

RESULTS OBTAINED IN TREATMENT WITH
THE ANTIHISTAMINIC SANDOSTENE AND
WITH SANDOSTENE + CALCIUM-SANDOZ

By

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Par. I.

Some years ago, a new antihistaminic was developed in the Sandoz laboratories. This drug was called Sandostene (AS 716) and it has the following formula:

1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine-
tartrate.

A study of the literature shows that it has the following properties:

1. it has an antihistaminic action (3, 14, 15), the intensity of which is medium in comparison with that of the antihistaminics so far known.
2. it has an anticholinergic action (14, 15), which is approximately 50 times weaker than that of an equal amount of atropine, but as the usual dose of the antihistaminic is 50-100 times larger than that of atropine, the parasympatholytic action may be assumed to be of the same value from the therapeutic point of view.
3. it has an adrenolytic action (14), especially when larger doses are administered, this action being 500 times weaker than that of ergotamine.

4. it has a local anaesthetic action (14) equal to that of procaine and 2.2 times less powerful than that of Panthesine.
5. it is highly effective in inhibiting permeability (1, 3, 9, 14).
6. it delays in vitro the coagulation of the blood by inhibiting the production of thromboplastin (6).
7. both its acute and its chronic toxicity are very low in comparison with those of other antihistaminics (3, 14, 15).

According to the literature Sandostene is particularly effective in the treatment of acute urticaria, acute angioneurotic edema (Quincke's edema), exsudative urticarious eczema, dermatitis medicamentosa (drug eruption) marked by reactions of the vessels of the skin, essential pruritus, neurodermatitis, hay fever and in the prevention of allergic symptoms which may appear in specific desensitization (4, 5, 7, 13, 16, 18).

The drug was found to have little effect in chronic urticaria, pruritus due to eczema and to neurodermatitis, and in bronchial asthma.

Naturally, it is difficult to evaluate the results of treatment in the event of associated disorders.

Unfortunately this condition, viz. that cases should have a recent history, cannot often be complied with, as only few patients are referred to our out-patient department, who have not previously consulted one or several specialists such as a thorax specialist, a dermatologist or a specialist in the treatment of diseases of the ear, nose and throat.

Our investigation was confined to moderately severe cases.

Patients with eczema were only treated with Sandostene when secondary infection was absent, when they had not undergone previous irradiation therapy and when the eczema had appeared within the last five years.

In addition, uncomplicated conditions were selected whenever possible and only patients with asthma were sometimes also affected with eczema, urticaria or vasomotor rhinitis. The evaluation of the effect of Sandostene was based on the effect on the attacks themselves in these cases.

As antihistaminics either have a favourable effect or a moderate action or are ineffective, the investigation could be confined to a brief period; the follow-up was never continued beyond a month.

Finally, with a view to obtaining comparable results wherever possible, I limited the dosage to 1-3 tablets daily of the sugar-coated tablets AS 716 25 mgr supplied to us by Sandoz and never administered the drug to children under 16 or to people over 65.

The statistical data were confined to *those* patients in whom a *beneficial* action of the drug was verified by administration of a placebo, with the exception of patients with pollinosis and drug allergy. Neither the patient nor I myself were acquainted with the time of administration of the placebo (double blind method).

When the patient treated with a placebo responded equally well both to the placebo and to the drug, I eliminated the case from the investigation. This occurred in 8 per cent of the cases.

RESULTS OF TREATMENT

Comment on the statistical data (table I) :

1. The small number of patients with pollinosis (3d) was due to the fact that my investigation was confined to the period from March 1 to May 31, 1955, inclusive.
2. Previous treatment with other antihistaminics had also failed in the two cases of migraine (2) showing an unfavourable response. One woman who failed to respond showed marked food allergy.
3. In the case of urticaria haemorrhagica (3b) the itching disappeared within one hour after administration of Sandostene, to recur 4 hours later, the haemorrhages continued unchanged.
4. It should be pointed out that administration of one or more antihistaminics had also failed in 5 of the 8 patients with chronic urticaria (3c) who failed to respond

TABLE I

Disorder	No. of cases	++	+	—	Thephorin		Phenergan	
					total	++/+	total	++/+
1. <i>Diseases of the respiratory tract</i>								
a. asthmatic bronchitis	45	17	11	17	45	30	45	34
b. bronchospasms	10	5	1	4	10	5	10	8
c. eosinophilic bronchitis	1	1	0	0	—	—	—	—
d. Quincke's edema	12	3	2	7	12	6	12	5
e. vasomotor rhinitis	27	12	11	4	27	20	—	—
2. <i>Migraine</i>					4	1	4	2
3. <i>Skin diseases</i>								
a. acute urticaria	4	2	0	2	4	3	4	3
b. urticaria haemorrhagica	1	1	0	0	0	0	0	0
c. chronic urticaria	13	3	2	8	13	6	13	7
d. pollinosis	13	8	2	3	13	11	—	—
e. essential pruritus	9	4	3	2	0	0	0	0
f. acute dermatitis medica- mentosa with urticaria	9	5	0	4	9	5	9	6
4. <i>Other disorders</i>								
a. prevention desensitization	5	3	1	1	0	0	0	0
b. regional enteritis	2	1	1	0	0	0	0	0
c. Menière's syndrome	1	1	0	0	0	0	0	0
5. <i>Total</i>					156	67	35	54
					65 %			
					137	88	97	65
					63 %		67 %	

to the treatment. I did not have the impression, that these patients would *not* respond to other antihistaminics.

5. Of the four patients with acute dermatitis medicamentosa (3f) who failed to respond to Sandostene, one did respond to treatment with Sandostene + Calcium-Sandoz, and in 2 cases the symptoms disappeared on treatment with corticotrophin.
6. The patient with Menière's syndrome (4c) was also affected with asthmatic bronchitis; Sandostene had no effect on the asthma.

7. The following values are reported by Sandoz in statistical studies on the results obtained in treatment with Sandostene and Sandostene + Calcium-Sandoz (5) :

No. of cases	++	+	-
1052	683	204	165
	64.9 %	19.3 %	
	<u>84.2 %</u>		

However, as the results obtained in treatment with Sandostene + Calcium-Sandoz have also been incorporated in these statistics and the Sandoz Laboratory states that the combined preparation is the more effective, the statistical data as published by the Sandoz Laboratory and my own findings may be assumed to be identical.

As primarily any evaluation of the clinical results obtained with drugs will depend on the views of the various investigators, as, secondly, the response will vary with the people studied, and as thirdly the statistics usually do not state the months during which the investigation was carried out, I have compared the results obtained with Sandostene with the personal results obtained with Phenergan and Thephorin in out-patients, the effects of equal doses of these drugs having been verified over identical periods.

I do not use Phenergan in all cases of pollinosis and vasomotor rhinitis, because its hypnotic action often has a disturbing effect in the daytime. Thephorin, Plimasin, etc., however, are well tolerated in the daytime.

Therefore, although not all the patients studied for response to Sandostene were included in the statistical data compiled for purposes of verification and the ratio as expressed in percentages cannot be claimed to be entirely correct, these data do show that the results run more or less parallel to one another.

In addition to the above results, noxious side-effects are another important factor in deciding whether a drug is of sufficient social value to be prescribed for out-patients.

I found Sandostene to have side-effects in 20 cases (13 per cent), viz. (table III):

- a. disturbances of the gastro-intestinal tract.
 1. pain in the stomach or oesophagus in 1 patient.
 2. nausea in 1 patient.
- b. nervous reactions.
 1. somnolence in 10 cases.
 2. vertigo in 5 cases.
- c. one patient complained of excessive thirst.
- d. one developed photophobia.
- e. one showed anginous symptoms.

Whenever treatment had unpleasant side-effects, it was immediately discontinued when the side-effects were such that I believed to be justified in classifying these cases under the heading "poor results".

In comparing the noxious side-effects of Sandostene with those of other antihistaminics, I believe they may be regarded as slight. As a rule, Sandostene may also be prescribed for out-patients for use in the daytime.

Finally, the effect of any antihistaminic will be more beneficial in one patient than it is in another and every drug of this group can fail, so that alternating treatment is indicated.

Par. 2.

RESULTS OBTAINED IN TREATMENT WITH THE COMBINED PREPARATION SANDOSTENE + CALCIUM-SANDOZ

Details:

In the combined preparation Sandostene + Calcium-Sandoz the action of the two constituents is potentiated (3, 11, 9, 14). Sandostene + Calcium-Sandoz is supplied in effervescent tablets containing 25 mgr of Sandostene and 1.373 gr of calcium lactate-gluconate or in ampoules of 5 ml and 10 ml,

TABLE II

Type of disorder	Sandostene tablets			Sandostene + Calcium-Sandoz tablets			Sandostene + Calcium-Sandoz injections		
	Number of cases	++	+	—	No. of cases	++	+	—	No. of cases
1. Disorders of the respiratory tract									
a. asthmatic bronchitis	45	17	11	17	19	8	5	6	25
b. bronchospasm	10	5	1	4	10	4	2	4	11
c. eosinophilic bronchitis	1	1	—	—	—	—	—	—	—
d. pollinosis	13	8	2	3	13	7	2	4	—
e. vasomotor rhinitis	27	12	11	4	27	12	12	3	32
2. Migraine	4	1	1	2	1	—	—	1	—
3. Skin diseases									
a. acute urticaria	4	2	—	2	4	3	—	1	—
b. urticaria haemorrhagica	1	1	—	—	—	—	—	—	—
c. chronic urticaria	13	3	2	8	13	8	1	4	—
d. Quincke's edema	12	3	2	7	12	6	1	5	10
e. essential pruritus	9	4	3	2	—	—	—	—	—
f. acute urticaria dermatitis medicamentosa ...	9	5	—	4	9	5	1	3	3
g. contact eczema	—	—	—	—	1	—	1	—	—
h. allergic eczema (dietetic error)	—	—	—	—	1	—	—	1	—
4. Other disorders									
a. prevention desensitization	5	3	1	1	1	1	—	—	—
b. regional enteritis	2	1	1	—	—	—	—	—	—
c. Menière's syndrome	1	1	—	—	1	—	—	1	—
d. insect bite	—	—	—	—	2	2	—	—	—
Total	156	67	35	54	114	56	25	33	81
		65%				71%			
						40	23	18	78%

¹ The patient's response to intravenous injection of Sandostene + Calcium-Sandoz was regarded as negative, when one or two injections made on 4 days in succession failed to have any effect. This low dosage was chosen to enable the comparison of the effects of the preparations to be as accurate as possible. When used for therapeutic purposes 2-3 injections daily may naturally be

TABLE III

Side-Effects of Sandostene and Sandostene + Calcium-Sandoz.

	Sandostene tablets	Sandostene + Calcium tablets	Sandostene + Calcium injections
<i>A. disturbances of the gastro-intestinal tract</i>			
1. pain in the stomach	1		—
2. nausea	1	3	—
3. vomiting	—	1	—
4. diarrhoea	—	1	—
<i>B. nervous reactions</i>			
1. somnolence	10	7	15 ¹
2. vertigo	5	3	6
3. headache	—	1	1
<i>C. thirst</i>	1	—	1
<i>D. photophobia</i>	1	—	
<i>E. anginous symptoms</i>	1	—	
Total	20	16	23
Total number of patients	156	114	81
	13 %	14 %	28 %

¹ Somnolence was *not* considered a side-effect in evaluating the response to intravenous therapy as favourable or unfavourable.

10 ml containing 50 mgr of Sandostene and 1.375 gr of calcium gluconolactobionate for intravenous injection.

The indications for Sandostene + Calcium-Sandoz are the same as those for Sandostene. For purposes of comparison, the investigation was identical with that on Sandostene and was in part carried out simultaneously with the latter.

I have gained the impression that the sense of heat, which frequently follows intravenous injections of preparations containing calcium is not felt so often in injections of Sandostene + Calcium-Sandoz.

Somnolence is a prominent feature in intravenous injections, but this is a symptom previously known to occur. Nasemann

found somnolence to follow injections 6 per cent of his 169 patients.

Therefore I do not allow my patients to leave the out-patient department until half an hour has elapsed after injections of Sandostene + Calcium-Sandoz. I found no changes in the haemograms of 134 patients treated with over 10 intravenous injections of Sandostene + Calcium-Sandoz; I did not examine any others. Like all antihistaminics, Sandostene + Calcium-Sandoz does not cure all allergic diseases, although it is one of a series of pharmacological preparations, which are very useful in the treatment of allergic patients.

Par. 3.

DISCUSSION

In comparing the two reports, a number of questions immediately arise.

1. Are there patients who do respond to Sandostene + Calcium-Sandoz, but not to Sandostene?

Lindemayr (11) has reported some data on the subject and this also occurred in some of my own patients (so far, in four cases), while *Kail & Lindemayr* (10) previously reported favourable results of the combination of calcium and antihistaminics.

2. *a.* If Sandostene and Sandostene + Calcium-Sandoz contain the same amount of the antihistaminic drug per therapeutic unit, can truly be stated that Sandostene + Calcium is more effective than Sandostene?

b. Does the addition of calcium to Sandostene constitute an actual improvement or is the therapeutic action solely due to the antihistaminic and will the addition of calcium result in contraindications?

sub 2 a. Each sugar-coated tablet of Sandostene contains 25 mgr of theno-phenopiperidine tartrate, each effervescent tablet of Sandostene + Calcium-Sandoz contains an equal amount of this substance, in addition to 1.37 gr of calcium gluconogalactogluconate.

Does this mean that Sandostene + Calcium is more effective than Sandostene? Naturally, it is difficult to answer this question. Schuppli writes: "We used Sandostene in sugar-coated tablets of 25 mgr, in tablets combined with Calcium-Sandoz and in ampoules of 50 mgr of Sandostene in 10 ml of 10 % Calcium-Sandoz. We usually administered 10 ml of Sandostene + Calcium-Sandoz as an initial dose by intravenous injection in severe cases, oral administration of 1-2 sugar-coated tablets or ordinary tablets three times daily being substituted for this treatment when any improvement was observed. Oral treatment with Sandostene usually was sufficient in the milder cases. In doing so, however, we gained the impression that Sandostene + Calcium-Sandoz tablets were more effective than Sandostene sugar-coated tablets".

As regards the question as to whether the addition of calcium to Sandostene constitutes an actual improvement, at the moment I can merely state: I believe so, but I cannot prove this. The answer to this question would require a detailed discussion of the action of calcium alone in allergic diseases. Especially *Undritz* (19, 20) offers detailed pharmacotherapeutic data on this subject.

sub 2 b. The various papers written on the subject show that the antihistaminic action, the anticholinergic effect and the local anaesthetic action of Sandostene are not modified by the addition of Calcium-Sandoz, toxicity being reduced and the action on vascular permeability being increased.

For the study of these problems, I refer the reader to the papers written by: *Rothlin* and *Cerletti* (3, 14, 15); *Huber* (9); *Nasemann* (12); *Essellier*, *Forster* and *Morandi* (7); *Dobes* (5); *Combes* (4); *Saffron* (16); and *Thüer* (18).

Finally, the addition of calcium does not involve any contraindications. The digitalis-like action of calcium (which is merely transient, however), calling for caution in digitalized patients, is markedly reduced by the antihistaminic. As far as side-effects are concerned, according to all papers published so far these are very slight.

It will suffice to cite *Clein's* report (2), which is mainly con-

cerned with treatment of children and which runs as follows: "Our investigation of this new antihistaminic shows that it is effective and it appears to be more advantageous than other antihistamines because of the almost complete lack of side-effects".

In conclusion and for the sake of completeness, I shall briefly report two interesting cases:

One concerned a 29-year-old woman with asthma, who was resistant to every form of treatment (various antihistaminics, other drugs, even including ACTH, cortisone and prednisone) and who was again fully capable of performing her duties as a dentist's assistant following 3 intravenous injections of Sandostene + Calcium-Sandoz, the patient having had no relapse for 2 months after the injections. From Argentine (8) and U.S.A. (4, 5, 8, 16) there have also been reports of favourable results obtained with this drug in cases resistant to treatment with cortisone and ACTH. It was also given as an adjunct to treatment. In certain cases this may save a considerable quantity of hormone, which also reduces the risk of side-effects (8, 16).

The other patient, a 38-year-old woman, suddenly lost the power of her right arm when playing tennis. After she had played for 10 minutes, the wrist showed acute swelling and she had to give up the game, as she was no longer able to hold the racket. The joint was fairly painful on movement, but there were no other symptoms of acute inflammation, tendovaginitis, etc. The symptoms disappeared within an hour after two Sandostene tablets had been administered; this result was attributable either to rest, to the Sandostene or to both; naturally, this is open to question, but other cases of joint disease responding to treatment with Sandostene or Sandostene + Calcium-Sandoz have been reported in the literature (13, 21).

SUMMARY

Description of the therapeutical results obtained with the antihistaminics Sandostene and Sandostene + Calcium-Sandoz.

The drugs were given to 156 and 114 patients, in the usual dosage (1-3 times 1 tablet daily) and the effect was verified by administration of a placebo and compared with Thephorin and Phenergan. In addition to the results, side-effects are described.

This experiment has been performed at the request of the Dutch Allergological Pharmaceutical Committee.

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