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BP 400 IN BRONCHIAL ASTHMA

By

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Even at present, status asthmaticus still constitutes a major therapeutic problem and, consequently, the discovery of every new agent capable of controlling the asthmatic attack must be noted with pleasure.

BP 400, chemically 9-(N-methyl-piperidylidene-4')-thioxanthene, a recent development by Sandoz, possesses some theoretically interesting pharmacological properties. Tests performed both in vitro and in vivo have demonstrated that this substance exerts an antihistaminic, anticholinergic as well as antiserotonin action. Its antihistaminic activity is among the strongest currently known, being 20 to 80 times more potent than that of Thenalidine (Sandosten) and 3 times more potent than that of Mepyramine. Besides, it has a prolonged action. Its anticholinergic effect is mainly central. In tests performed in vitro the anticholinergic effect of BP 400 is only 2 times weaker than that of atropine and in vivo it is 100 times weaker than the corresponding effect of atropine. Its antiserotonin activity is equal in strength with that of LSD 25 but of longer duration. As to the other pharmacological properties it may be mentioned, that in animal experiments on cats no definite effect on blood pressure was noted. The toxicity of BP 400 is low.

So far, synthetic antihistaminics have not proved effective

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in the treatment of bronchial asthma. According to the opinion of Serafini, the "intrinsic histamine,, released during an asthmatic attack would to a minor extent only be susceptible to the effect of antihistaminics. It has been found, in addition, that during an asthmatic attack a so-called "slow reacting substance A", and possibly serotonin, are released in the bronchioli. It is obvious that an antihistaminic cannot influence them at all. Neither has atropine become a routine therapy in bronchial asthma, and among others *Pearson* (1958) was of the opinion that belladonna alkaloids were of no essential value in the treatment of bronchial asthma. *Chamberlain* and associates (1962), however, found that atropine methonitrate, administered as inhalation therapy, possessed a definite bronchodilatory effect which was also verified by spirometry. The maximum effect most often appeared first after 60 minutes and the duration of action was about 3 hours. The significance of serotonin in bronchial asthma still remains unexplained. Among others, *Samter* has not been able to verify any positive effect when using serotonin antagonists in bronchial asthma. But as BP 400 has all three properties (anticholinergic, antihistaminic and antiserotonin), it is reasonable to see its affect on the chemical mediator substances which are released in asthma attacks, compared with the effect of atropine alone.

A preliminary report on the use of BP 400 in the treatment of bronchial asthma was presented by *Girard*, from the Geneva University Hospital. He gave 4 mg of BP 400 in 10 cc of physiological saline solution in 19 cases of status asthmaticus with a prompt effect in 15 cases. In 6 cases of milder asthma he had performed spirometric examinations after i.v. administration of BP 400. The respiratory function values had definitely improved in all. Drowsiness is the only actual side-effect reported by him. *Eisenberg* (1962) administered BP 400 to 200 patients with allergic rhinitis, 1 mg three times daily. 69.5 per cent of this group obtained good to excellent relief of symptoms, 9.5 per cent noted fair result and 21 per cent had poor or no result. Side effects, mostly sedation, occurred in 9 per cent.

MATERIAL AND METHODS

This series consisted of 16 patients, 4 males and 12 females. The average age is 53.8 years and the average duration of the asthma is 16.3 years. There were six cases of definite intrinsic asthma, 5 had allergic or extrinsic, asthma, and 5 had so-called mixed asthma with apparently exogenic origin while infection had subsequently come to the foreground. Three patients had a mild, one had moderate, and one had severe emphysema as a complication of protracted asthma. Specific hyposensitization had been started or planned for 8 patients.

The series thus includes rather chronic asthmatics and it is feasible that more dramatic results might have been obtained in asthma patients with a lower average age. On the other hand asthmatic attacks most often occur particularly in this type of asthmatics and, consequently, this material must, from a practical point of view, be considered fairly appropriate.

In all, 32 recorded administrations of BP 400 were performed for these 16 patients. The series is divided into two groups. In the first group, BP 400 was administered 22 times to 10 patients with either status asthmaticus or an asthmatic attack of such severity that respiratory function studies were not practicable. To the 9 patients belonging in the group II BP 400 was given 10 times. These patients were either suffering from a mild asthmatic attack or subjectively asymptomatic. Three patients (number 9, 10 and 15) belong both to group I and group II. The respiratory function was recorded by using the Wright's Peak Flowmeter. If used properly this apparatus will yield readings (l./min.) which reveal eventual variations in the bronchial obstruction quite as reliable as the FEV 1.0 of spirometry. Moreover, blowing into the Peak Flowmeter is considerably less strenuous for the patient than spirometry. As a rule, the highest value of 3 blowings was recorded. If the third blowing was better than the 2 first ones the patient was urged to go on blowing until the improvement of the reading ceased. The idea as to obtain the Peak flow value immediately before and 5, 15, 30, 60, 120, 180, 240 minutes etc. after the injection of BP 400, up to the point when definite deterioration of the respiratory function was again observed. Unfortunately, however, it was not possible to perform the study as schematically as this in all patients. The time of observation of the respiratory function varied from 1 hour to 7 hours 45 minutes, the average being 3 hours 30 minutes. The patients received 4 mg of BP 400 in 10 ml of physiological saline solution i.v., injected over a period of 3 to 4 minutes. During the period of observation of the respiratory function the patients received no further antiasthmatic medication. In cases of infection antibiotics were administered and chronic corticosteroid users received their normal maintenance dose.

RESULTS

Group I.

As can be seen from Table I the effect of the drug was excellent in 17 cases of 22. In most cases, relief of dyspnea was experienced by the patient during the injection. Immediately after the injection, definite alleviation or even total subsidence of the dyspnea was evident and also definite improvement of the auscultatory findings. The patient was able to leave his sitting forward-bearing position and lie down, and in 60 to 70 per cent of the cases fell asleep. Only one injection was administered its effect lasting about 5 hours. Most of the patients were resistant to epinephrine. Fatigue and drowsiness as well as falling asleep of the patient must be regarded as an exclusively positive phenomenon. Actual side-effects were rare. Dizziness occurred in 3 patients of 22, it being mild in one and moderate in 2. Three different patients experienced at 8 separate occasions either burning, pricking or motorrestlessness in the extremities.

Group II.

As is apparent from the Table 2 the Peak flow increased on the average 25.8 per cent the maximum being reached about one hour following the administration. The smallest increase was 16 per cent and the biggest one was noted in the patient no. 9 after 3 hrs 19 min. and was 45 per cent. If the second Peak flow maximum value after 7 hours 36 minutes in the patient no. 10 is taken into consideration, it is 62.5 per cent above the initial value.

In this group of asthmatics, however, the determination of the respiratory function was hampered by a generally quite severe fatigue and drowsiness. The bronchial spasm often disappeared almost entirely by auscultation but the improvement of the Peak flow value was nevertheless surprisingly trivial. One got the impression that the fatigue was accompanied by considerable muscular weakness. The subjective relief was clear although not as dramatic as in the status asthmaticus group.

Side-effects. In this group, the excessive fatigue and drowsiness must be considered a disadvantage. It occurred in almost all patients and generally it was the more troublesome the milder the asthma was in the patient in question. Four patients had dizziness, in the patient no. 5 there was nausea. Pricking or motor restlessness in the extremities occurred 3 separate times in 2 patients.

TABLE I
Effect of BP 400 in 22 patients suffering from asthma.

Patient No.	Age	Sex	Effect	Duration	Side-effect
1 a)	58	F	+++	4 hrs	----
b)			++	3 hrs	Moderate dizziness
2	73	F	+++	5 hrs	----
3 a)	55	F	+++	4 hrs	----
b)			++	2 hrs	----
4 a)	65	F	+++	4½ hrs	-----
b)			++	3 hrs	----
7 a)	52	F	+++	5 hrs	Pricking and twitching in feet
b)			+++	5 hrs	Pricking and twitching in feet
c)			+++	4½ hrs	-----
9 a)	42	M	+++	4-5 hrs	----
b)			+++	4-5 hrs	-----
c)			+++	4-5 hrs	----
d)			+	2 hrs	----
10 a)	40	F	+++	6 hrs	Motor restlessness in feet
b)			+++	6 hrs	Motor restlessness in feet
c)			+++	5½ hrs	Motor restlessness in feet
d)			+++	4 hrs	Motor restlessness in feet
e)			+++	5 hrs	
14	29	F	+++	5 hrs	----
15	55	M	+++	2½ hrs	Some dizziness
16	48	F	++	2 hrs	Dizziness burning in the extremities, pricking in the tongue

Effect:

- +++ = excellent control of asthmatic attack.
 ++ = moderate relief.
 + = slight relief.

TABLE II
Average increase of the Peak flow 25.8 per cent in 59. min. 30 sec.

Patient No.	Age	Sex	Peak flow initial value l/min	Peak flow maximum l/min	Increase of P. flow in %	Maximum effect after	Side-effect (besides fatigue)
5	57	M	276	386	36.2	7 min.	Dizziness, nausea, pricking in fingers
6	51	F	135	160	18.5	1 h. 37 min.	Dizziness
8 a)	68	M	125	145	16.0	50 min.	---
b)	68	M	150	180	20.0	35 min.	Dizziness
9	42	M	167	242	45.0	3 h. 10 min.	---
10	40	F	120	161	34.2	36 min.	Motor restlessness in the feet
11	56	F	85	195	62.5	7 h. 36 min.	---
12	50	F	130	103	21.2	55 min.	---
13	62	F	128	167	28.4	5 min.	---
15	55	M	213	154	20.3	60 min.	---
				252	18.3	60 min.	Dizziness

DISCUSSION

According to this study, intravenously administered BP 400 is most effective in the treatment of status asthmaticus and severe asthmatic attacks. In these cases also side-effects are mild and rare. Since the patient at the time of admission often has remained awake at home for several nights it is most advantageous that there be promptly relieved of distress and even be made to fall asleep. BP 400 occasionally avoids the use of corticosteroids completely.

In mild asthma, an i.v. injection, BP 400 causes too much fatigue, and dizziness occurred in about 40 per cent. The use of BP 400 in tablet form should be investigated. Should the result prove beneficial this would provide an opportunity of disentangling many chronic corticosteroid users from this rather dangerous hormonal treatment.

On what is the action of BP 400 based? On the basis of previous literature it seems probable that its effect is mainly anticholinergic. In general the antihistamine with an antiasthmatic effect also possess anticholinergic properties.

An example of this kind of substances is Multergan. It has, however, the disadvantage of exerting its anticholinergic action mainly peripherally and severe drying of the mouth and accommodation paresis, render its use inconvenient. Apparently the most valuable property of BP 400 is its strong central anticholinergic effect. None of the patients in this study, for instance, complained of dry mouth or blurred vision. Since, the BP 400 is a most potent antihistaminic agent, it is naturally quite possible that some of its effectiveness depends on this property. Nobody knows yet the significance of anti-serotonin action. It is also possible that all the different properties of BP 400 would still have a synergistic effect on the "slow reacting substance A" which is regarded as an important chemical mediator in the human asthma.

SUMMARY

BP 400, or 9-(N-methyl-piperidylidene-4')-thioxanthene, has been found (at the Sandoz Pharmacological Laboratories) to exert a central anticholinergic, antihistaminic and antiserotonin action. In the present study, 4 mg of BP 400 in 10 cc. of physiological saline solution was injected intravenously 32 times to 16 asthmatics. The series is divided into 2 groups. In the group I, BP 400 was administered 22 times to 10 patients with either status asthmaticus or severe asthmatic attacks. The results were excellent in 17 cases of 22, moderate in 5. Most patients fell asleep, and dizziness occurred 3 times. To the 9 patients in the group II, BP 400 was administered 10 times. These patients had a mild to moderate asthma, and pulmonary function was registered on the average for 3½ hours. On the average, the Peak flow increased 25.8 per cent in about one hour. Excessive drowsiness and fatigue were disadvantageous for these patients, and dizziness occurred in 4 cases of 10. BP 400 must be regarded as a promising compound in alleviating airway obstruction in asthmatic attack.

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