			Total	3

The data contained in Table III indicate BP-400 to be the most efficacious of the three preparations examined. A further analysis of therapeutic response to BP-400, on the basis of age and dosage, is afforded by Table V, while Table IV documents the paucity of side-effects (3 of 44 patients) incident to long-term (30-210 days) administration of BP-400.

TABLE V. THERAPEUTIC RESPONSE TO BP-400 ACCORDING TO AGE AND DOSAGE IN 247 ALLERGIC PATIENTS

Age	Number of Patients Treated	Dose in mgs./day	Average Dose in mgs./kg.	Results +++	++	+	0	Side Effects (Number of Patients)
3 months to	1	2	0.26	—	1	—	—	0
8 months	3	4	0.52	1	2	—	—	0
(9 patients)	5	6	0.78	3	2	—	—	0
9 months to	3	2	0.13	—	1	2	—	0
24 months	8	4	0.26	4	3	1	—	0
(17 patients)	6	6	0.39	4	2	—	—	0
2 years to	2	4	0.20	—	1	1	—	0
4 years	6	6	0.30	1	3	2	—	1
(16 patients)	8	8	0.40	3	3	2	—	5
5 years to	3	4	0.13	—	1	2	—	0
9 years	12	6	0.20	1	4	5	2	2
(28 patients)	13	8	0.26	6	4	2	1	5
10 years to	2	4	0.08	—	—	1	2	0
14 years	7	6	0.12	—	2	3	2	0
(20 patients)	7	8	0.16	—	5	2	—	0
	2	12	0.24	—	—	2	—	1
	2	16	0.32	—	1	1	—	2
15 years to	17	4	0.06	—	—	9	8	0
72 years	40	6	0.08	3	14	21	2	4
(156 patients)	47	8	0.11	13	26	7	1	10
	27	12	0.17	21	4	2	—	9
	21	16	0.23	12	9	—	—	12
	4	20	0.27	4	—	—	—	2
Total	246			76	88	65	18	53

At the conclusion of this study, patients requiring therapy of a prolonged nature (chronic allergic dermatoses, perennial allergic rhinitis, recurrent headaches) were switched to commercially-available, anti-allergic preparations. The great majority of these individuals stated that the degree of relief obtained with BP-400 was vastly superior to that incident to therapy of any other type.

SIDE EFFECTS

Side effects, reported by 118 of the 247 patients, are summarized by Table VI. The data therein indicate that with the exception of appetite stimulation and weight gain, chlorprophenpyridamine was responsible for a higher incidence than either BP-400 or placebo. Particular reference is made to sedation, weakness, nervousness, dizziness and the inability to "think clearly." Several patients manifested more than one untoward response to a particular preparation.

Discontinuance of medication was necessary in only one instance, i.e., a 27-year-old woman with acute allergic rhinitis, pulmonary sarcoidosis and

recurrent bouts of vasovagal syncope who reported severe drowsiness and dizziness incident to the use of both BP-400 and chlorprophenpyridamine.

TABLE VI. SIDE EFFECTS OF BP-400, CHLORPROPHENPYRIDAMINE, AND PLACEBO IN 247 ALLERGIC PATIENTS

Side Effect	BP-400	Chlorprophen-pyridamine	Placebo	Total
Sedation, mild	23	87	19	129
Sedation, moderate	9	28	5	42
Weakness, fatigue	14	31	11	56
Inability to "think clearly"	3	23	2	28
Dizziness	1	6	0	7
Dryness	23	29	3	52
Nervousness	0	19	5	24
Nausea	22	36	17	75
Appetite stimulation only	18	7	3	28
Appetite stimulation & weight gain	11	2	0	13
Total	*124	268	65	†454

*Of the 247 patients receiving BP-400, 53 patients exhibited 124 side effect symptoms.
†Several patients exhibited more than one side effect.
Several patients exhibited side effects to more than one medication.

DISCUSSION

The prime purposes of this study were to ascertain, in addition to clinical efficacy, the minimally-effective dose and side effects, if any, attendant to the use of BP-400 in treating a variety of allergic disorders. Physician and/or patient bias was eliminated by conducting the evaluation on a double blind basis, comparing thereby BP-400 with chlorprophenpyridamine and placebo. Because of the long pollination season and abundance of mold growths in the north Texas area, it was possible to conduct the study for a period of one year.

There is evidence in experimental animals that serotonin increases tissue permeability, partially by histamine liberation. It has been suggested by Page[16] that serotonin may help mediate vascular changes in the earliest phases of inflammation and be partly responsible for the pain, since it causes pain in low concentrations. The swelling and edema produced in the rat's paw by serotonin injection (1 mcg) can be blocked with serotonin antagonists.[44] In patients with rheumatoid arthritis 10 to 100 micrograms of serotonin injected in the afflicted area will produce pain, swelling, and edema which can be abolished with 1 or 2 milligrams of the serotonin antagonist UML 491.[46] A vascular site of action of BP-400 is postulated due to its outstanding therapeutic effect in urticaria and angioneurotic edema. The marked antipruritic effect of BP-400 is probably related to its beneficial effect on the disease process rather than to primary peripheral sensory action.

Although serotonin has not been definitely implicated in gastrointestinal allergy, various authors have described celiac-like symptoms in patients excreting large amounts of 5-HT in the gastrointestinal tract. Green, Cooke

and Lattanzi[47] described the occurrence of celiac-like symptoms in three patients who had either a ganglioneuroma or ganglioneuroblastoma. These authors hypothesized that the tumors produced excessive amounts of 5-HT which in turn produced an effect upon the gastrointestinal tract. Kowlessar et al[48] demonstrated a significant increase in the secretion of 5-hydroxyindoleacetic acid in six patients with symptomatic non-tropical sprue. The satisfactory results obtained by the serotonin antagonist BP-400 in the 15 patients with gastrointestinal allergies may be due to its ability to block the action of serotonin in a specific fashion. Possibly BP-400 attaches itself to the receptors, which serotonin normally becomes attached to, in order to act on the mucous membrane and smooth muscle, thus preventing serotonin from taking its part in normal function. Woolley[49] states that the serotonin antagonists are like ill-fitting keys which exclude the proper key (serotonin) from its vital lock.

Herxheimer[50] indicated the possible role serotonin plays in the production of vasodilating headache. The beneficial effects of serotonin antagonist UML 491[51,52] have been reported in the treatment of headaches. BP-400 exhibited most satisfactory results in the treatment of "common migraine" and the "cluster" type headaches in this study.

Segal[53] has reported the possible role of serotonin in human allergy and its bronchoconstrictor effects. Berg[54] found in a study of fifty-two asthmatic patients, the concentration of the urinary 5-hydroxyindoleacetic acid varied with the severity of symptoms. Levy et al[55] reported the presence of 5-HIAA which is the breakdown product of serotonin, in the bronchial mucus of 9 of 10 patients with acute bronchial asthma. West[56] stated that serotonin is possibly stored in the lungs of the asthmatic patient during a paroxysm and is not excreted in the urine.

Herxheimer[57] has shown that inhalation of an aerosol containing 0.67 per cent of serotonin for periods of 60 seconds can provoke asthmatic attacks of varying severity. On the other hand, Brocklehurst[58] added serotonin and antihistamine directly to sensitized human bronchial ring preparations *in vitro* and observed bronchodilatation, rather than constriction. This, along with the observed failure of serotonin to produce asthmatic symptoms upon intravenous administration to both normal and asthmatic (human) subjects, raises questions pertaining to the existence of a cause-effect relationship. It is possible that 5-HT has an asthmagenic effect in man, not through a bronchomotor mechanism but through a vasoconstriction at the level of the pulmonary arteries.[59] The possible role of serotonin in the production of pulmonary hypertension in congenital heart disease has been considered.[60] There has been speculation about release of amines from lung depots as a factor which may influence bronchiolar tone.

The therapeutic results of BP-400 in bronchial asthma were disappointing but no more so than with other serotonin antagonists.[61]

At the conclusion of the study, 14 asthmatic patients were treated with an intravenous injection of BP-400 during an acute attack. Only five patients showed any improvement in pulmonary function and this was negligible by comparison with the results obtained with a subcutaneous injection of adrenalin hydrochloride given at the 120 minute level after the injection of BP-400.

An analysis of the results of this clinical study indicates that there is no parallel between the drug's antiallergic properties in the human being and its antianaphylactic effect as obtained in the experimental animal. The results obtained with BP-400 in allergic rhinitis were not equal to chlorprophenpyridamine.

BP-400 is a potent agent for the specific therapy of a wide variety of allergic disorders possessing antihistaminic, antiserotonin and anticholinergic actions. Any one (or a combination) of these properties could in theory be responsible for the effectiveness of BP-400 in a given allergic state. For example, although serotonin has been somewhat implicated in the human allergy, compounds of known antiserotonin activity (benadryl, di-paralene, hydroxyzine,[62] promazine, promethazine, pyribenzamine and trilafon) have not proven as effective for the control of clinical manifestations controllable by BP-400. It is of further interest to note that neither antihistamine, chlorprophenpyridamine nor BP-400 are able to alleviate markedly the symptoms of bronchial asthma prompting the supposition that other, as yet unidentified, chemical mediators may play a causative role. Considerable further study will be required to establish a clear concept of the role of intermediary substances in the production of hypersensitive reactions of the immediate type and the mechanism involved.

Although a number of relatively effective antiserotonin and antihistaminic agents are available, the search continues for effective agents of both types which should ideally possess low toxicity and effective, prolonged action. The marked individual variation among patients, with respect to symptomatic relief and undesirable side effects[63,64,65,66] of the presently available antiallergic drugs, serves to emphasize the need for a number of preparations possessing similar but not absolutely identical properties.

SUMMARY AND CONCLUSIONS

The clinical efficacy of BP-400 (9-(N-methyl-piperidyliden-4')-thioxane maleate), a new antiserotonin, antihistaminic agent, was evaluated by the double blind method in 247 patients requiring treatment for acute and chronic allergic disorders. BP-400 was compared with chlorprophenpyridamine (reference drug) and placebo. A satisfactory response was obtained in 92.7 per cent of the cases treated with this compound.

BP-400 was found to be superior to any comparable, currently available preparation for management of allergic dermatoses (urticaria, angioneurotic

edema, atopic dermatitis, contact dermatitis) in 69 patients. Its usefulness has also been documented in the presence of allergic headaches, drug reactions and allergic conjunctivitis. Minimal effectiveness was observed in allergic rhinitis and bronchial asthma.

BP-400 is suitable for use in the infant, child and adult (Table V). Doses employed ranged from 0.26 mg/Kg/24 hrs (average minimal effective dose) to 0.4 mg/Kg/24 hrs (often required to obtain maximum therapeutic effect in infants). Side effects were minimal, consisting in the main of mild to moderate sedation and fatigue, tending to disappear in the majority of cases, with continued use and without decrease in dosage of the drug. Withdrawal of medication due to excessive drowsiness and dizziness (caused by both BP-400 and chlorprophenpyridamine) was necessary in but one instance. No significant alterations in hemoglobin, white or differential counts were observed during periods of treatment extending up to a duration of seven months.

Administration of BP-400 during pregnancy produced no adverse effects upon either mother or baby.

Clinical trials have shown BP-400, an antiserotonin-antihistaminic agent, to be a safe, effective, well-tolerated agent, suitable for use in the management of numerous allergic disorders.

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