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Research Article

STUDIES ON THE PREVENTION OF RHEUMATIC FEVER: THE EFFECT OF TIME OF INITIATION OF TREATMENT OF STREPTOCOCCAL INFECTIONS ON THE IMMUNE RESPONSE OF THE HOST [1]

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Previous studies have established the fact that penicillin treatment of acute streptococcal pharyngitis results in a marked suppression of antibody formation (1, 2, 3). This is in contrast to the failure of penicillin treatment to alter the immune response in patients with pneumococcal pneumonia (4). It has been suggested that in the latter case, sufficient pneumococcal antigen is formed during the early phases of pneumonia to provide a maximal antigenic challenge before penicillin therapy is instituted (4). The capacity of penicillin to suppress the production of streptococcal antibodies suggests that in streptococcal infections the antigenic challenge may be presented more gradually. Under such circumstances, it would be expected that the effectiveness of penicillin in this regard would be related to the time of institution of therapy. Since no definitive information on this point has hitherto been obtained, the present study was designed to test this hypothesis.

DESCRIPTION OF STUDY

All patients fulfilling the following criteria were included in the study: the presence of exudative pharyngitis, history of onset of symptoms less than 31 hours before admission, and subsequent isolation of group A streptococci from the initial throat culture. Patients with a past history of rheumatic fever or chorea were excluded. A throat culture and a serum specimen were obtained on each patient at the time of admission and on the fourteenth, twenty-first and twenty-eighth days from the onset of symptoms.

Bacteriological and serological studies were performed by methods previously described (5, 6, 7). Antistreptolysin "O" titers were determined on all sera from each patient in a single test, and all tests were performed with the same lot of streptolysin and read by the same observer.

RESULTS

Each of the 349 patients studied was assigned to one of four treatment groups according to a random sequence previously determined by a shuffled deck of cards. Table I indicates the distribution of the patients among four treatment groups according to the time of initiation of therapy and the amounts of penicillin employed. The groups were essentially comparable, as shown in Table II, with respect to the admission leukocyte count, predominance of group A streptococci on initial throat culture, history of sore throat within the previous four weeks, and initial antistreptolysin titer. There was some variation in the distribution of serological types of infecting streptococci in the four treatment groups, and analysis revealed only slight differences in the antistreptolysin responses to infection with the different types.

Table III shows the average increase in antibody in each group. Early treatment with penicillin was followed by a much smaller average antibody rise than that found in the control group. In those groups of patients in which treatment was delayed for three or five days, there was progressively less suppression of antibody response. Nevertheless, considerable reduction in antibody response was obtained even when treatment was delayed for five days.

Figure 1 shows the per cent of patients in each group who developed an antibody rise of 200 units or over. It can be seen that twice as many patients developed this response when treatment was de-

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TABLE I

Distribution of cases according to treatment groups

Group	Number of cases	Time of initial injection*	Therapy
Immediate treatment	86	22–31 hours	Three injections of 600,000 units of penicillin† at 3 day intervals
3 day delay in treatment	89	70–79 hours	
5 day delay in treatment	87	118–127 hours	
Control	87	—	Saline placebos given on first and fifth hospital day

* Time from onset of symptoms.

† Procaine penicillin G in sesame oil, with 2 per cent aluminum monostearate.

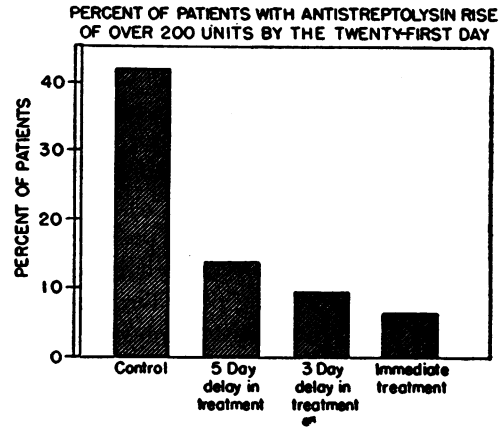

FIG. 1

TABLE II

Comparability of the treatment groups

		Number of patients in treatment groups			
		Immediate treatment (86)	*3 day delay in treatment (89)*	*5 day delay in treatment (87)*	*Control (87)*
Admission leucocyte count 12,000 and over		64	63	65	69
Initial antistreptolysin titer 125 units and under		56	66	64	65
History of sore throat within previous 4 weeks		8	12	7	11
Group A streptococci predominant* growth on initial culture		81	79	76	81
Type of group A streptococci from initial throat culture	14	10	14	20	20
	30	19	26	23	28
	3	9	6	4	2
	18	15	14	13	13
	6	8	9	8	6
	5	10	9	10	7
	Others	15	11	9	11

* Over 50 colonies on plate.

TABLE III

Average antistreptolysin response in relation to time of initiation of penicillin therapy

		Antistreptolysin "O" titers									
		Average units				Average units rise			Per cent inhibition as compared to controls		
Treatment groups	Number of cases	*Initial*	*14 day*	*21 day*	*28 day*	*14 day*	*21 day*	*28 day*	*14 day*	*21 day*	*28 day*
Immediate treatment	86	137	214	224	231	77	87	94	58.4	60.3	56.0
3 day delay in treatment	89	121	205	229	235	84	108	114	55.0	50.3	46.8
5 day delay in treatment	87	120	222	251	246	103	131	126	44.8	40.0	41.1
Control	87	119	304	337	333	186	218	214	—	—	—

layed five days, compared to the group who received immediate therapy.

In this study one case of rheumatic fever occurred in the control group. This patient showed a 375 unit antistreptolysin rise by the fourteenth and twenty-first days, and a 750 unit rise by the twenty-eighth day.

Reinfections and recurrences of positive cultures at follow-up examination remained under 13 per cent in all groups receiving penicillin, and did not appreciably alter the antistreptolysin responses of any group.

DISCUSSION

These data indicate that there is a correlation between the time of institution of penicillin therapy and the degree of suppression of antistreptolysin formation: the earlier the treatment the greater the suppression. Therapy, begun not later than 31 hours after the onset of symptoms of streptococcal pharyngitis, effectively reduces the subsequent antistreptolysin response at 21 days by approximately 60 per cent, while therapy begun five days after the onset of symptoms results in a 40 per cent suppression. These observations support the hypothesis that the antigenic challenge during acute streptococcal pharyngitis occurs gradually, over a period of several days, and that an appreciable percentage of the total immune response develops as a result of antigen formed after the fifth day of disease.

It is difficult to relate these data to the overall problem of the prevention of rheumatic fever, since the present study was too limited to yield any direct evidence as to the effectiveness of delayed penicillin therapy in reducing the attack rate for this complication. It has been shown that there is a correlation between high convalescent antibody titers following streptococcal infections and the development of rheumatic fever (8). It would thus seem that early therapy of streptococcal infections would be advisable; delayed therapy, however, might exert some effect on the incidence of rheumatic fever. It is hoped that studies now in progress will provide information on this point.

CONCLUSIONS

Early treatment of streptococcal pharyngitis with penicillin is more effective than delayed therapy in suppression of antistreptolysin formation. Treatment instituted as late as five days from onset of symptoms of pharyngitis results in significant antibody suppression.

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