A CLINICAL EVALUATION OF A PIPERIDINE COMPOUND ALONE, AND COMBINED WITH CALCIUM INTRAVENOUSLY IN ANTIHISTAMINE THERAPY

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The generally accepted mechanism of allergy is still that it depends predominantly on the presence of histamine or chemically similar substance in abnormal quantities in the affected tissues, or an unusual and unexplained sensitivity to histamine. This activity is specific for histamine in that it requires the presence in the molecule of

\[ \text{--N} = \overset{\bigcap}{\text{C}} - \overset{\bigcap}{\text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2} \]

or

\[ \text{==N} = \overset{\bigcap}{\text{C}} - \overset{\bigcap}{\text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2} \]

Similar compounds not containing this molecular configuration are devoid of histamine activity.

For obvious reasons it is not only impossible but impractical to check histamine formation. Almost a century ago attempts were initiated to make available an antagonist which would either successfully combat formation of histamine or nullify its effects. This presented many difficulties. Naturally, attention was first directed to the sympathomimetic drugs such as epinephrin, but since these substances do not prevent the capillary dilatation induced by histamine, they were discarded.

In 1953 Rothlin and Cerletti (1), and Huber (2) evaluated a new antihistaminic drug, designated Sandostene. Chemically this is 1-methyl-4-amino-N'-phenyl-N' (2'-thenyl)-piperidine-tartrate.

Rothlin and Cerletti combined this substance with calcium for intravenous administration. The logic of this combination was based on experimental and clinical experience which followed the use of calcium with various other antihistaminic drugs. There was some apparent synergism with benefits not obtainable from either substance alone. While calcium is by no means an antihistaminic it does have a decongestive effect. Calcium also exerts a sedative effect on the cortical sensory centers, the medulla and spinal cord. Combining an antihistaminic with calcium seemed to offer advantages over each substance individually, but the clinical substantiation was still to be demonstrated.

Many antihistaminics inhibit acetylcholine; some, however in doses far beyond their therapeutic range. Since acetylcholine seems to play a role in allergic reactions and may even participate in development of vegetative disturbances associated with allergy, some anticholinergic action would be desirable.

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Received for publication July 22, 1954.
The same investigators concluded that Sandostene possesses great antihistaminic activity as well as anticholinergic activity, local anesthetic properties, plus antipermeability properties.

In the fall of 1953 we undertook a clinical evaluation of Sandostene by mouth, alone, and combined with calcium gluconogalactogluconate intravenously, in order to determine the effects on pruritus, insomnia due to pruritus, and the decongestive effect in inflammatory processes, many of an allergic nature. To facilitate control of patients it was deemed advisable to conduct this study on private patients. This principle was adhered to with the exception of several hospitalized patients who received intravenous medication.

METHOD

One hundred thirty five patients were included in this study, twenty five of whom received intravenous injections of Sandostene plus Neocalglucon (calcium gluconogalactogluconate). Patients were not grouped according to the dermatoses from which they suffered; nor was any attempt made to classify them in homologous groups with respect to age, sex, severity or duration of the disease. The reason for this was that the action of both medications was essentially empiric; evaluation of effects was based on subjective and objective evidence of symptomatic relief, the former especially as it related to insomnia and pruritus.

All patients, as far as could be determined, were apparently in good health except for their dermatoses.

The latter included over two dozen various dermatoses associated with itching which interfered with the patient’s normal activity and with sleep. In a few dermatoses the purpose of administration was to overcome anxiety and stress.

Sandostene was given in compressed tablets, each containing 25 mgm. of the active ingredient; dosages varied daily from 75 to 250 mgm. The maximum total dosage was 43.2 grams (approximately 250 mgm. daily), over a six month period.

Those patients treated intravenously received 10 cc containing 1.375 gm. of calcium gluconogalactogluconate plus 0.05 gm. of Sandostene.

One patient received intravenous medication once daily for 37 days.

RESULTS WITH COMMENT

No adverse effects were noted in urinary findings or hemograms of any patient. Icterus indices were not altered.

Both parenteral and oral medication exhibited antihistaminic and sedative effects. The latter were not apparent from the mouth medication when only one or two tablets were given. However three tablets caused drowsiness, even during daytime hours of normal activity. After intravenous medication sedation was quite noticeable; ambulatory patients were advised to abstain from driving automobiles for two hours after medication. In many instances intravenous medication given as early in the day as noon was followed by a restful night and freedom from pruritus. In general, sedation and relief from pruritus lasted for from six to eight hours after injection. One thin, elderly woman (aged 75 years) experienced a brief attack of syncope a half hour after receiving 10 cc of the intravenous medication. It is advisable to give smaller doses in the elderly.
The relief from pruritus did not seem due to any evident cortical sedation as there was no complaint of drowsiness after the oral medication, although the itch reflex was partially or completely abolished. On the contrary this relief from pruritus did not seem wholly dependent on any decongestant effect, as urticarial lesions would persist although the pruritus had subsided.

Best results were obtained in disseminate neurodermatitis (atopic eczema), and contact dermatitis, especially of the generalized type. Many of the atotics had associated hay-fever and/or asthma. These were in general relieved.

Clinicians are at present evaluating the limitations of cortisone and adrenocorticotropic hormone in the treatment of the stress syndrome associated with tissue injury. While response to these is quite dramatic, they have side reactions and contraindications which, if not respected, may endanger life. There are certain similarities between the activity of these substances and the antihistaminics. When cells are injured there is consequent inflammation and release from the injured cell of histamine and histamine-like compounds which flood the entire organism. These substances are considered by many to be the actual cause of systemic toxicity ("histamine shock syndrome"). Similar histamine response follows allergic shock and many instances of drug reactions due to idiosyncrasy to dose. Many instances of dermatitis medicamentosa respond dramatically to cortisone. The response to an effective antihistaminic, especially when given by intravenous injection with calcium is sometimes equally dramatic. Three of our patients had better results from Sandostene than from hormonal therapy of their allergy. In the more protracted allergies, such as chronic urticaria, atopic dermatitis and asthma, calcium and Sandostene are preferred; and while not regularly as prompt in effect, are after several weeks of administration, more effective and free of any side effects and toxicity.

The antihistaminics act directly on histamine as antagonists, thus neutralizing its toxicity to tissues and relieving in whole or in part objectionable subjective and objective symptoms. Adrenocorticotropic hormone and cortisone have no effect on itching per se; they only relieve it indirectly by overcoming systemic and local tissue stress.

SUMMARY AND CONCLUSIONS

1. Sandostene was administered orally to 110 subjects with the following results:

   Excellent  11
   Good       69
   Failure    26
   Doubtful   4

2. Sandostene plus Neocalglucon was administered intravenously to 25 subjects with the following results:

   Excellent  5
   Good       16
   Failure    3
   Doubtful   1
3. Side actions consisted of one case of cramps and diarrhea a half hour after ingestion of each tablet. Drowsiness followed more than two tablets by mouth and all instances of intravenous medication.

4. No instance of toxicity was encountered.

5. The incidence of side effects was lower than that reported with equivalent doses of other histamine antagonists at present in general use.

6. The combination of Neocalglucon and Sandostene as used in this study seems to be low in toxicity and highly suitable to supplement and widen the therapeutic range of calcium. The combination is well tolerated and possesses high antipermeability action resulting in manifold therapeutic effects which favor its use in treatment of the protean manifestations of allergic disease of the skin.

The material for conducting this investigation was supplied by Sandoz Pharmaceuticals, Division of Sandoz Chemical Works, Inc.

REFERENCES
