LONGIEEN - A New Antihistaminic with Prolonged Action
by Knud WILKEN-JENSEN.

The action of most antihistaminics is but short-lived (2-6 hours), and the secondary effects are not insignificant. That is why the American Medical Association (9) has suggested that endeavours be made towards the production of antihistaminics

1) of increased potency over the preparations now available
2) with fewer secondary effects, and
3) with a prolonged action - preferably 24 hours.

Antihistaminics may be divided into four groups:

I - Derivatives of ethylenediamine
II - Derivatives of ethanolamine
III - Monoamines
IV - Derivatives of piperazine.

The antihistaminic effect of the preparations seems independant of the constitutional formula, since preparations with small and strong effect are found in each group.

I) Derivatives of ethylenediamine

\[ >N - CH_2 - CH_2 - N< \]

a. ALLERCUR Schering Berlin
b. ANTHISAN May & Baker (Pyranisamin maleat, mepyramin maleat)
c. NEOANTERGAN Rhone-Poulenc

d. ANTISTINA Ciba
e. HISTADYL Eli Lilly (thenylpyraminhydrochloride)
f. NILISTIN Lundbeck
g. PHENERGAN May & Baker (prometazin hydrochloride)
h. PYRIBENZAMIN Ciba (tripelenamin hydrochloride)
i. SOVENTOL Knoll
j. SYNOPEN Geigy
k. TAGATHEN Lederle (chlorothencitrate)

II) Derivatives of ethanolamine

\[ -O - CH_2 - CH_2 - N< \]

a. AMIDRYL MCO (diphenhydramine hydrochloride)
BENADRYL P.D. & Co.
b. ANAUTIN CMS
   DRAMAMIN (dimenhydrinate NNR)
   NEPTUSAN AB (diphenhydramine 8-chlortheophyllinate)
c. ANTIN ASA
d. HISTAPHENE U.C.B. (medrylamine maleat)
e. PARADRYL Ido
f. REGIDYL MCO

III. Monoamines

\[
>CH - CH_2 - CH_2 - N<
\]
a. CHLOR-TRIMETON Schering U.S.A.
b. THEPHORIN Roche
c. TRIMETON Schering U.S.A.
   UNAN Hoechst.

IV. Derivatives of piperazine

\[
\begin{array}{c}
  CH_2 - CH_2 \\
  \downarrow \\
  N \quad N \quad N \\
  \downarrow \\
  CH_2 - CH_2
\end{array}
\]
a. DI-PARALENE Abbott (chlorcyclizin hydrochloride)
   PERAZIL Burroughs Welcome
   TRIHISTAN Gea
b. LONGIFEN U.C.B. (buclizin hydrochloride)
c. POSTAFEN U.C.B. (meclizin hydrochloride)

There seems to be a certain correlation between molecular weight and properties, so that the higher the molecular weight the greater the fulfilment of the requirements set up by the American Medical Association.

Compounds with a piperazine nucleus that may perhaps be traced to the derivatives of ethylenamine have shown a prolonged action, e.g. a single dose of chlorcyclizene (Diparalene = Trihistan) remains effective for 12 hours.

\[
\begin{array}{c}
  Cl \\
  \downarrow \\
  CH - N \\
  \downarrow \\
  \begin{array}{c}
    CH_2 - CH_2 \\
    \downarrow \\
    CH_2 - CH_2
  \end{array}
\end{array}
\]

chlorcyclizin = 1(p. chlorbenzhydryl)4.methylpiperazin hydrochloride
In Belgium Eugene GRIVSKY [7] and [12] has produced a series of aralkylpiperazines as he thought it probable that one or more of these preparations possessed the properties that A.M.A. had stated as desirable. Pharmacological experiments showed that two of the compounds he produced possessed a potent and prolonged antihistaminic action. Consequently they were tested clinically, and proved to meet the requirements of the A.M.A. Those preparations were POSTAFEN and LONGIFEN.

\[
\text{POSTAFEN = } \text{l(p.chlorbenzhydryl)4 m-methylbenzylpiperazin dihydrochloride.}
\]

POSTAFEN is being produced by UNION CHIMIQUE BELGE S.A. Animal experiments [14] showed that its inhibition of histamine outclassed that of the antihistaminics available. The effect lasted for about 24 hours, and there were no secondary effects worth mentioning [6] [14]. In human clinic it has proved particularly active against travel sickness [2] [3] [4] [6], hyperemesis gravidarum, allergic rhinitis and urticaria [14]. Whereas the action on allergic dermatose affections like prurigo and eczema etc. has not been satisfactory. Against such complaints on the other hand LONGIFEN proved good [5].

\[
\text{LONGIFEN = l(p.chlorbenzhydryl)4(p.tertiobutylbenzyl)piperazin dihydrochloride.}
\]

LONGIFEN is a white, microcrystalline, tasteless, and odourless powder, which is unalterable when exposed to air and light. It is insoluble in most organic solvents, and slightly soluble in hot water acidulated by hydrochloride acid [7].

After administration to guinea-pigs by i.v. injection of 2.5 mg/kg of LONGIFEN toxic doses of histamine are tolerated as follows:
200 toxic doses after 1 hour
1000 " " " 4 hours
1000-1500 " " " 24 "
600 " " " 7 days

Toxicity (in mice): minimum always lethal dose = 2.5 g/kg
LD$_{50}$ = 1.85 g/kg (8)

On the basis of these results and some reports on clinical tests (11)(13)(15) LONGIFEN (*) has been successfully tested in the Allergic Childrens' Clinic of the Danish National Hospital (the Rigshospitalet) and in private practice.

The action of Longifen in 35 patients has been observed, namely 8 aged 3-10 years, 15 between 10 and 15 years, and 12 adults (19-56 years). The principal complaints were asthma, allergic rhinitis (including hay-fever) and allergic skin-diseases, but as will be seen in the table there were other symptoms too, and on the said 35 patients the preparation was tested against 46 symptoms, some patients having more than one allergic manifestation.

The dosage for those treated first was only 1-2 tablets of 25 mgm over 24 hours, which may account for some of the negative results. Later up to 1 tablet 3 times a day was administered to children, if necessary more to adults. The doses have always been kept as low as possible, and the patients have been instructed to reduce the doses once action had been ascertained. In several cases it has been possible very soon to reduce the dose to 1 tablet at night, which proved sufficient to prevent nightly attacks of asthma and pruritus as well as morning sneezes.

Placebo tablets have not been administered, but in many cases the patients have tried other remedies - with varying effects. Some of these patients stated that LONGIFEN produced in them the maximum action, others that its action was like that of other antihistaminics.

Two patients have complained of secondary effects; an 11 year old boy got 3 tablets a day and felt somewhat drowsy, a 7 year old girl was given 3 x 1 - 2 x 1 but felt tired after the intake.

Six of the patients have had relapses of the symptoms a shorter or longer time after the cessation of the treatment with LONGIFEN: two of them evinced good effect on retreatment with the same preparation. Two cases evinced reduced and two cases no effect; this often happens with other antihistaminics too when they have been taken for some time.

(*) The preparation was kindly placed at our disposal by Nordisk Droge- & Kemikalieforretning A/S, as representative for UNION CHIMIQUE BELGE S.A., Brussels.
ARDESMAN (1), who has tested LONGIFEN in the U.S.A., had unfortunately for the sake of comparison - only 2% = 12 patients with urticaria against 478 with nasal symptoms. He too finds very few secondary effects, and optimum effect on cutaneous symptoms, but he does not find the action of very long duration, whereas my patients often manage over 24 hours on 1-2 tablets.

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The table shows the results of the treatment. The figure above the stroke indicates the number of patients evincing good results with regard to the symptom in question, the figure below the stroke indicates the total number of patients with the same diagnosis. Where there has been any doubt at all as to the judgment the result is always - as in an earlier similar work (16) - counted as negative.

Pulmonary symptoms means asthma bronchiale or bronchitis asthmatica, nasal symptoms are always allergic rhinitis, including febris aestivalis, cutaneous symptoms indicates urticaria, strophulus chr., eczema, oedema Quincke, or prurigo Besnier; the one case of "generalized allergy" is a patient suffering from oedemata, vertigo, optical confusions, gastrointestinal symptoms and periodic hypurianuri.

It will be seen that LONGIFEN is particularly active against allergic dermatoses, probably because of its anti-pruritic action.

A few brief cases will show the favourable action:

Pt. No. 2227, girl aged 12, asthma bronchiale and rhinitis allergica (febris aestivalis) is extremely troubled by sneezes in the morning (by series). 1 tablet of LONGIFEN in the evening prevents the sneezing.

Pt. No. 2721, boy aged 3, eczema infantile pityriasiformis. Has been subjected to various topical treatments in the Childrens' and the Dermatologic clinics with varying success. Given 1 tablet of LONGIFEN in the evening he ceases scratching himself, and his mother declares that he has not been so well for a long time, and that never before has he looked so neat.
Summary:

After a brief exposition of the preparations now available that are professes to possess antihistaminic potency the results of treatments of a number of patients with LONGIFEN are reported. An outstanding feature is its marked antipruritic action for which reason it is particularly active against other allergic symptoms. A distinctive characteristic is its few and slight secondary effects and the duration of its action.

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