

From the Municipal Out-patient Clinic for Allergic Diseases in Children,
Copenhagen, Denmark (Physician-in-chief: E. Winge Flensburg, M.D.).

PROLONGED PROPHYLAXIS OF ASTHMA IN CHILDHOOD WITH SULFAMETHOXYPYRIDAZINE (KYNEX)

By

ERIK RYSSING

As the upper respiratory infections very often provoke asthmatic symptoms in asthmatic children a long-term anti-infectious prophylaxis with antibiotics or chemotherapeutics has been tried by several authors with either penicillin (5, 6, 7, 14, 17, 18), tetracyclines (2, 5, 7, 14), or sulfonamides (8, 9).

The evaluation of such a prophylaxis in asthma is very difficult because of the variety of etiological factors and the unpredictable course of the disease unless proper control studies are concurrently made. Most authors consider the prophylaxis effective without establishing any convincing proof. The trials are usually compared with a pre-treatment period or with untreated controls. Placebo has been used by Grater (cit. 14), who prescribed tetracyclin and placebo to 25 children on alternate months with good results. *Lewis-Faning & Davies* (14) administering oral phenoxymethylpenicillin (calcipen) with double-blind technique were unable to demonstrate any effect on the frequency, duration or severity of the asthmatic attacks.

The present work is a trial on the effect of a long-term prophylaxis with sulfamethoxypyridazine (Kynex) partially using a double-blind technique. Sulfamethoxypyridazine is a new sulfonamide with a rapid absorption and a slow elimination

thus a single daily dose is sufficient to maintain an effective plasma concentration. Untoward reactions are usually mild and rare though severe cases of leucopenia and thrombopenia have been observed (10, 15, 16, 19).

MATERIAL AND METHODS

Our clinic works as a clinic for diagnosis and treatment and as the children receive all their allergen injections here with intervals of from 2 to 28 days their condition and symptoms are exactly recorded. Each of the three physicians treats and controls his own group through out.

Kynex and placebo were distributed according to the following principle.

Children with at least two periods of asthmatic symptoms during the preceding year were chosen for the trial. The tablets were distributed to the two physicians by the author. Without knowledge to the content of the tablets one of the physicians received Kynex for administration to his group and the other physician received placebo to his group. In the author's own group patients born on even dates received Kynex and patients born on odd dates received placebo.

The trial ran from september 1958 through march 1959. At every clinic visit the patients and the adult companion were closely questioned on whether the patients had had any symptoms during the past time. By request some of the children coming alone brought a note from the mother with the desired information. The necessity of a regular intake of the tablets was impressed and new supplies were distributed. The hyposensitization and the symptomatic treatment were continued.

The children received an initial dose of 14 mg per kilo of body weight followed by a maintenance dose of 7 mg per kilo. The initial dose was repeated in case of interruption. The placebo was administered as a corresponding number of tablets.

RESULTS

After the trial the records were examined by the author. For each patient the number of weeks with asthmatic symptoms has been summed up. If, for instance, a total of 9 weeks with symptoms for one patient has been summed up, then this means that he has had symptoms in 9 different weeks, but it doesn't mean that he has had symptoms for a total of 9 weeks. Perhaps his symptoms have lasted only 2 or 3 days each week. The application of a more exact standard was impossible on account of the difficulties by demarcating precisely the asthmatic periods.

TABLE 1
Survey of the 35 patients primarily omitted.

Cause of omission	Kynex no. of patients	Placebo no. of patients	Total
Refusal of taking the tablets	3	1	4
Steroid treatment started	0	2	2
Duration of treatment, 10 weeks or less	10	11	21
Uncertain or unreliable information obtained	2	3	5
Discontinued on account of:			
Urticaria	2	0	2
Dyspepsia	0	1	1
Total.....	17	18	35

Originally the material comprised 231 children of whom 110 received Kynex and 121 placebo. 35 children have been omitted for the reasons indicated in table 1. The remaining 196 children were grouped according to the frequency of symptom periods during the previous year using the scale of *Kraepelin* (13). (Table 2).

TABLE 2
The 196 patients grouped according to the severity of asthmatic symptoms during the year previous to the trial.

Group	No. of symptom periods the year before the trial	Kynex no. of patients	Placebo no. of patients	Total
I	2 - 5	38	22	60
II	6 - 10	39	37	76
III	More than 10	8	34	42
IV	Continuous	8	9	17
	Unknown	0	1	1
Total.....		93	103	196

It became obvious that for the final statement only the two first groups, that is the mild and moderate cases, could be used. Patients with previous persisting symptoms continued to have

persisting symptoms and among the severe cases (group III) the range of the number of symptom periods was so wide that a single patient could affect the results unfavourably.

The applicable 136 patients were grouped according to duration of treatment with Kynex and placebo. Eight patients were omitted on account of a short time of treatment and one because he had persisting symptoms during the trial. This patient received Kynex.

The result of the trial is evaluated on the basis of the 127 children who received the drugs for 22 weeks or more. The information as far as the Kynex group is concerned originates from 1043 clinic visits plus 8 stays in a sanatorium in Norway, each of 4 months' duration, and one stay in a hospital. The information about the placebo group originates from 766 clinic visits. 56 children out of the Kynex group and 33 children out of the placebo group have been studied according to the double-blind technic. The remaining 38 children are the author's own group of which 16 received Kynex and 22 placebo.

TABLE 3
The final result of the prophylaxis with Kynex and placebo.

Duration of treatment weeks	Kynex			Placebo		
	Total number of weeks with symptoms	Number of children	Average number of weeks with symptoms	Total number of weeks with symptoms	Number of children	Average number of weeks with symptoms
26	85	37	2.3	49	19	2.6
25	34	14	2.4	35	11	3.2
24	76	17	4.5	41	13	3.2
23	6	1	6.0	24	10	2.4
22	7	3	2.3	3	2	1.5
	208	72	2.9	152	55	2.8

Table 3 indicates the final result. The first line comprises the children who have received the drugs for 26 weeks. It is shown that 37 Kynex treated children have had a total of 85 weeks with symptoms during that period. This averages 2.3

weeks a patient. 19 placebo treated children have had a total of 49 weeks with symptoms during the same period. This averages 2.6 weeks a patient.

In the same way the following lines show the total and average figures for those children who got the drugs for 25 through 22 weeks respectively. The incidence of symptoms for the two groups averages 2.9 and 2.8 weeks. This signifies that a difference between the groups cannot be demonstrated.

So far the composition of the groups has not been considered.

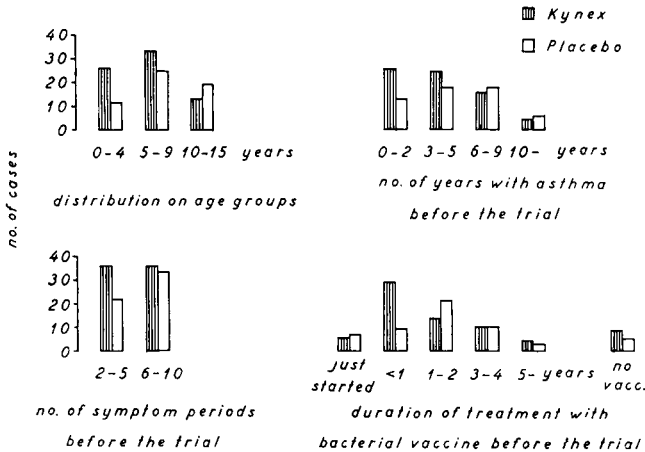


Fig. 1.

The figure indicates that the children in the Kynex group belong to a younger age group, have a shorter history of asthma and have had less attacks during the year prior to the trial. Furthermore the figure shows that more children out of the Kynex group than out of the placebo group have been given bacterial vaccine for at short time only.

Fig. 1 shows some of the factors which may possible have influenced the result. From this it appears that the children in the Kynex group belong to a younger age group, have a shorter history of asthma and have had less attacks during the year prior to the trial.

So the groups are not matched but if the differences have been of any importance the influence of the two last mentioned factors probably may have been in favour of Kynex. Further-

more the figure indicates that more children out of the Kynex group than out of the placebo group have been given bacterial vaccine for a short time only. Probably this factor might have an opposite influence on the result.

It is impossible to determine which of these factors are carrying most weight. Judging from the result they must be either of no importance or compensate for each other. The last possibility seems hardly probable because the material is rather arbitrarily selected.

At last the incidences of proved manifest and subclinical allergy to inhalant allergens are identical in the two groups namely 31 % and 34 %.

Consequently a continuous prophylaxis with a long-acting sulfonamide through half a year has not been of any effect on the frequency of symptoms in asthmatic children.

UNTOWARD EFFECTS

The medication has been discharged in only three patients on account of untoward effects. One placebo treated child discontinued the medication after a fortnight owing to dyspeptic symptoms. Two Kynex treated children developed urticaria after nine and ten days of treatment and one of these children had a severe case of angioedema of the legs. However, both of them had previously had recurrent urticaria due to some particular foods. Of the 93 Kynex treated children urticaria occurred in seven cases of whom five had had it previously. Of the 102 placebo treated children urticaria occurred in three cases of whom two have had it previously. 15 out of the 93 Kynex treated children had dyspeptic symptoms compared with 18 out of the 102 placebo treated children. However, these high figures may probably be explained by the fact that an epidemic disease with gastrointestinal symptoms occurred in the city during the trial. Of the Kynex group one child had a transient anorexia and vertigo, a second one had nausea in the morning and a third one headache in the morning.

During the last month of the trial leucocyte and differential

counts have been carried out in 99 Kynex treated and in 76 placebo treated children. In five children the number of neutrophil leucocytes was below the lower normal limit which is fixed to about 1500 in children younger than 10 years of age and to about 1800 in children older than 10 years of age (1). In two Kynex treated children, 7½ and 8½ years of age, counts of 1480 and 1360 have been found and in three placebo treated children, 3¼, 5½, and 15 years of age, counts of 1360, 1440 and 1730 neutrophil leucocytes have been recorded. So a complicating leucopenia has not been found.

Presumably only some cases of urticaria and dyspepsia may be interpreted as untoward effects of the sulfonamides.

DISCUSSION

In several studies sulfamethoxypyridazine has a proved therapeutic effect on infections caused by sulfonamide sensitive bacterias (10, 15, 16, 19). The prophylactic use of sulfonamides decreases the frequency of recurrent upper respiratory infections (3, 11) and relapses in rheumatic fever (4, 12). Consequently, a decrease in the number of asthmatic attacks following infections might have been expected but this was not confirmed by the trial. An explanation of this lack of effect is impossible. The negative results is comparable with that obtained by *Lewis-Faning & Davies* (14) in a trial with penicillin per mouth using the double-blind technic. Contrary to these results are the beneficial effect observed by the other authors the investigations of whom, however, are made without sufficient control studies.

In conclusion a long-term prophylaxis with sulfonamides or penicillin per mouth is not routinely indicated in the treatment of asthma in childhood.

SUMMARY

The present work failed to show any effect of a long-term prophylaxis with sulfamethoxypyridazine (Kynex) on the fre-

quency of asthmatic attacks. The study was carried out partially using the double-blind technic.

Dyspepsia and urticaria occurred with almost the same frequency in both the Kynex group and in the placebo group. Presumably only a few of these reactions may be interpreted as untoward effects of the sulfonamide. A complicating leucopenia has not been found.

In conclusion, a long-term prophylaxis with sulfonamides is not routinely indicated in the treatment of asthma in childhood.

ACKNOWLEDGEMENT

The author is indebted to the Lederle Laboratories Division, American Cyanamid Company, New York, U.S.A., who have kindly placed sulfamethoxypyridazine (Kynex) and placebo tablets at my disposal.

LITERATURE

1. *Albritton, E. C.*: Standard Values in blood, p. 51. W. B. Saunders Co., 1952.
2. *Blatt, H.*: Antibiotic Med. and Ther., vol. V., No. 1, p. 19, 1958.
3. *Burke, J. B.*: Brit. Med. J. *1*, 538, 1956.
4. *Faber, V.*: U. f. L. *119*, 829, 1957.
5. *Finke, W.*: Antibiotics and Chemoterap. *4*, 319, 1954.
6. *Finke, W.*: Antibiotics Annual, p. 287, 1956-57.
7. *Finke, W.*: ibid. p. 431, 1957-58.
8. *Fishmann, A. E.*: Ann. Allergy. *8*, 684, 1950.
9. *Fishmann, A. E.*: J. Alb. Einstein Med. Center. *5*, 108, 1956-57.
10. *Griehle, H. G. & Jackson, G. G.*: New Engl. J. Med. *258*, 1, 1958.
11. *Hardy, L. M. & Traisman, H. S.*: J. Ped. *48*, 146, 1956.
12. *Johnson, E. E., Matheus, M. J. & Stollermann, G. H.*: J. Ped. *54*, 468, 1959.
13. *Kraepelien, S. & Engström, I.*: Sven. Läk. Tidn. *53*, 734, 1956.
14. *Lewis-Faning, E. & Davies, W.*: Acta allergol. *13*, 67, 1959.
15. *Nichols, R. L. & Finland, M.*: J. Lab. and Clin. Med. *49*, 410, 1957.
16. *Schwartz, M. J. & Norton, W. S.*: J.A.M.A. *167*, 457, 1958.
17. *Shuey, C. B. & Grater, W. C.*: Ann. Allergy. *12*, 601, 1954.
18. *Szanton, V. L., Cohen, H. & Rapaport, H. G.*: Ann. Allergy. *14*, 30, 1956.
19. *Weihe, C.*: Antibiotic Med. and Clin. Ther., vol. V, No. 3, 1958.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.