Technical Papers

Hemolytic Streptococcal Sore Throat: Antibody Response Following Treatment With Penicillin, Sulfadiazine, and Salicylates[1]

LOWELL A. RANTZ, *Stanford University Hospital, San Francisco*; PAUL J. BOISVERT, *New Haven Hospital*; and WESLEY W. SPINK, *University Hospital, Minneapolis*

Information has recently been obtained during a field study with regard to the formation of antistreptolysin and antifibrinolysin following acute Group A hemolytic streptococcal sore throat in military personnel. A complete description of the relationship of these and other streptococcal antibodies to the observed clinical phenomena will be presented elsewhere. Many of the infected individuals were treated by the administration of penicillin, sulfadiazine, or salicylates. Because of the great interest in chemo- and antibiotic therapy, it seemed desirable to present immediately the results of this study in so far as it bears on antibody response in treated and untreated cases.

Sera were obtained on approximately the third and twenty-first days from 351 cases of acute Group A hemolytic streptococcal sore throat. The diagnosis was made on clinical and bacteriological grounds. The exact criteria and techniques will be described elsewhere. The antistreptolysin titers were determined by a modification of the usual technique (*5*). Antifibrinolysin titers were also measured at similar intervals in 321 cases (*1*).

Two hundred and thirty-three cases received no treatment except hot saline gargles. Chemo- or antibiotic therapy was begun in the others on the second or third day of the acute illness and continued according to the following schedules:

Salicylates: 10 grams of sodium salicylate were administered by mouth each day for approximately one week.

Sulfadiazine: 4 grams of sulfadiazine were administered by mouth as an initial dose, followed by 1 gram every four hours, day and night. The average total dose for the group was 39 grams and the duration of therapy 6.5 days.

Penicillin followed by sulfadiazine: 200,000 units of penicillin were administered intramuscularly in 18 to 24 hours, the individual injections being given at intervals of four hours. A standard oral course of sulfadiazine was begun with the last dose of penicillin, an average of 33 grams being given in 5.8 days.

Penicillin—short course: 200,000 to 400,000 units of penicillin were administered intramuscularly, at four-hour intervals in from 32 to 64 hours.

Penicillin—long course: 500,000 or 1,000,000 units of penicillin were administered intramuscularly at four-hour intervals in 80 hours.

Hemolytic streptococci usually disappeared from the throat during the exhibition of penicillin but frequently returned when the agent was withdrawn. At this time a clinical relapse often was observed.

The results of this study are included in Table 1. A 50-per cent increase in the antistreptolysin titer or a prolongation of clot lysis of more than eight hours were regarded as measures of significant antibody response.

TABLE 1

ANTISTREPTOLYSIN AND ANTIFIBRINOLYSIN RESPONSE IN ACUTE GROUP A HEMOLYTIC STREPTOCOCCAL SORE THROAT TREATED WITH VARIOUS CHEMICALS

Treatment	No. of cases	No. with bacteriological relapse	No. with clinical relapse	Antistreptolysin				Antifibrinolysin		
				No. of cases	Cases with antibody response	Per cent with antibody response	Mean increase titer units	No. of cases	Cases with antibody response	Per cent with antibody response
Salicylates	25	..	..	25	22	88.0	477	25	10	40.0
Sulfadiazine	36	..	..	36	30	83.3	327	31	15	48.5
Penicillin and sulfadiazine	25	20	9	25	22	88.0	263	25	8	32.0
Penicillin—short course	16	16	8	16	14	87.5	442	16	7	43.5
Penicillin—long course Bacteriological relapse	7	7	4	7	7	100.0	241	7	1	14.0
Penicillin—long course No bacteriological relapse	9	0	0	9	4	44.5	182	9	1	11.1
None	233	..	..	233	190	81.6	204	208	73	35.1

[1] This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army. The laboratories of the Department of Medicine, Stanford University School of Medicine, San Francisco, were made available to the Commission for certain studies.

None of the therapeutic procedures prevented the formation of antistreptolysin or antifibrinolysin. The administration of salicylates, sulfadiazine, and/or a short course of penicillin failed to diminish the percentage of individuals exhibiting an antibody response, or the mean increase in antistreptolysin. The latter was greater in certain treated groups than in the controls. This result is probably not significant for the reasons stated below.

When penicillin was administered over a longer interval, the frequency of the antifibrinolysin response was decreased. An antistreptolysin response was also observed less often in those individuals in whom bacteriological relapse did not occur.

These latter observations suggest that the exhibition of penicillin in amounts adequate for the elimination of the hemolytic streptococcus from the throat may interfere with the formation of these antibodies. It is necessary to be very guarded in reaching such a conclusion based upon the study of small groups f individuals infected by a variety of types of Group A streptococci, since it has been demonstrated that the different types vary in their ability to stimulate the production of antistreptolysin (*4*) and antifibrinolysin (*2, 4*), and that great individual differences exist between various human beings in their ability to react to the antigenic stimulus of infection by these organisms (*3*).

References

1. Boisvert, P. J. *J. clin. Invest.*, 1940, **19**, 65.
2. Commission on Acute Respiratory Diseases, in collaboration with Melvin Kaplan. *Science*, 1945, **101**, 120–122.
3. Rantz, L. A. *Arch. int. Med.*, 1944, **73**, 238.
4. Rantz, L. A., Boisvert, P. J., and Spink, W. W. (To be published.)
5. Rantz, L. A., and Randall, E. *Proc. Soc. exp. Biol. Med.*, 1945, **59**, 22.

Blood Levels of Penicillin After Oral Administration With Various Antacids

Lloyd D. Seager

Department of Pharmacology, Woman's Medical College of Pennsylvania

Many antacids have been employed with apparent success (*2, 3, 5, 6, 7, 12*) in an attempt to protect penicillin from destruction when given orally. Considerable discrepancy appears in the results reported, and it was felt that a comparison of the effectiveness of various antacids in a group of normal adults would be desirable. Though there may be considerable variation in gastric acidity from time to time in the same individual, comparative studies made largely on the same group of individuals, under stated conditions, should be more valid than those made on different groups with a variety of illnesses.

Methods

Subjects were allowed to have a soft diet, low in protein and fat. They were given 100,000 units of calcium penicillin along with the equivalent of 2.5 grams of one of the antacids. Aluminum hydroxide, magnesium trisilicate, and magnesium hydroxide were given as magmas or gels. The penicillin was freshly mixed with these preparations before use according to the method of Welch (*12*). Trisodium citrate and aluminum dihydroxy amino acetate were used in tablet form with penicillin incorporated in them. Seven control tests were made with penicillin administered in tap water, and in one case it was given in tap water to a pernicious anemia patient. Blood samples were obtained at hourly intervals for 4 hours, and urines were collected up to 6–12 hours. Blood levels of penicillin were determined by the Fleming Slide cell method (*4*) and urine concentrations by the Oxford cup method (*1*).

TABLE 1

Blood Levels of Penicillin After the Oral Administration of 100,000 Units of Calcium Penicillin in Tap Water

Subject	½ hr.	1 hr.	1½ hrs.	2 hrs.	3 hrs.	4 hrs.	Per cent excretion
*S	...	0.06	0.03	0	0	...	6.6
*S	...	.12	...	.03	0	...	....
*W	.12	.12	...	.06	0	...	15.9
†S	0	0	0	0	...	...	1.9
†W	...	0	0	0	0	...	1.5
†S	...	.12	0	0	0	...	1.25
†W	.03	0	0	0	0	...	0.48
‡R	...	0.24	...	...	0.24	0.03	24.2

* Empty stomach.
† Full stomach.
‡ Pernicious anemia.

TABLE 2

Blood Levels of Penicillin After Oral Administration With 100,000 Units of Calcium Penicillin in Aluminum Hydroxide Gel

Subject	1 hr.	2 hrs.	3 hrs.	4 hrs.
K	0	0.06	0.015	0.015
L	0.03	0.015	0.015	0
R	0.12	0.06	....	0
F	0.12	0.03	0.03	0
W	0.24	0.12	0.015	....
G	0.03	0.03	0.03	0.03
ST	0.24	0.24	0.06	0
Average	0.11	0.079	0.03	0.007

Results

Of the tap water controls (Table 1) these tests were made with 100,000 units on an empty stomach, and